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Improving outcomes in diabetic foot care - a worldwide perspective

Edited by
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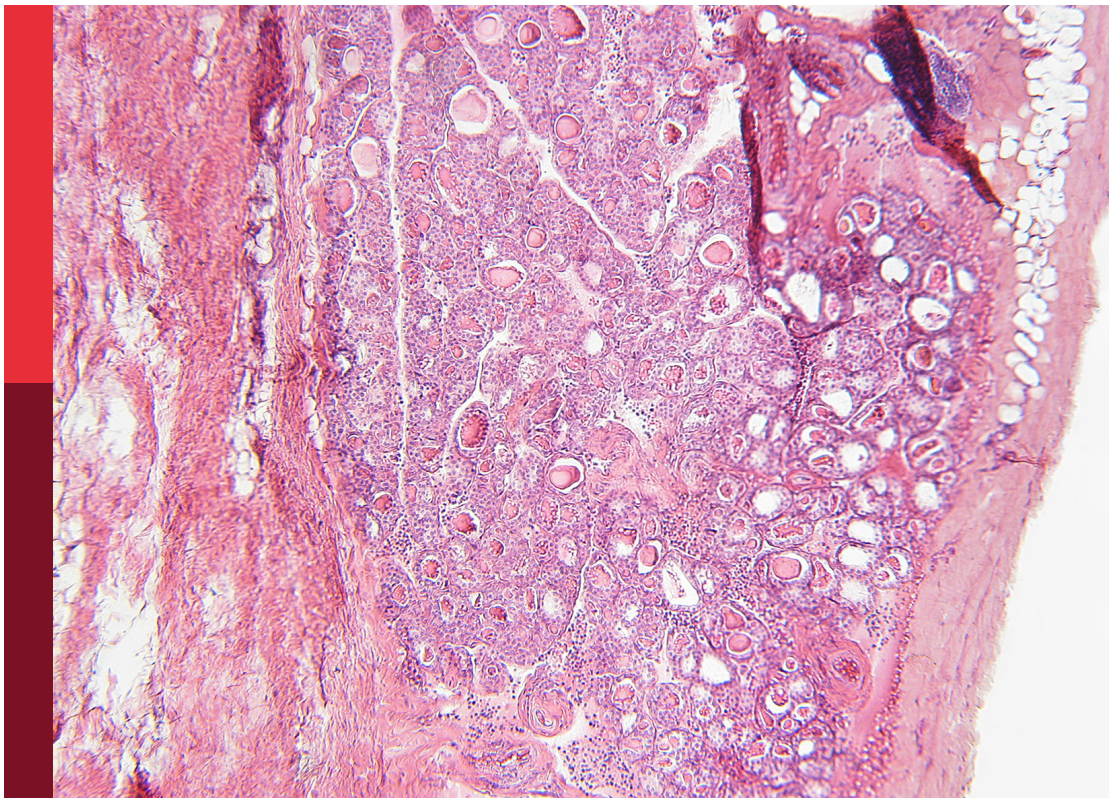

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Improving outcomes in diabetic foot care - a worldwide perspective

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Editorial: Improving outcomes in diabetic foot care - a worldwide perspective

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Editorial on the Research Topic
Improving outcomes in diabetic foot care - a worldwide perspective

The International Diabetes Federation has documented the challenging increase in prevalence of diabetes mellitus now evident in virtually every country in the world (1). Over 90% have type 2 diabetes, and the majority of those living with diabetes live in low- or middle-income countries (2). The specific diabetes associated complications-retinopathy, nephropathy and neuropathy are compounded by the enhanced risk of atherosclerotic vascular disease. Peripheral neuropathy, peripheral vascular disease and susceptibility to infection result in a high incidence of diabetic foot disease manifested by foot deformity, ulceration, ischaemia and infection (3). The intractable nature of diabetic foot disease severely affects the quality of life and survival of those affected, impacts livelihood and family life and incurs enormous health care costs (4). The incidences and outcomes for diabetic foot disease are influenced by age, ethnicity, deprivation and availability of early diagnosis and treatments (5, 6).

In this Research Topic we have sought to collate a worldwide perspective to encourage sharing of differing approaches to diabetic foot care and cross-cultural debate. We have been privileged to receive manuscripts from high-, middle- and low-income countries, which have provided insights into- assessment of strategies to prevent and heal foot ulceration; risk factors for foot ulceration; morbidity and mortality; established and novel treatment options.

The key to prevention of diabetic foot wounds in high-risk subjects lies with patient engagement, and the group from Malaga assess the reliability and validity of a self-management questionnaires. The Birmingham group have shown that individuals with new-onset type 2 diabetes who had moderate to high risk of diabetic foot disease were more likely to die compared to those at low risk. Those who did not have foot examination had high risk both of foot ulceration and mortality. A review of wound healing from China offers hope that better preparation of exosomes could help healing in diabetic foot wounds. A metanalysis from India tackles the important issue of micronutrient deficiencies in Diabetic foot ulcer patients. Articles from Indigenous peoples in Canada and Nepal emphasize the need for a holistic approach to patient care and antimicrobial stewardship is

evaluated in Peru. Dressings and debridement are reviewed in articles from Guizou in China and the intricacies of total contact casting versus removable casts and footwear in another metanalysis. From Chengdu in China another tackles the issue of standard versus advanced methods of debridement. Ozone therapy, platelet rich plasma application for DFU and micronutrient status in DFU are also presented. A single centre study from the UK highlights the value of national and local data analysis which has shown worse outcomes for diabetic foot disease in deprived populations during the Covid-19 epidemic. Finally, an important surgical report of distally based sural neurocutaneous flaps in severe foot wounds has shown considerable success with good healing and subsequent excellent patient mobility.

The scope of these articles is wide, highlighting the need for more insights from around the world, to share innovations to help reduce the incidence and improve outcomes in diabetic foot disease.

Author contributions

RP: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. JL: Data curation, Supervision, Writing – review & editing. FG: Data curation, Supervision, Writing – review & editing. HH: Data curation, Supervision, Writing – review & editing. JP: Data curation, Supervision, Writing – review & editing.

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Conflict of interest

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Diabetic Foot Risk Classification at the Time of Type 2 Diabetes Diagnosis and Subsequent Risk of Mortality: A Population-Based Cohort Study

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Aim: We aimed to compare the mortality of individuals at low, moderate, and high risk of diabetic foot disease (DFD) in the context of newly diagnosed type 2 diabetes, before developing active diabetic foot problem.

Methods: This was a population-based cohort study of adults with newly diagnosed type 2 diabetes utilizing IQVIA Medical Research Data. The outcome was all-cause mortality among individuals with low, moderate, and high risk of DFD, and also in those with no record of foot assessment and those who declined foot examination.

Results: Of 225,787 individuals with newly diagnosed type 2 diabetes, 34,061 (15.1%) died during the study period from January 1, 2000 to December 31, 2019. Moderate risk and high risk of DFD were associated with increased mortality risk compared to low risk of DFD (adjusted hazard ratio [aHR] 1.50, 95% CI 1.42, 1.58; aHR 2.01, 95% CI 1.84, 2.20, respectively). Individuals who declined foot examination or who had no record also had increased mortality risk of 75% and 25% vs. those at low risk of DFD, respectively (aHR 1.75, 95% CI 1.51, 2.04; aHR 1.25, 95% CI 1.20, 1.30).

Conclusion: Individuals with new-onset type 2 diabetes who had moderate to high risk of DFD were more likely to die compared to those at low risk of DFD. The associations between declined foot examination and absence of foot examinations, and increased risk of mortality further highlight the importance of assessing foot risk as it identifies not only patients at risk of diabetic foot ulceration but also mortality.

Keywords: type 2 diabetes, diabetic foot risk, diabetic foot disease, mortality, foot risk examination

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INTRODUCTION

Diabetic foot disease (DFD) has been recognized as a significant clinical condition that causes hospitalization and morbidity in people with diabetes (1). Approximately 34% of patients with diabetes are likely to be affected by foot ulcers, and 20% of those require an amputation (2, 3). DFD also significantly worsens the quality of life in people with diabetes (4, 5). Notably, diabetic foot ulceration (DFU) and amputation were associated with increased mortality among people with diabetes (6–8). Approximately 50% of those developing a DFU and up to 70% of individuals with amputation die within 5 years in the UK (6). Although it aggravates the health burden and increases mortality in people with type 2 diabetes, DFD is preventable by early detection of foot risk and by implementing appropriate preventative care before the development of active foot disorders (9–11). For this reason, National Institute for Health and Care Excellence (NICE) guidelines recommend that all adults with newly diagnosed diabetes should have a foot examination (6). There are, however, still a large number of people with diabetes who do not have a foot examination either in primary or in secondary care (12, 13).

Diabetic foot risk including neuropathy, deformity, peripheral arterial disease, and history of ulcer or amputation has been highlighted to increase the risk of diabetic ulcer and amputation (9, 14, 15). However, evidence for an association of at-risk foot in the early course of type 2 diabetes, before the development of active foot disorder, with mortality is lacking. Evidence linking peripheral neuropathy at the time of diagnosis of type 2 diabetes with cardiovascular disease (16) or mortality (16, 17) is limited to modest-sized studies. In the UKPDS outcomes model, PVD, amputation, and ulcer are predictors of mortality (18) while available data of peripheral neuropathy do not form part of the model. It is worth considering the mortality of individuals with at-risk foot as it can identify individuals who are at greater risk of mortality at the time of diagnosis of type 2 diabetes, hence enabling implementation of preventative interventions to reduce the mortality in the long run. There is also a paucity of data describing the risk of mortality among type 2 diabetes patients who do not have a foot examination. We hypothesized that individuals with newly diagnosed type 2 diabetes who were at increased risk of DFD would be associated with higher risk of mortality. Highlighting at-risk foot as a significant indicator of death at the time of diagnosis of type 2 diabetes will ensure early intervention rather than at a later stage. Therefore, we aimed to compare the mortality of individuals at low, moderate, and high risk of DFD, and also those with no record and who declined foot examination in the context of newly diagnosed type 2 diabetes.

Abbreviations: AF, Atrial fibrillation; CPRD, Clinical Practice Research Datalink; DExtER, Data extraction for epidemiological research; DFD, Diabetic foot disease; DPN, Diabetic peripheral neuropathy; DPP-4, Dipeptidyl peptidase-4; GLP-1, Glucagon-like peptide 1; HRQOL, Health-related quality of life; IMRD, IQVIA Medical Research Data; IHD, Ischemic heart disease; IRR, Incidence rate; MREC, Multi-centre Research Ethics Committee; NICE, National Institute for Health and Care Excellence; PVD, Peripheral vascular disease; QOF, Quality Outcomes Framework; SF-36, Medical Outcomes Study Short Form 36 Healthy Survey; SGLT-2, Sodium-glucose co-transporter-2; THIN, The Health Improvement Network; TIA, Transient ischemic attacks.

METHODS

Study Design and Data Source

We conducted a population-based cohort study of individuals with newly diagnosed type 2 diabetes between January 1, 2000, and December 31, 2019 in the IQVIA Medical Research Data (IMRD). IQVIA, incorporating data from The Health Improvement Network (THIN), is a longitudinal, clinical primary care database of over 18 million patient records in the UK (19). Read codes describing concepts related to health in GP records are used to record diagnoses in the IMRD database (20). Collection for data in IMRD was approved by the NHS South East Multi-centre Research Ethics Committee (MREC) in 2003. We obtained approval to conduct this analysis from the Scientific Review Committee (reference number: 21SRC030).

The Data Extraction for Epidemiological Research (DExtER) tool, an extract transform load-based software framework, was used to extract this dataset (21). This platform enables users to extract high-quality and individual-patient-level data from primary care databases (21). The outcome measures (e.g., prevalence) calculated in IMRD datasets extracted from DExtER have produced comparable results to those from Clinical Practice Research Datalink (CPRD) and other national datasets (21).

Study Population

Adults ≥18 years with a record of type 2 diabetes diagnosis and registered with an eligible practice for at least 1 year before study entry were eligible for the study. Type 2 diabetes diagnosis was ascertained by the presence of any type 2 diabetes clinical (Read) code in the individual's medical record. Adults with a recording of type 1 diabetes were excluded.

Exposure and Outcome Measures

The main exposure was the risk of DFD based on Read codes that have previously been used in a microvascular complications study (22). Based on NICE guidelines, risk of DFD was categorized into three groups—low, moderate, and high (6). We considered individuals with no evidence of diabetic peripheral neuropathy (DPN), no peripheral vascular disease (PVD), and no presence of foot deformity, impairment, or previous ulcer to be at low risk (6, 22, 23). Individuals presenting with deformity, neuropathy, or non-critical limb ischemia were considered to be at moderate risk (6, 22, 23). Previous ulceration, amputation, and more than 2 of 3 parameters of DPN, PVD, or deformity were defined as high risk (6, 22, 23). The outcome was all-cause mortality among those newly diagnosed with type 2 diabetes with low, moderate, and high risk of DFD.

Follow-Up

The index date was defined as 15 months following the date of diagnosis of type 2 diabetes (24), which was chosen because of the

requirement to measure foot risk soon after diagnosis of diabetes and reassess the risk annually as per NICE guidelines and Quality Outcomes Framework (QOF) in the UK (6, 25). The QOF indicator is defined as the percentage of patients with diabetes with a record of a foot examination and risk classification within the preceding 15 months (25). Follow-up started at the index date of 15 months post type 2 diabetes diagnosis and ended at exit date defined as the occurrence of one of the following events (whichever came earliest): (a) death, (b) individual left the practice, or (c) study end date (December 31, 2019). In an additional analysis, we took an index date of 30 months following diagnosis of type 2 diabetes, giving additional time for foot risk assessment to take place after a diagnosis of type 2 diabetes.

Covariates

Baseline characteristics included age, sex, BMI (kg/m^2), smoking status, ethnicity, social deprivation status, history of CVD, and HbA1c (mmol/mol). BMI was classified according to NICE BMI classification as follows: underweight (BMI of <18.5 kg/m^2), normal weight (BMI of 18.5 to <25 kg/m^2), overweight (BMI of 25 to <30 kg/m^2), obesity class I (BMI of 30 to <35 kg/m^2), obesity class II (BMI of 35 to <40 kg/m^2), and obesity class III (BMI of ≥40 kg/m^2) (25). Smoking status was categorized as smoker, non-smoker, and ex-smoker. Ethnicity was classified based on UK census ethnic groups (White; Black, African, Caribbean, or Black British; Asian or British Asian; mixed or multiple ethnic groups; and other ethnic groups). The Townsend deprivation index of social deprivation status was based on quintiles with 1 being the least deprived and 5 being the most deprived (26). CVD was defined as atrial fibrillation (AF), heart failure, ischemic heart disease (IHD), and stroke and transient ischemic attacks (TIA). HbA1c was categorized as ≤47.5 mmol/mol, 47.5–58.5 mmol/mol, 58.5–69.4 mmol/mol, and >69.4 mmol/mol (24). Drugs included lipid drugs, metformin, insulin, and other diabetes drugs (glitazones, glinides, acarbose, glucagon-like peptide 1 [GLP-1] receptor agonists, dipeptidyl peptidase-4 [DPP-4] inhibitors, sodium-glucose co-transporter-2 [SGLT-2] inhibitors, and sulfonylureas). Missing data for BMI, Townsend deprivation index, smoking status, ethnicity, and HbA1c were assigned to a separate category and included in the analyses.

Statistical Analysis

In the analysis, means (± SD) were used to summarize continuous variables, and percentages were used to summarize categorical variables. Crude and adjusted HR and 95% CIs were calculated for the occurrence of death in DFD risk groups using a Cox proportional model. The log–log plots were used to check proportional hazards assumption with almost parallel curves indicating that the assumption was not violated. Baseline characteristics including age, sex, Townsend score, ethnicity, smoking status, BMI, CVD, HbA1c, and drug use were included as covariates in the regression model. Kaplan–Meier survival curves were generated for different DFD risk groups, and the log-rank test was performed to test the equality of the survivor function between groups.

Sensitivity analysis I involves setting the index date 30 months after diagnosis with type 2 diabetes, and was performed using the same statistical methods as in the main analysis; sensitivity analysis II concerns the exclusion of individuals who had incomplete data on BMI, smoking status, and Townsend score.

We considered 2-tailed p-value <0.05 to be statistically significant. All statistical analyses were conducted using Stata version 16 software.

RESULTS

Study Population Characteristics

In total, 225,787 individuals who had been newly diagnosed with type 2 diabetes were included in the study with 77,346 (34%), 14,929 (7%), and 2,808 (1%) at low, moderate, and high risk of DFD, respectively. There were 1,118 (0.05%) individuals who declined the foot examination and 129,586 (57%) who had no recording of foot risk. **Figure 1** described the flow of the study population selection. Baseline characteristics are summarized in **Table 1**. The population was mostly male (55.7%) and over 50 years old (83.6%). Mean (SD) BMI and HbA1c were observed to be similar in three risk groups (BMI: 31.8 kg/m^2 [6.6] vs. 31.8 kg/m^2 [7.1] vs. 31.6 kg/m^2 [7.4] and HbA1c: 51.5 mmol/mol [12.7] vs. 51.5 mmol/mol [12.5] vs. 52.5 mmol/mol [13.2], respectively); 16.3% of the individuals were active smokers. Individuals who refused a foot examination were more likely to be from more deprived groups. The prevalence of hypertension at baseline was higher in both the moderate-risk (59.3%) and high-risk (59.9%) groups compared with those in the low-risk group (51.6%).

Mortality Among Individuals at Risk of DFD. Among the study population, 34,061 (15.1%) died during the study period. A total of 4,322 (5.6%), 1,904 (12.8%), and 549 (19.6%) deaths occurred in those who were at low, moderate, and high risk of DFD, respectively. Among individuals who declined foot examination and those with no recording, there were 178 (15.9%) and 27,108 (20.9%) deaths, respectively.

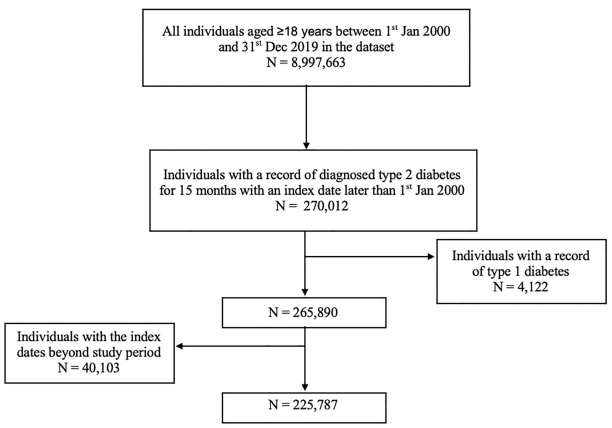

FIGURE 1 | Study flowchart.

TABLE 1 | Baseline characteristics of new-onset type 2 diabetes individuals at risk of DFD.

	Low risk	Moderate risk	High risk	Foot examination declined	No recording
Population, *n*	77,346	14,929	2,808	1,118	129,586
Age, year, mean (SD)	61.6 (12.8)	68.3 (12.6)	69.9 (12.6)	60.9 (14.3)	63.7 (13.1)
Age, years, *n* (%)					
18–29	623 (0.8)	36 (0.2)	9 (0.3)	12 (1.1)	756 (0.6)
30–39	3,162 (4.1)	208 (1.4)	28 (1.0)	64 (5.7)	4,452 (3.5)
40–49	10,865 (14.0)	1,051 (7.0)	165 (5.9)	197 (17.6)	15,334 (11.8)
50–59	19,695 (25.5)	2,516 (16.9)	441 (15.7)	275 (24.6)	28,791 (22.2)
60–69	22,130 (28.6)	3,909 (26.2)	682 (24.3)	259 (23.2)	36,204 (27.9)
≥70	20,871 (27.0)	7,209 (48.3)	1,483 (52.8)	311 (27.8)	44,049 (34.0)
Sex, *n* (%)					
Male	43,379 (56.1)	8,270 (55.4)	1,679 (59.8)	639 (57.2)	71,771 (55.4)
Female	33,967 (43.9)	6,659 (44.6)	1,129 (40.2)	479 (42.8)	57,815 (44.6)
Ethnicity, *n* (%)					
White	36,837 (47.6)	7,324 (49.1)	1,353 (48.2)	554 (49.5)	53,007 (40.9)
Black, African, Caribbean, or Black British	1,301 (1.7)	130 (0.9)	19 (0.7)	15 (1.3)	1,534 (1.2)
Asian or Asian British	3,051 (3.9)	244 (1.6)	24 (0.8)	23 (2.1)	3,700 (2.9)
Mixed or Multiple ethnic groups	737 (1.0)	52 (0.4)	2 (0.1)	5 (0.5)	657 (0.5)
Other ethnic group	246 (0.3)	22 (0.1)	3 (0.1)	1 (0.1)	245 (0.2)
Missing	35,175 (45.5)	7,157 (47.9)	1,407 (50.1)	520 (46.5)	70,443 (54.3)
Townsend Score					
1 (Least deprived)	13,197 (17.1)	2,409 (16.1)	410 (14.6)	142 (12.7)	25,552 (19.7)
2	13,246 (17.1)	2,426 (16.3)	498 (17.7)	140 (12.5)	23,655 (18.3)
3	13,801 (17.8)	2,764 (18.5)	514 (18.3)	188 (16.8)	24,177 (18.7)
4	12,931 (16.7)	2,669 (17.9)	534 (19.1)	195 (17.4)	22,442 (17.3)
5 (Most deprived)	9,480 (12.3)	2,241 (15.0)	469 (16.7)	228 (20.4)	17,110 (13.2)
Missing	14,691 (19.00)	2,420 (16.2)	383 (13.6)	225 (21.2)	16,650 (12.8)
Smoking, *n* (%)					
Non-smoker	37,903 (49.0)	6,347 (42.5)	1,116 (39.7)	485 (43.4)	60,476 (46.7)
Ex-smoker	27,416 (35.4)	5,928 (39.7)	1,164 (41.5)	365 (32.6)	46,679 (36.0)
Smoker	12,016 (15.5)	2,653 (17.7)	528 (18.8)	266 (23.8)	21,257 (16.4)
Missing	11 (0.01)	1 (0.01)	0 (0.0)	2 (0.2)	1,174 (0.9)
BMI, kg/m^2, mean (SD)	31.8 (6.6)	31.8 (7.1)	31.6 (7.4)	33.1 (7.7)	31.0 (6.4)
BMI, kg/m^2, *n* (%)					
Underweight <18.5	275 (0.4)	103 (0.7)	25 (0.9)	6 (0.6)	759 (0.6)
Normal weight 18.5 to <25	9,177 (11.9)	2,046 (13.7)	414 (14.7)	118 (10.5)	18,910 (14.6)
Overweight 25 to <30	24,663 (31.9)	4,533 (30.4)	866 (30.8)	294 (26.3)	43,608 (33.6)
Obesity class I 30 to <35	22,157 (28.6)	4,152 (27.8)	738 (26.3)	297 (26.6)	35,205 (27.2)
Obesity class II 35 to <40	11,911 (15.4)	2,169 (14.5)	358 (12.8)	191 (17.1)	16,911 (13.0)
Obesity class III ≥40	8,209 (10.6)	1,687 (11.3)	340 (12.1)	178 (15.9)	10,866 (8.4)
Missing	954 (1.2)	239 (1.6)	67 (2.4)	34 (3.0)	3,327 (2.6)
HbA1c, mmol/mol, mean (SD)	51.5 (12.7)	51.5 (12.5)	52.5 (13.2)	54.3 (15.2)	52.0 (13.8)
HbA1c, mmol/mol, *n* (%)					
≤47.5	31,117 (40.2)	5,754 (38.5)	983 (35.0)	266 (23.8)	12,045 (9.3)
47.5–58.5	28,833 (37.3)	5,672 (38.00)	1,026 (36.5)	242 (21.7)	11,672 (9.0)
58.5–69.4	7,218 (9.3)	1,323 (8.9)	289 (10.3)	99 (8.9)	3,176 (2.5)
>69.4	5,421 (7.0)	980 (6.6)	213 (7.6)	96 (8.6)	2,375 (1.8)
Missing or implausible	4,757 (6.2)	1,200 (8.0)	297 (10.6)	415 (37.1)	100,318 (77.4)
CVD, *n* (%)					
Hypertension	39,922 (51.6)	8,853 (59.3)	1,683 (59.9)	623 (55.7)	73,934 (57.1)
Atrial fibrillation	4,271 (5.5)	1,912 (12.8)	525 (18.7)	66 (5.9)	8,678 (6.7)
Heart failure	2,212 (2.9)	1,019 (6.8)	290 (10.3)	50 (4.5)	5,628 (4.3)
Ischemic heart disease	11,496 (14.9)	3,555 (23.8)	799 (28.5)	198 (17.7)	25,472 (19.7)
Stroke/TIA	4,708 (6.1)	1,794 (12.0)	452 (16.1)	102 (9.1)	10,337 (8.0)

DFD, diabetic foot disease; TIA, transient ischemia attack.

Association Between Risk of DFD and Mortality in Individuals With Newly Diagnosed Type 2 Diabetes

Table 2 shows the unadjusted and adjusted HRs from the Cox regression model. Compared with low risk of DFD, the unadjusted hazards of mortality were higher for moderate and high DFD risk groups (HR 2.42, 95% CI [2.29, 2.55], $p < 0.001$; HR 3.77, 95% CI [3.45, 4.11], $p < 0.001$, respectively). **Figure 2** shows the Kaplan–Meier curve for the mortality rate related to foot risk. The graph lines start to separate from the beginning, representing the

TABLE 2 | Unadjusted and adjusted HR of mortality rate in new-onset type 2 diabetes individuals at risk of DFD.

	Low DFD risk	Moderate DFD risk	High DFD risk	Foot examination declined	No recording
Population, *n*	77,346	14,929	2,808	1,118	129,586
Death, *n*	4,322	1,904	549	178	27,108
Person-years	253,883.4	46,511.5	8,586.0	4,827.8	887,710.2
Crude IRR	17.0	40.9	63.9	36.9	30.5
Unadjusted HR (95% CI), *p*-value	1	2.42 (2.29, 2.55), <0.001	3.77 (3.45, 4.11), <0.001	2.06 (1.78, 2.40), <0.001	1.62 (1.57, 1.67), <0.001
Adjusted HR (95% CI), *p*-value	1	1.50 (1.42, 1.58), <0.001	2.01 (1.84, 2.20), <0.001	1.75 (1.51, 2.04), <0.001	1.25 (1.20, 1.30), <0.001

IRR, Incidence Rate/1000 person-years.

Adjusted for age, sex, Townsend score, ethnicity, smoking, BMI, CVD event, HbA1c level, anti-diabetic medication use, lipid drug use, and hypertension.

significant reduction in mortality in the patient group with low risk compared to moderate and high risk. The difference between the curves was statistically significant ($p < 0.001$).

After adjusting for age, sex, Townsend score, ethnicity, smoking status, baseline BMI, CVD, baseline HbA1c, and medications, those with a moderate risk of DFD had 1.5 times greater risk of mortality (HR 1.50, 95% CI [1.42, 1.58], $p < 0.001$), and those with a high risk of DFD had double the risk of mortality (HR, 2.01, 95% CI [1.84, 2.20], $p < 0.001$) compared to those with a low risk of DFD. In addition, those who declined a foot examination or who had no recording were also 75% and 25%, respectively, more likely to die than those with a low risk of DFD (HR 1.75, 95% CI [1.51, 2.04], $p < 0.001$; HR 1.25, 95% CI [1.20, 1.30], $p < 0.001$).

Factors Associated With Increased Mortality

Age, Townsend score, smoking status, CVD events (AF, heart failure, IHD, and stroke), HbA1c, and antidiabetic drug use were associated with increased mortality (**Table 3**). Individuals who were recorded as being more deprived experienced higher mortality risk. Black, African, Caribbean, or Black British (HR 0.69, 95% CI [0.59, 0.80]); Asian or British Asian (HR 0.61, 95% CI [0.54, 0.68]); and mixed or multiple ethnic groups (HR 0.69, 95% CI [0.54, 0.90]) were less likely to die than those from the White ethnic group population. Former and current smokers had a higher risk of mortality compared to those who never smoked (HR 1.25, 95% CI [1.22, 1.28]; HR 1.77, 95% CI [1.72, 1.83], respectively). Moreover, hazards of mortality were lower in individuals with obesity and significantly higher in those who were underweight compared to those with normal weight (BMI 18.5 to <25 kg/m^2). Individuals who were categorized as obesity class II (35 to <40 kg/m^2) had approximately 25% reduced risk of mortality compared to those with a healthy weight with 0.75 (95% CI [0.72, 0.78]), while underweight individuals (<18.5 kg/m^2) had twice the risk of dying (2.24, 95% CI [2.04, 2.45]). A close association was noted between increasing baseline Hba1c and risk of mortality. Those prescribed lipid-lowering drugs had a 29% lower risk of death (HR 0.71, 95% [0.69, 0.73]), compared to those not prescribed.

Sensitivity Analyses

In the sensitivity analysis where the index date was set to 30 months after the diagnosis of type 2 diabetes, 190,422 people (among whom 28,065 died) with a diagnosis of type 2 diabetes were included in the analysis. There was a similar trend between DFD risk and mortality with an HR of 1.46 (95% CI [1.39, 1.54]) and an HR of 2.04 (95% CI [1.89, 2.21]) in groups with a

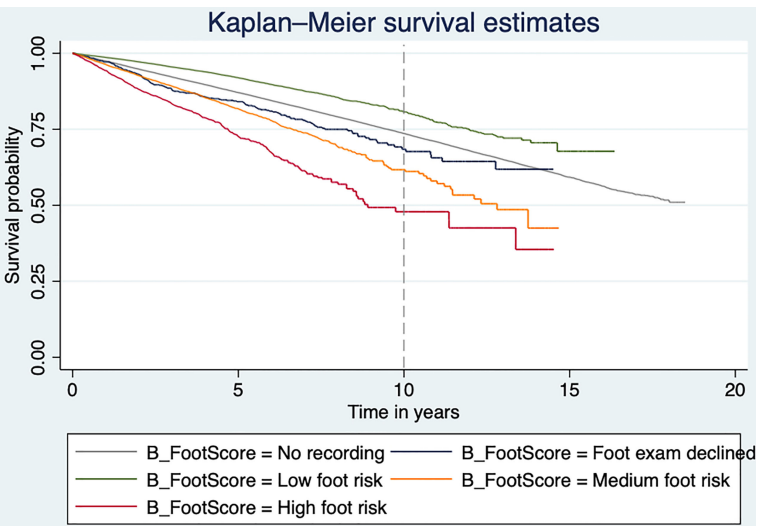

FIGURE 2 | Kaplan–Meier plot showing the mortality risk of type 2 diabetes individuals at risk of DFD.

TABLE 3 | Factors associated with mortality in new-onset type 2 diabetes individuals at risk of DFD .

	Death	HR (95% CI)
Age, years		
18–29	19/1,436	1.00
30–39	143/7,914	1.28 (0.79, 2.06)
40–49	828/27,612	2.26 (1.44, 3.57)
50–59	3,093/51,718	4.52 (2.88, 7.10)
60–69	7,830/63,184	9.11 (5.80, 14.30)
≥70	22,148/73,923	26.15 (16.66, 41.04)
Sex		
Male	18,777/125,738	1.00
Female	15,284/100,049	0.92 (0.89, 0.94)
Townsend score		
1 (Least deprived)	5,555/41,710	1.00
2	6,038/39,965	1.14 (1.10, 1.18)
3	6,323/41,444	1.21 (1.17, 1.26)
4	6,495/38,771	1.34 (1.29, 1.39)
5 (Most deprived)	4,968/29,528	1.42 (1.37, 1.48)
Missing	4,682/34,369	1.20 (1.15, 1.25)
Ethnicity		
White	12,601/99,075	1.00
Black, African, Caribbean, or Black British	157/2,999	0.69 (0.59, 0.80)
Asian or Asian British	297/7,041	0.61 (0.54, 0.68)
Mixed or Multiple ethnic groups	59/1,453	0.69 (0.54, 0.90)
Other ethnic group	28/517	0.75 (0.51, 1.08)
Missing	20,919/114,702	1.42 (1.39, 1.45)
Smoking		
Non-smoker	13,445/106,327	1.00
Ex-smoker	14,198/81,552	1.25 (1.22, 1.28)
Smoker	6,014/36,720	1.77 (1.72, 1.83)
Missing	404/1,188	0.99 (0.89, 1.10)
BMI		
Normal weight 18.5 to <25	7,258/30,665	1.00
Underweight <18.5	516/1,168	2.24 (2.04, 2.45)
Overweight 25 to <30	11,767/73,964	0.73 (0.71, 0.75)
Obesity class I 30 to <35	7,838/62,549	0.72 (0.70, 0.75)
Obesity class II 35 to <40	3,260/31,540	0.75 (0.72, 0.78)
Obesity class III ≥40	2,034/21,280	0.99 (0.95, 1.05)
Missing	1,388/4,621	1.56 (1.47, 1.65)
CVD		
Non-CVD	17,393/164,021	1.00
CVD	16,668/61,766	1.87 (1.83, 1.91)
HbA1c		
≤47.5	3,990/50,165	1.00
47.51–58.5	3,690/47,445	1.00 (0.96, 1.05)
58.51–69.4	929/12,105	1.13 (1.05, 1.21)
>69.41	665/9,085	1.37 (1.26, 1.49)
Missing or implausible	24,787/106,987	1.02 (0.98, 1.06)
Antidiabetic Medication use		
No medication or metformin	24,064/177,148	1.00
Other medication	8,410/41,666	1.37 (1.34, 1.41)
Insulin	1,587/6,973	2.09 (1.99, 2.20)
Lipid drug use		
Non-user	10,899/67,425	1.00
Lipid drug user	23,162/158,362	0.71 (0.69, 0.73)
Hypertension		
Non-hypertension event	12,522/100,772	1.00
Hypertension event	21,539/125,015	1.01 (0.99, 1.04)

DFD, diabetic foot disease; HR, hazard ratio.

moderate and high risk of DFD, respectively, compared to the group with a low risk of DFD (**Supplementary Tables 1**, **2**).

After excluding those with incomplete data for BMI, Townsend score, and smoking status in the main dataset (index date of 15 months post diagnosis), 186,862 individuals were available for analysis (28,015 deaths). Individuals with moderate and high risk of DFD remained at higher risk of death than those at low risk of DFD (**Supplementary Table 3**, HR 1.47, 95% CI [1.39, 1.57]; HR 2.00, 95% CI [1.81, 2.20], respectively).

DISCUSSION

In this large cohort of adults with type 2 diabetes, we found that the risk of DFD is significantly associated with increased risk of death. Individuals who declined foot examination or who had no record also had increased mortality risk. The findings highlight the importance of assessing foot risk as it not only identifies patients at risk of DFU but also mortality. In addition, age, deprivation status, smoking status, poor glycemic control, and presence of CVD also contributed to an increased risk of mortality.

Elevated mortality in patients with a high risk of DFD defined as history of foot ulcer, Charcot arthropathy, or lower extremity amputation has previously been demonstrated (7, 8). The findings in this study show a similar trend of elevated mortality in those with a moderate/high foot risk among people with newly diagnosed type 2 diabetes. In addition, the present study included those who declined a foot examination, and those who had no recording of a foot examination; both groups had a greater risk of death compared to those in the low DFD risk group. There was an increased rate of refusal of foot examination in more deprived groups, which may further contribute to health inequalities in this group, suggesting that specific strategies to engage more socially deprived groups after a diagnosis of type 2 diabetes are needed (24). Foot protection service, including assessing the biomechanical status of the feet and the vascular status of the lower limbs, and providing specialist footwear and orthoses, in those with elevated DFD risk at the time of diagnosis of type 2 diabetes may help prevent progression of DFD such as foot ulcer and limb amputation, reducing morbidity and the direct and indirect health costs for diabetes management (6).

The lower risk of mortality in patients with obesity compared to those with a BMI in the normal BMI range has been demonstrated in prior studies (27, 28). It is possible that increased mobilization of endothelial progenitor cells leading to better vascular function protects severely obese patients (29). Another potential explanation is the nutritional status and the effective treatment for certain conditions such as hyperlipidemia, avoiding progression of foot disorder in later stage (29, 30). Smoking also increased the risk of mortality, which is consistent with smoking increasing the risk of PVD (31). People from ethnic minorities also had a lower risk of mortality compared to the White ethnic group, which has been shown in a previous study on DFD (24). Genetics, microcirculation preservation, lower smoking frequency, and less alcohol intake possibly cause the lower rate of diabetic foot problem among ethnic minorities compared to the White ethnic group, eventually reducing the mortality (32, 33).

Mechanisms that increase the risk of mortality in patients with type 2 diabetes and moderate or high foot risk are multifactorial. PAD is a marker for systemic vascular disease and associated with an excess risk of CVD events and death (34). Ischemia caused by PAD predicts the risk of low-extremity amputation, particularly in people with diabetes, leading to a greater risk of mortality (34, 35). Autonomic neuropathy is associated with the development of DFU, and is a possible risk factor for mortality in patients with diabetes (36, 37, 38). Moreover, it has been shown that peripheral neuropathy was independently associated with incident CVD events and linked to an increased risk of mortality (16). Taken together, this may explain the high risk of mortality among type 2 diabetes patients who were at risk of DFD.

Strengths and Limitations

This study has a number of strengths ensuring a high-quality study with reliable results including a large sample size. Patients in IMRD are broadly representative of the UK population, and thus, these results should be generalizable. Sensitivity analysis where follow-up started 30 months after the diagnosis of type 2 diabetes allows sufficient time for the exposure to be recorded, and this also showed an increased risk of death for higher DFD risk. Further research is needed to explore the underlying reasons for declining foot examination/absence of recorded data, and the elevated mortality identified in these groups.

Limitations include missing data for some covariates; however, it was a small proportion of the total dataset, and the sensitivity analysis excluding those with missing data showed a consistent association. Renal replacement therapy was not considered as high risk of DFD although it was suggested to be at high risk in NICE guidelines (6). However, there were only a small number of participants (≤0.2%) recorded with this therapy, which did not influence the reliability of the results. We did not have information on the cause of death, and this should be considered in further studies to determine important risk factors that should be targeted to reduce the risk of death among people with newly diagnosed type 2 diabetes who are at risk of DFD.

CONCLUSION

In conclusion, individuals with new-onset type 2 diabetes who are at increased risk of DFD experienced a higher risk of death compared to those at low risk of DFD. This key finding of the association of DFD risk and mortality highlights the importance of foot risk assessment in people with type 2 diabetes, and a potential role for early identification and management of at-risk patients. The increased proportion of individuals declining foot examination in more deprived groups and the associated increased mortality are a particular concern, as they may further exacerbate health inequalities; the development of strategies that target these groups is warranted.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the study is based on The Health Improvement Network (THIN) database licenced by IQVIA, in which individual patient data are not allowed to be shared to the public. Researchers may apply for individual patient data access at https://www.iqvia.com/contact. Requests to access the datasets should be directed to Researchers may apply for individual patient data access at https://www.iqvia.com/contact.

AUTHOR CONTRIBUTIONS

ZW, KN, FC, and JH contributed to study design, acquisition of data, and statistical analysis. ZW wrote the manuscript and FC, JH, KN, AT, WH, NT, JW, and CS critically revised the manuscript. ZW is the guarantor of this work. All authors contributed to this work. All authors approved the final version of submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.888924/full#supplementary-material

Supplementary Table 1 | Baseline characteristics of new-onset type 2 diabetes individuals at risk of DFD (30 months)

Supplementary Table 2 | HR of mortality rate in new-onset type 2 diabetes individuals at risk of DFD and factors associated with mortality (30 months)

Supplementary Table 3 | Sensitivity analysis excluding missing data for Townsend score, smoking, and BMI

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Application of the distally based sural neurocutaneous flaps in the management of foot and ankle defects in patients with diabetic foot

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Background: We report our experience on the use of a distally based sural flap for soft tissue reconstruction of foot and ankle defects in patients with diabetic foot.

Methods: The actual study is a retrospective, open, non-controlled, and clinical study of 25 patients treated with diabetic foot on whom reconstruction with distally based sural neurocutaneous flaps was performed from May 2019 to December 2021.

Results: The mean age was 64.9 years, and there were 15 male and 10 female patients. The mean follow-up was 9.8 months, which ranged from 6 to 12 months. The size of the flaps ranged from 6 × 5 to 15 × 9 cm^2. Twenty-two of the 25 flaps survived intact with sufficient blood supply. Two cases had a small superficial necrosis, which was resolved after a change of daily dressing and was healed eventually. In one case, partial necrosis was observed that was managed with minor revision and the use of split-thickness skin graft.

Conclusions: The distally based sural flap is considered to be useful for reconstruction of foot and ankle defects in patients with diabetic foot.

KEYWORDS

diabetic foot, diabetic wound defect, distally based sural flap, wound healing, foot and ankle reconstruction

Introduction

Diabetic foot is one of the most significant and devastating complications of diabetes (1). Impaired wound healing in patients with diabetes can lead to infections, chronic ulcers with a recurrence rate of 66%, and even lower extremity amputation, which significantly affects the patients' quality of life (2).

In patients with diabetic foot, reconstruction of soft tissue in the distal lower extremities is a significant challenge as a result of peripheral neuropathy and diabetic microangiopathy (3). After primary debridement, it is difficult to obtain a primary closure for the subsequent defect in foot and ankle. Skin grafts are usually unacceptable when bones or tendons are exposed. Local flaps are not always reliable because of the presence of varying severity of peripheral arterial disease (4). Free flap transfer allows for more options and is widely used in recent years. Despite the high success rates of free flaps even in patients with diabetes, pronounced microsurgical skills and proper case selection are required (5).

In 1992, Masquelet et al. first introduced the concept of neurocutaneous island flaps supplied by the vascular axis of the sensitive superficial nerves in the leg (6). Since then, the distally based sural flap has received more attention and eventually became a mainstay in the reconstruction in the lower leg, ankle, and heel (7). Many studies have been reported the versatility of the distally based sural flap for soft tissue coverage originated by traumatic or infectious events (8). However, there are few reports on the use of these flaps as a reconstructive option in patients with diabetic wound. In this study, we presented our experience on the use of distally based sural neurocutaneous flaps for coverage of foot and ankle defects in patients with diabetic foot ulceration.

Material and methods

This study is a retrospective, open, non-controlled, and clinical study of patients with diabetic foot on whom reconstruction with distally based sural neurocutaneous flaps was performed from May 2019 to December 2021 at the Department of Orthopedic Surgery, Sixth People's Hospital affiliated to Shanghai Jiao Tong University, Shanghai, China. This retrospective study was approved by our institutional review board.

Patients who were diagnosed with type 2 diabetes based on the diagnostic criteria recommended by the American-Diabetes-Association (American-Diabetes-Association) in 2010 were included (9). DFU is defined as "ulceration of the foot (distally from the ankle and including the ankle) associated with neuropathy and different grades of ischemia and infection", according to the World Health Organization (10). All of the included patients had preservation of at least one major artery (anterior tibial artery, posterior tibial artery, and peroneal artery). We excluded chronic wound caused by pressure ulcer, vasculitis, pyoderma gangrenosum, and diseases that cause ischemia (11).

In this study, we recorded patients' age, sex, duration of diabetes, location of defect, size of defect, size of flap, outcomes, postoperative complications, and follow-up. All surgery was performed by one surgeon (CH). Appropriate medical treatment included blood glucose regulation, perfusion improvement by prostaglandins or antiplatelet drugs, appropriate antibiotics administration, and routine sterile dressing change.

Surgical technique

In debridement, we removed and debrided non-viable infected soft tissues and bones. The edges of debridement were achieved until the soft tissues and bones presented to be generally healthy.

After debridement, the flap was designed with respect to the defect. The patient was placed in a prone position, with the application of a tourniquet. A line of incision was traced over the presumed course of the sural nerve and the lesser saphenous vein. The pivot point of the pedicle was preoperatively marked 5 cm proximal to the tip of the lateral malleolus. The flap was harvested including the medial sural nerve, the lesser saphenous vein, and the deep fascia. The incision was made along the superior border of the flap, and the terminal perforator was easily found at the fascial plexus of the flap and was carefully dissected. The flap was then harvested in the subfascial plane and rotated from 90° to 180° to cover the recipient site and inset without tension. The donor site defect was reconstructed using a skin graft or finally closed primarily.

Results

A total of 25 patients with diabetic wound were included in this study. There were 15 male and 10 female patients. The mean age of the patients was 64.9 years. The detailed clinical characteristics of the patients are presented in Table 1. The mean follow-up was 9.8 months, which ranged from 6 to 12 months.

The size of defect ranged from 5 × 5 to 13 × 6 cm^2, and the size of flap ranged from 6 × 5 to 15 × 9 cm^2. The donor site was closed primarily in 10 cases, and split-thickness skin grafts were used in 18 cases and survived entirely. Twenty-two of the 25 flaps survived intact with sufficient blood supply (Figures 1, 2). Two cases had a small superficial necrosis, which was resolved

TABLE 1 Summary of the patients receiving distally based sural neurocutaneous flaps for foot and ankle reconstruction.

Case	Gender	Age	BMI (kg/m^2)	Duration of diabetes (years)	Ulcer location	Smoking (yes/no)	HbA1c (pre-op)	Renal function	Complicated with osteomyelitis (yes/no)	Wagner classification (grade)	Flap size (cm^2)	Wound size (cm^2)	Outcome	Follow-up (months)
1	M	64	22.41	5	Plantar midfoot	No	10.2	Normal	No	2	15*6	12*4	Survived completely	12
2	M	67	21.53	13	Plantar hindfoot	Yes	9.8	CKD II	No	2	10*5.5	8*4	Survived completely	9
3	M	59	22.12	6	Fourth and fifth toes and lateral forefoot	Yes	15.8	Normal	Yes	3	12*6	10*4	Survived completely	9
4	M	78	21.76	22	Plantar hindfoot	No	13.7	CKD II	No	3	14*7.5	11*6	Superficial necrosis	9
5	M	55	25.25	5	Dorsal midfoot	Yes	12.4	Normal	No	3	9*8	7*7	Survived completely	9
6	M	62	23.34	9	Fifth toe and lateral forefoot	Yes	11.7	CKD I	Yes	3	14*5	12*3	Survived completely	9
7	M	65	22.38	12	Plantar midfoot	Yes	13.2	CKD I	No	3	12*7	11*5	Survived completely	9
8	M	73	22.11	18	Plantar hindfoot	Yes	11.9	CKD II	No	3	10*8	8*6	Survived completely	9
9	M	66	23.34	13	Lateral ankle	Yes	16.6	CKD II	Yes	4	14*8	11*6	Survived completely	12
10	M	69	23.98	11	Plantar hindfoot	Yes	14.1	Normal	No	3	12*7	9*5	Survived completely	9
11	M	72	22.56	20	Behind the Achilles tendon	No	8.9	Normal	No	2	6*6	4*3	Survived completely	6
12	M	61	22.34	10	Lateral ankle	No	9.2	CKD I	No	2	5*6	5*5	Survived completely	6
13	M	58	24.26	4	Lateral ankle	No	12.7	Normal	No	3	9*7.5	6*5	Survived completely	9
14	M	63	22.75	4	Dorsal midfoot	Yes	10.3	Normal	No	2	8*6	5*5	Survived completely	6
15	M	71	21.25	9	Plantar hindfoot	Yes	9.6	CKD I	No	2	11*9	10*7	Survived completely	12
16	M	68	20.77	5	Plantar hindfoot	Yes	12.6	CKD I	No	3	10*6	9*4	Survived completely	12
17	F	65	21.54	8	Fifth toe and lateral foot	No	13.1	Normal	Yes	3	15*9	13*6	Partial necrosis	12
18	F	63	22.36	11	Plantar hindfoot	No	15.8	CKD II	Yes	4	14*9	12*6	Superficial necrosis	12
19	F	67	21.83	15	Heel	No	12.1	CKD I	No	3	12*8	10*5	Survived completely	9
20	F	62	22.42	6	Medial ankle	No	11.9	Normal	No	3	11*6	9*4	Survived completely	12
21	F	59	21.78	4	Dorsal midfoot	No	8.7	Normal	No	2	10*7	7*5	Survived completely	9
22	F	69	22.13	12	Fifth toe and lateral plantar foot	No	11.4	CKD I	Yes	3	12*8.5	10*5	Survived completely	12
23	F	61	21.35	3	Heel	No	10.2	Normal	No	2	8*8	6*6	Survived completely	12
24	F	63	20.67	5	Second and third toes and dorsal forefoot	No	11.2	Normal	Yes	3	11*6	9*5	Survived completely	12
25	F	62	21.81	7	Plantar hindfoot	No	9.3	Normal	No	3	10*5	7*3	Survived completely	9

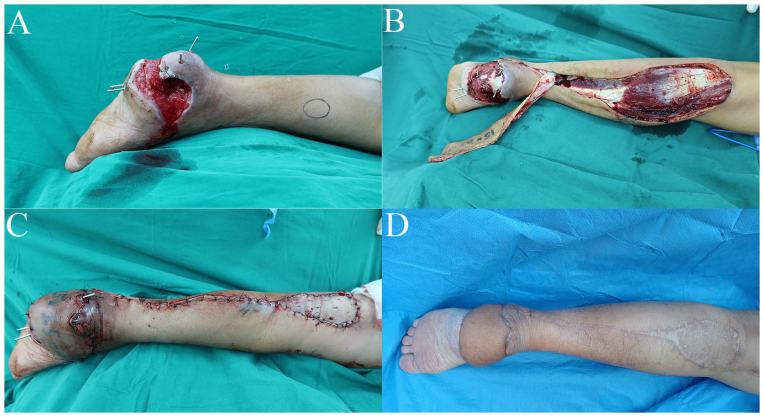

FIGURE 1
Case 1: Te distally based sural neurocutaneous flaps for reconstruction of the heel soft tissue defect. **(A)** Diabetic wound at the heel. **(B)** Harvest of the distally based sural neurocutaneous flap. **(C)** The defect was reconstructed with a flap, and the donor site was covered with skin graft. **(D)** The flap and the donor site were completely healed at follow-up.

after a change of daily dressing and was healed eventually. In one case, partial necrosis was observed that was managed with minor revision and the use of split-thickness skin graft. No infections or hematomas were encountered in this study. All of 25 flaps gained partial sensorial recovery, except for six patients complaining of anesthesia in the donor site during extended follow-up. No ulcer recurrence was observed in the follow-up. All the patients have good HbA1c levels in the follow-up period. Eighteen of the 25 patients were able to walk unaided, and seven patients with walking stick at follow-up.

Discussion

As the combination of neuropathy and angiopathy and the propensity to infection, patients with diabetic foot are at greater risk of severe limb ischemia, often with extensive soft

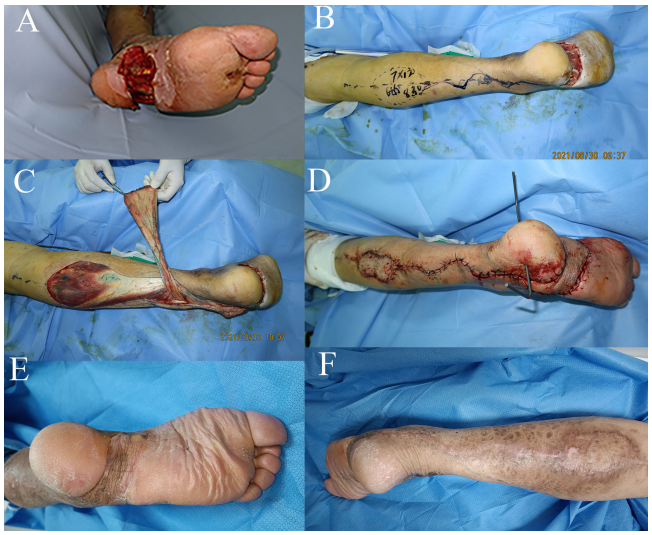

FIGURE 2
Case 2: The distally based sural neurocutaneous flaps for reconstruction of the sole soft tissue defect. **(A)** Diabetic wound at the sole. **(B)** Design of the flap. **(C)** Harvest of the distally based sural neurocutaneous flap. **(D)** The defect was reconstructed with a flap, and the donor site was covered with skin graft. **(E, F)** The flap and the donor site were completely healed at follow-up.

tissue loss (12). An amputation is sometimes required when patients suffer from diabetic wound with bone or tendon exposure. It has been found that 40%–70% of all non-traumatic amputations of the lower limbs occur in patients with diabetes (13). Successful reconstruction of distal lower leg wounds in patients with diabetes can, therefore, be limb-saving and lifesaving.

A wide variety of flaps have been reported in the literature for soft tissue defect reconstruction in patients with diabetic foot. Lee et al. (4) conducted a retrospective study of 17 patients with diabetic foot ulcers reconstructed with the proximal lateral leg perforator flap. The authors found one total flap failure and one other flap complicated by venous thrombosis, which was successfully salvaged. Sato et al. (14) reviewed 23 cases of free flap reconstruction for diabetic foot ulcers. Five patients lost their flaps, and the other 16 patients had flap success. Demiri et al. (5) compared outcomes between reverse neurocutaneous and propeller perforator flaps in diabetic foot reconstruction, and uneventful healing was recorded in 20 of the 34 neurocutaneous flaps and in 12 of the 20 propeller flaps. Because of the presence of peripheral neuropathy and microangiopathy in patients with diabetes, the treatment of soft tissue defects in this population is expected to be complicated (15).

Since Masquelet et al. first introduced the concept of neurocutaneous island flaps supplied by the vascular axis of the sensitive superficial nerves in the leg, more anatomical and clinical studies have confirmed the usefulness of these flaps (16, 17). Anatomical basis of the distally based sural flap is represented by vascular axis also accompanied with the sural nerve and the lesser saphenous vein. The blood supply of the sural neurocutaneous flap comes from neurocutaneous perforators from the sural nerve, venocutaneous perforators from the lesser saphenous vein, and septocutaneous perforators from the peroneal artery and the posterior tibial artery. All these perforators connect to each other at the subcutaneous plane, forming a longitudinal chain–linked vascular plexus along sensitive superficial nerves. These characteristics make the distally based sural neurocutaneous flaps predictable and reliable for soft tissue defect coverage of the foot and ankle and less technically demanding than a free flap.

Although the distally based sural neurocutaneous flaps have been widely used for soft tissue coverage in the distal lower extremities, there are few reports on the use of these flaps for diabetic foot treatment. Assi et al. (3) described the sural flap in treating soft tissue defects of the complicated diabetic foot in 14 patients. The authors reported one flap necrosis and three skin edge necrosis, and a hypoesthesia of the lateral aspect of the foot has been noted in 10 patients. Ignatiadis et al. (18) presented their experience with the use of sural fasciocutaneous flaps for the treatment of traumatic wound or diabetic foot in 16 patients. Five cases had a superficial necrosis; two cases experienced a partial skin necrosis, which were treated with a secondary flap; and another case demonstrated a delayed skin healing. In our study, 22 of the 25 flaps survived intact with sufficient blood supply. Two cases had a small superficial necrosis, which was resolved after a change of daily dressing and was healed eventually. In one case, partial necrosis was observed that was managed with minor revision and the use of split-thickness skin graft. Our results were in line with those studies, in which the distally based sural neurocutaneous flaps are useful, reproducible, and reliable in treating soft tissue defects in patients with diabetes with a low frequency of serious complications.

A study by Malokov et al. (19) evaluated the vascular anatomy of the sural flap in patients suffering from arteriopathy. The author demonstrated a theoretical anatomical possibility of using the sural flap in 23 of the 24 amputation specimens with severe vascular disease. Assi et al. (20) conducted a comparative study to analyze the outcomes of the reverse sural flap in reconstructing soft tissue defects in the lower leg and foot, comparing patients with diabetes and trauma. Patients with diabetes were found to have a similar high success rate and a low complication rate when compared with patients with trauma. A study by Kim et al. (21) compared the outcome of propeller perforator flap between diabetic and non-diabetic patients in the distal lower leg reconstruction. The authors found that sex, diabetes, chronic renal failure, and diabetic neuropathy were associated with flap complication and concluded that the propeller perforator flap might not be effective for diabetic foot ulcer reconstruction. Our study demonstrates good outcomes for flap healing in persons with diabetes and foot wounds, in contrast to previous small-scale studies reported in the literature.

In this study, we performed routine preoperative computed tomographic angiography to evaluate the blood supply in the distal lower leg. All of these patients had preservation of at least one major artery. Even in patients with diabetes with compromised circulation, a major vascular axis (most commonly the peroneal artery) remains patent with viable perforators to supply a perforator flap (22). Therefore, this surgical technique did not require a prior revascularization and microsurgery skills.

Therefore, the distally based sural neurocutaneous flap is an optimal choice for reconstruction of foot and ankle defects in patients with diabetic foot. In the appropriate patient, the distally based sural neurocutaneous flap is a simple and effective procedure with reliable results, good thin skin quality, minimal donor site morbidity, and preservation of the leg vessels. A long-term follow-up is required to confirm whether a wide excision with flap reconstruction provides good functional recovery and contributes to maintaining a reasonable quality of life when compared with amputation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethic Review Board of Shanghai Six People's Hospital affiliated to Shanghai Jiao Tong University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conceptualization: HC; investigation: JD; methodology: JD, YZ, and SM; writing—original draft: JD; writing—review and editing: JD, YZ and HC. All authors have read and approved the manuscript and ensure that this is the case.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.1009714/full#supplementary-material

SUPPLEMENTARY FIGURE S1
The ulcer was located in the dorsum of foot and covered with the distally based sural neurocutaneous flaps.

SUPPLEMENTARY FIGURE S2
The ulcer was located in 3-5 toes and lateral dorsum of foot. We have excised 3-5 toes and partial metatarsal bone. The wound was covered with the distally based sural neurocutaneous flaps.

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How to maximize the therapeutic effect of exosomes on skin wounds in diabetes mellitus: Review and discussion

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Chronic skin wound healing, especially in diabetes mellitus, is still unsolved. Although many efforts have been made to treat diabetic skin wounds, current strategies have achieved limited effectiveness. Nowadays, a great number of studies have shown that exosomes might be a promising approach for treating diabetic wounds. Many studies and reviews have focused on investigating and discussing the effectiveness and mechanism of exosomes. However, maximizing its value in treating skin wounds in diabetes mellitus requires further consideration. In this review, we reviewed and discussed the aspects that could be further improved in this process, including finding a better source of exosomes, engineering exosomes, adjusting dosage and frequency, and combining more efficient delivery methods. This review provided an overview and idea of what we can do to improve the therapeutic effect of exosomes on skin wounds in diabetes mellitus. Only by combining all the factors that affect the effectiveness of exosomes in diabetic wound healing can we further promote their clinical usefulness.

KEYWORDS

diabetes, skin wounds, exosomes, maximize, therapeutic effect

1 Introduction

The healing of chronic skin wounds, especially diabetic skin wounds, is one of the most intractable problems for clinicians and a heavy burden for patients, both physically and financially (1, 2). To date, there are numerous strategies and methods to treat diabetic wounds, and however, these are not exempt from limitations (3, 4). Hence, there is a crucial and urgent need for effective and safe methods to promote diabetic wound healing. Exosomes are one type of extracellular vesicles (EVs) secreted by various cells and show a double-layer membrane structure and a particle size ranging from 30 to 200 nm. They are involved in cell-cell communication and intracellular signaling. Exosomes show a lot of

advantages, such as being stable, easily stored, and not rejected by the immune system, offering a homing effect, and the dosage can be easily controlled (5). Recent research results indicated that exosomes participated in the development and outcome of diabetes and its related complications (6). For the difficult-to-heal skin wounds caused by diabetes, exogenous exosome therapy could promote the functional recovery of multiple essential cells. They effectively promoted angiogenesis, collagen synthesis, and modulating inflammation (7), so exosome therapy might become very important in wound healing strategies in order to enhance antimicrobial stewardship (8).

Although exosome therapies hold great potential for facilitating diabetic skin wound healing and regeneration, for any drug, its clinical efficacy will also depend on many other factors, like dosage, application frequency, and delivery methods (9, 10). In this review, according to published studies on the application of exosomes in diabetic wound healing, we first summarized the characterization of skin wounds in diabetes mellitus and the role of exosomes in promoting this type of wound healing. More importantly, we reviewed and discussed the aspects that could be further improved to maximize the value of exosomes in detail.

2 Characterization of skin wounds in diabetes mellitus

The healing of skin wounds follows four steps, hemostasis, inflammation, proliferation, and remodeling. However, in diabetes mellitus, several factors impair these processes, making healing longer and more difficult. For example, the high glucose in diabetic wounds can lead to the gathering of bacteria and the weakening of leukocyte phagocytosis, ultimately leading to serious local infection and inflammation. The neurons are the most sensitive and initially affected cells in diabetes mellitus, and diabetic neuropathy is one of the major causes of diabetic ulcers (11). Moreover, the blood vessels of diabetic wounds are damaged, and their angiogenic capacity is weak, leading to insufficient nutrition supply and low oxygen concentration in diabetic wounds (12). In addition to an inadequate oxygen supply, high oxygen consumption by wound cells during inflammation also induces hypoxia. Likewise, hypoxia further amplifies the inflammatory response, thereby prolonging injury by increasing the levels of oxygen radicals (13). Therefore, improving these factors is the key to treating skin wounds in diabetes mellitus.

3 Effect of exosomes on promoting skin wound healing in diabetes mellitus

It has been reported that endothelial cells (ECs), fibroblasts, macrophages, and keratinocytes participate in angiogenesis, collagen synthesis, and anti-inflammatory processes, which are significant in diabetic wound healing. However, in the diabetic environment, the number and function of these cells are restricted to varying degrees, and the wound-healing process is delayed or interrupted. Studies found that exosomes could greatly promote survival and inhibit the apoptosis of ECs (14–17), fibroblasts (11), keratocytes (11), and neurons (11). Mostly, exosomes were reported to promote the proliferation, migration, and angiogenesis of endothelial cells, and a variety of pathways were involved, like PI3K/AKT pathway, ERK1/2 pathway, FGF4/p38MAPK pathway and HIPK2 pathway (15, 17–29). This greatly enhances the ability of local vascular regeneration in diabetic wound healing. Exosomes could also promote the proliferation and migration of keratinocytes (28, 30, 31) and fibroblasts (20, 25, 28, 32–35), and the associated pathway could be seen in Figure 1. It was reported that exosomes played a role in polarizing pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages (36–38), and the inhabitation of the phosphorylation of AKT might contribute to this progress (37). Especially, the increase of nerve fiber density and the functional recovery of neurons induced by exosomes played an important role in diabetic skin wound healing (39). All the functions of exosomes confirmed the potential application value of exosomes for wound healing in diabetes mellitus. However, how to maximize or further improve the therapeutic effect of exosomes is still a problem that needs a further breakthrough.

4 How to maximize the therapeutic effect of exosomes

4.1 Which is the better source of exosomes

Up to now, exosomes from various cell sources have been used to promote wound healing in diabetes. Stem cells are the most studied, including adipose stem cells (ADSCs) (11, 17, 28, 31, 35, 38, 40–47), bone marrow mesenchymal stem cells (BMSCs) (15, 16, 23, 26, 32, 33, 37, 44, 48–51), human umbilical cord-derived mesenchymal stem cells (hUCMSCs) (27, 52, 53), synovium mesenchymal stem cells (SMSCs) (18, 21), gingival mesenchymal stem cells (GMSCs) (39), human urine-derived stem cells (USCs) (22), menstrual blood-derived mesenchymal stem cells (MenSCs) (36), placental mesenchymal stem cells (PMSCs) (54), human endometrial stem cells (hEnSCs) (34), hair follicle-derived mesenchymal stromal cells (55), epidermal stem cells (ESCs) (56, 57). Other cells, like fibrocytes (58), human umbilical cord blood endothelial progenitor cells (19, 59), human umbilical cord blood mononuclear cells (hUCBMNCs) (30), macrophages (24), human amniotic epithelial cells (25), dermal fibroblasts (DFs) (14), M2 macrophages (60), human umbilical vein endothelial cells (HUVECs) (61), also were used for exosome isolation. Among these sources, ADSCs and BMSCs were chosen by most researchers. Considering the abundant sources and guaranteed effectiveness, these two kinds of stem cells might be the most reliable source of exosomes. It was reported that there were differences in the efficacy of the two types of stem cell-derived exosomes. For example, M. Pomatto et al. found that BMSCs-derived exosomes were shown to mainly promote cell proliferation, whereas ADSCs-derived

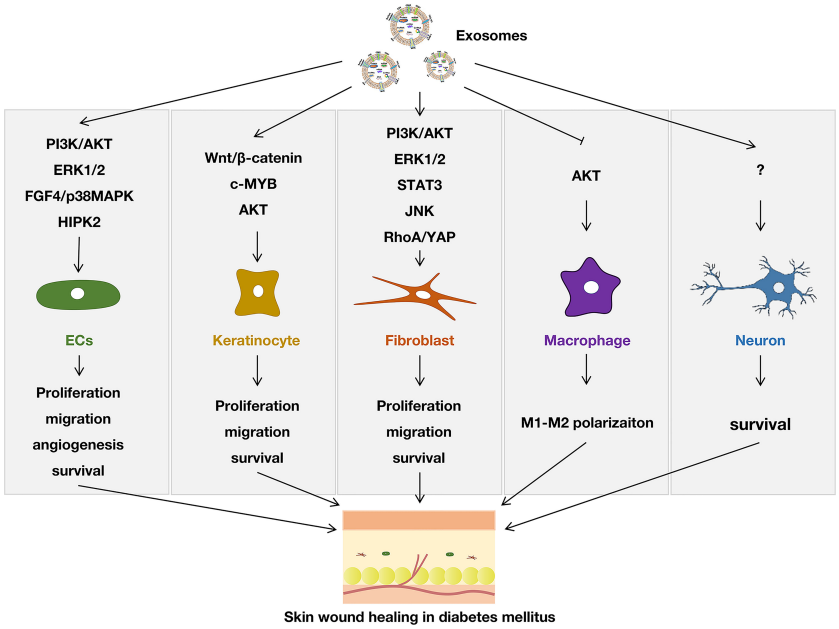


FIGURE 1
Effect of exosomes on modulating different cells in diabetic skin wound healing.

exosomes demonstrated a major effect on angiogenesis (44). Therefore, the better source of exosomes still needs more comprehensive assessments.

Of course, the source of exosomes might not be limited to cells. For example, Chen et al. found that serum exosomes could accelerate diabetic wound healing by promoting angiogenesis and extracellular matrix formation (62). Guo et al. and Xu et al. isolated exosomes from platelet-rich plasma (PRP) and found this type of exosome could effectively induce the proliferation and migration of endothelial cells and fibroblasts to improve angiogenesis and re-epithelialization in diabetic skin wounds (20, 63). Besides, milk was also reported to be a source of exosome isolation (64). In our view, serum, PRP, and milk were abundant sources of exosomes. However, due to insufficient studies, its effectiveness and stability need to be further confirmed. Especially, a recent study reported that plant-derived exosomes were of therapeutic value (65); although it was not applied to skin wounds, it provided an excellent idea for exosome isolation. Perhaps it is a new direction for us to find exosomes from the proper kind of plants because many drugs contain plant extracts.

4.2 Engineering exosomes

In addition to finding more effective natural exosomes, due to their structural characteristics, exosomes are also highly engineerable. Engineering of exosomal surface confers cell and tissue specificity. Besides, exosomes are considered delivery vehicles of diverse biological molecules, including the delivery of nucleic acid, proteins, and lipids. Studies showed that some molecules in the exosomes were particularly beneficial to wound healing, so increasing these components in exosomes through various engineering technologies could enhance the function of exosomes. Engineering strategy could be divided into direct engineering of exosomes (chemical modification and physical modification) and indirect engineering of exosomes (genetic modification of exosome-donor cells) (66). To enhance the therapeutic effect of exosomes in diabetic wound healing, some researchers have tried to use an engineering strategy (Figure 2).

Directly loading cargoes to exosomes was adopted by many studies. For example, direct loading miR-21-5p to ADSCs-derived exosomes by electroporation exhibited excellent effects on promoting the proliferation and migration of keratinocytes and accelerating diabetic wound healing by increasing re-epithelialization, collagen remodeling, angiogenesis, and vessel maturation (31). Loading miR-155 inhibitor to BMSCs-derived exosomes showed synergistic effects in keratinocyte migration and anti-inflammatory action, leading to accelerated wound healing by negative regulation of miR-155 (50). ESCs-derived exosomes loaded with VH298 were also found to have a better therapeutic effect on wound healing and angiogenesis in diabetes mellitus (56). Yan et al. used milk-derived exosomes as a novel system for miR-31-5p delivery and successfully encapsulated miR-31-5p mimics into milk exosomes through electroporation. Then, they proved that the miR-31-5p loaded in exosomes achieved higher cell uptake and improved endothelial cell functions *in vitro*, promoting angiogenesis and enhanced skin wound healing *in vivo* (64).

Genetic modification of donor cells was also adopted because it was a convenient and stable method. Briefly, donor cells were infected by lentivirus carrying target cargoes and stably expressed these cargoes. Then, target cargoes-carried exosomes were isolated from these donor cells. For example, SMSCs were infected by lentivirus carrying miR-126-5p. Then, miR-126-3p overexpressed exosomes (SMSCs-126-Exos) were isolated. SMSCs-126-Exos

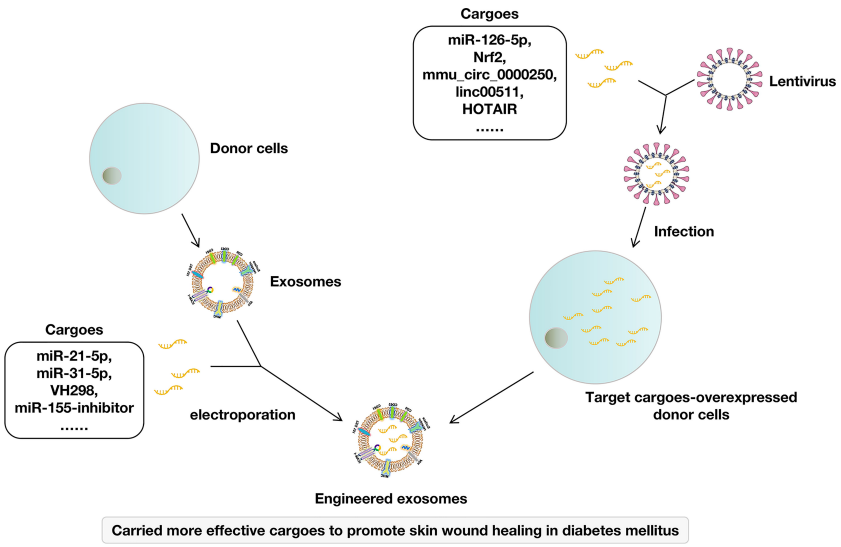


FIGURE 2
Engineering exosomes for skin wound healing in diabetes mellitus.

showed more effectiveness in promoting the proliferation of endothelial cells and fibroblasts and more effective in promoting angiogenesis in diabetic wound healing (18, 21). Similarly, exosomes isolated from Nrf2-overexpressed ADSCs could increase the granulation tissue formation and the levels of growth factor expression and reduce the levels of inflammation and oxidative stress-related proteins (40). Exosomes derived from mmu_circ_0000250-overexpressed ADSCs enhanced the therapeutic effect of exosomes to promote wound healing in diabetes by absorption of miR-128-3p and upregulation of sirtuin (SIRT)1 (43). Exosomes from linc00511-overexpressed ADSCs accelerated angiogenesis in diabetic foot ulcer healing by suppressing PAQR3-induced Twist1 degradation (45). Long non-coding RNA HOX transcript antisense RNA (HOTAIR)-overexpressed BMSCs produce exosomes with increased HOTAIR content that promote angiogenesis and wound healing in diabetes (48). Exosomes from mmu_circ_0001052-overexpressed ADSCs promote angiogenesis of DFU *via* miR-106a-5p and FGF4/p38MAPK pathway (17).

Other studies have enhanced the role of exosomes by changing the cultural environment of donor cells. Although it was not targeted to modify certain cargoes, it did change the cargoes in exosomes, thereby enhancing the role of exosomes in promoting diabetic wound healing. For example, Melatonin-pretreated MSCs-derived exosomes increased the ratio of M2 polarization to M1 polarization by upregulating the expression of PTEN and inhibiting the phosphorylation of AKT in diabetic wound healing (37). Exosomes derived from atorvastatin-pretreated MSCs accelerate diabetic wound repair by enhancing angiogenesis *via* AKT/eNOS pathway (26). Exosomes derived from pioglitazone-pretreated MSCs accelerate diabetic wound healing by enhancing angiogenesis (15). Hypoxia adipose stem cell-derived exosomes promote high-quality healing of diabetic wounds involving activation of PI3K/Akt pathways (35) and to improve wound healing in diabetic mice *via* delivery of circ-Snhg11 and induction of M2-like macrophage polarization (38).

Although exosome engineering used by different studies showed benefits to the therapeutic effect of exosomes, the contents of exosomes were diverse and complex. Therefore, avoiding ineffective and even harmful ingredients being transferred to the wound is difficult. In our view, the ultimate goal of exosome engineering might be to maximize the valuable components and minimize the useless components rather than focus on a single component. In addition, exosomes mainly play a role in regulating the function of cells and show no direct antibacterial effect. Therefore, it may be an effective strategy to increase its antibacterial ability to use engineering technology to wrap antibacterial drugs in exosomes.

4.3 Adjust the dosage and frequency

The dosage and frequency are unavoidable issues for any drug use. Some studies show that a better therapeutic effect can be achieved simply by increasing the dosage of exosomes, especially in some *in vitro* studies. For example, the proliferation and migration of fibroblasts induced by exosomes could be increased by increasing the dose of exosomes (21, 24, 32, 46). The uptake of exosomes by endothelial cells also resulted in dose-dependent increases in tube formation and angiogenesis (19, 32). For the frequency, Helena et al. reported that multiple carefully timed applications of exosomes had superior regeneration than a single dose of the same total concentration of exosomes (30). Although there are few exploratory experiments and discussions on dosage and frequency up to now, they are critical factors in the process of exosome application. They should be discussed together with the content of active cargoes in the exosomes. Therefore, it is necessary to test the dose and frequency in the application of exosomes in the

same way as conventional drugs are tested (minimum effective dosage, therapeutic dosage, maximum dosage, lethal dosage, etc.).

4.4 Improve the delivery methods

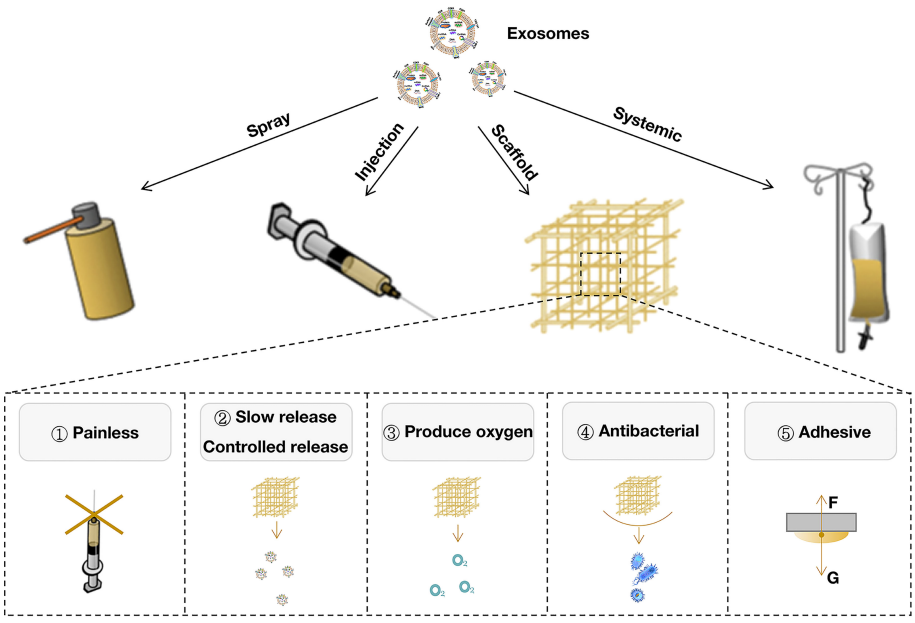
Through the above aspects, exosomes could solve some problems of diabetic wounds that are difficult to heal, such as difficulties in angiogenesis, nerve damage, and some inflammation problems. However, the hypoxia, bacteria, and high glucose levels have not been resolved. This requires better delivery methods to assist the therapeutic effect of exosomes. Drug delivery methods for treating skin wounds can be divided into four types: spraying, local injection, application combined with scaffold materials, and systemic application (Figure 3).

4.4.1 Local application

Most studies delivered exosomes by subcutaneous injection around the wounds at 2 points (62), at 4 points (14, 17, 19, 22, 23, 35, 38, 43, 51, 56, 59), at multiple points (15, 26, 37) or points unknown (24, 47, 48, 50). Others combined subcutaneous injection around the wounds and injection onto the wound bed to deliver exosomes for diabetic wound healing (58). Moreover, some studies indicated that exosomes were delivered by injection onto the wound bed only (31, 57). Some studies applied exosomes by intradermal injection around the wounds (33, 36), which was regarded as a drug delivery method that could directly stimulate the active cells in the dermis. No matter which injection method was used, it can only maximize the function of exosomes themselves.

To assist the therapeutic effect of exosomes, diverse scaffolds were used to deliver exosomes. Different scaffolds played different regulatory and auxiliary roles in the function of exosomes. In general, the use of all scaffolds reduces the iatrogenic trauma and pain caused by the local injection. It has the effect of slowly releasing exosomes to varying degrees, including some simple (20, 21, 44), thermosensitive (52), photosensitive (56, 61), pH-responsive (41), and biomimetic (67) scaffolds. To control the release of exosomes, Jiang et al. fabricated a matrix metalloproteinase degradable polyethylene glycol (MMP-PEG) smart hydrogel, which could release exosomes by reacting to MMP stimulating (28). Both slow and controlled releases are designed to prolong the exosome's action time and maintain the wounds' local drug concentration.

Many studies improved the performance of the scaffolds, including increasing the release of oxygen (11, 18, 60) and improving the antibacterial (41, 49) and adhesive properties (42), which were important in diabetic wound healing (Figure 3). Hydroxyapatite (HAP) was reported to release oxygen (68, 69). Therefore, Li et al. combined HAP and Chitosan (HAP-CS) to form a hydrogel loaded with exosomes to enhance bioactivities, support angiogenesis and promote diabetic wound healing (18). Parvaiz et al.



Several types of multifunctional scaffolds for exosome delivery	advantages
Matrix metalloproteinase degradable polyethylene glycol (MMP-PEG) smart hydrogel	①②
Hydroxyapatite-Chitosan (HAP-CS) hydrogel	①②③
Polyurethane-based calcium peroxide (PUAO-CPO) cryogels	①②③
Carboxyethyl chitosan-dialdehyde carboxymethyl cellulose (CEC-DCMC) hydrogel	①②④
Pluronic F127 (F127), oxidative hyaluronic acid (OHA), and Poly-ε-L-lysine (EPL) FHE hydrogel	①②④
Pluronic F127 (F127), polyethylenimine (PEI), and aldehyde pullulan (APu) (FEP) hydrogel	①②④⑤

FIGURE 3
Exosome delivery methods for diabetic wounds and the advantages of scaffolds.

fabricated polyurethane-based oxygen-releasing antioxidant scaffolds (PUAO-CPO) to load exosomes by incorporating calcium peroxide (CPO) in polyurethane (PUAO) cryogels, which showed the sustained release of oxygen and exosomes for more than 10 days. This exosome-loaded scaffold could increase cell survival under hypoxic conditions (11). It was also reported that manganese dioxide (MnO_2) could induce the decomposition of endogenous ROS (H_2O_2) into oxygen and effectively ameliorate oxidative stress and a hypoxic environment. Thus, integrating MnO_2 into antibacterial injectable hydrogels fulfill multiple requirements, such as ROS depletion, oxygen production, and antibacterial property. Therefore, loading exosomes to this scaffold is helpful for the repair of diabetic skin wounds (60). Geng et al. indicated that carboxyethyl chitosan-dialdehyde carboxymethyl cellulose (CEC-DCMC) hydrogel showed excellent antibacterial properties and provided a physical and chemical barrier for further infection of diabetes wounds, which played an auxiliary role in the function of exosomes (49). Wang et al. also developed an injectable self-healing polypeptide-based hydrogel that exhibited inherent antibacterial activity (41). In addition to the above characteristics, some studies included the viscosity of scaffold materials to achieve good adhesion to wounds (42).

To maximize the therapeutic effect of exosomes, Wang Min et al. fabricated a thermosensitive, injectable, self-healing, and adhesive polysaccharide-based multifunctional hydrogel scaffold that exhibited efficient antibacterial activity, fast hemostatic ability, good UV-shielding performance, and pH-responsive exosome release for promoting diabetic wounds. These biomedical functions for exosomes-loaded FEP dressing probably enhance their high capability in angiogenesis and wound healing (42). Although this kind of scaffold material with extremely rich functions shows various excellent properties, it is difficult to avoid adding more complex non-medical components, which will delay its clinical transformation. Therefore, how to achieve the balance between effectiveness and safety might need to be comprehensively evaluated.

4.4.2 Systemic application

For diabetic wound healing, we only found one study that delivered exosomes by systemic application *via* tail vein injection (16). For non-diabetic wound healing, one study has compared the effect of exosomes on wounds by topical injection and intravenous injection and interestingly found that intravenous injection of exosomes could enhance the healing of skin wounds compared to local injection (70). In another study, Zhou et al. systematically compared the effect of different exosome delivery methods for non-diabetic wound healing, and the results showed that the combined application of local smearing and intravenous administration offered the optimal impact on promoting wound healing, accelerating re-epithelialization, reducing scar widths, and enhancing angiogenesis and collagen synthesis (71).

Although the local application can play a good role in treating diabetes wounds, diabetes, as a metabolic-disorder disease, not only causes skin wounds to be difficult to heal but also faces some other physical problems, such as kidney disease, retinopathy, and neuropathy. Moreover, some studies reported that the significant upregulation of miRNAs (miR-20b-5p (72, 73), miR-15a-3p (74), miR-181b-5p (75) were observed in exosomes isolated from patients with diabetes mellitus), and these miRNAs could suppress the angiogenesis of ECs *via* different signaling pathways. Inhibition of circulating exosomal miRNAs accelerates diabetic wound repair (Figure 4). Therefore, we speculated that the

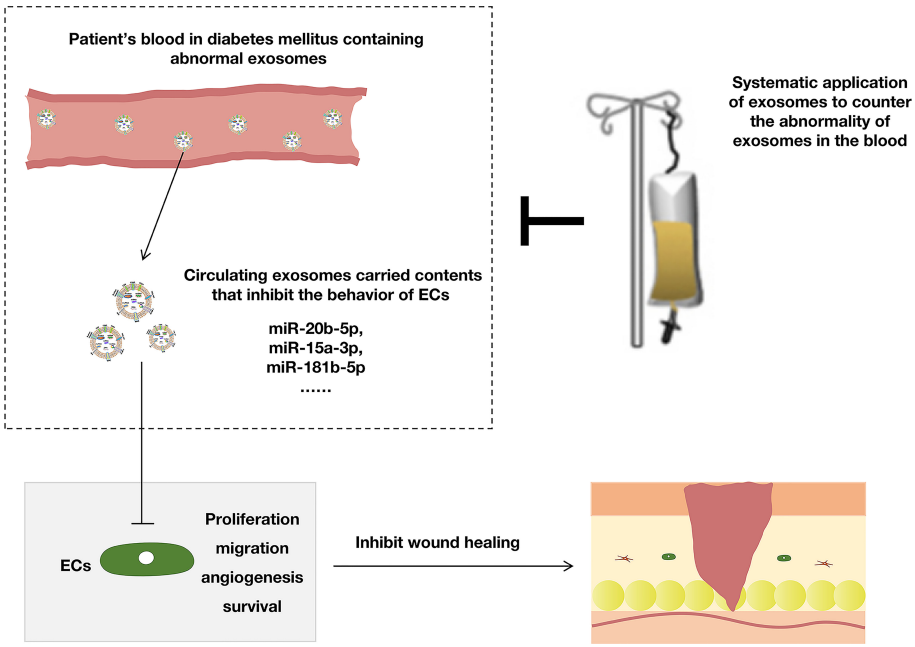


FIGURE 4
The systemic application of exosomes was beneficial to diabetic wounds.

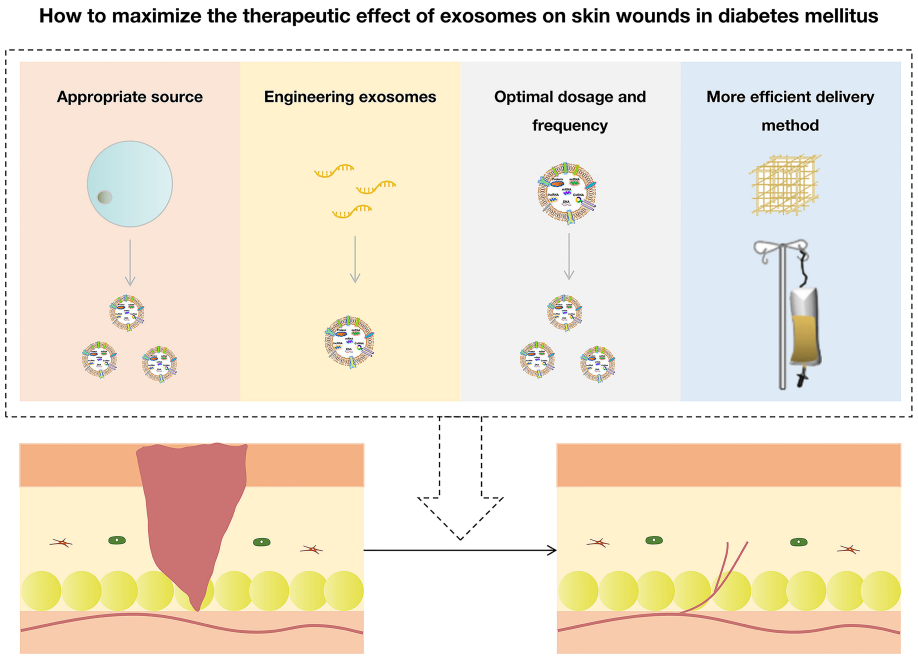


FIGURE 5
How to maximize the therapeutic effect of exosomes on skin wounds in diabetes mellitus.

combined local and systemic application of exosomes might benefit diabetic wound healing, and this requires further research.

5 Conclusions

Exosomes are a promising therapy for wounds in diabetes, and various ways to maximize their value are discussed in this paper. In this article, we reviewed and discussed the aspects that could be improved, including choosing appropriate donor cells, engineering exosomes, mediating dosage and frequency, and combining more efficient delivery methods (Figure 5). This review might provide an overview and idea for better-using exosomes to treat skin wounds in diabetes mellitus. Further reviews will be necessary to stay up to date with this rapidly evolving area of research.

Author contributions

JD, BW, and WT jointly conceived and discussed the manuscript. JD wrote the original manuscript. WT revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The association between micronutrient levels and diabetic foot ulcer: A systematic review with meta-analysis

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Background: Diabetic foot ulcers (DFU) are a major complication of diabetes mellitus (DM). Nutrient deficiencies are among the major risk factors in DFU development and healing. In this context, we aimed to investigate the possible association between micronutrient status and risk of DFU.

Methods: A systematic review (Prospero registration: CRD42021259817) of articles, published in PubMed, Web of Science, Scopus, CINAHL Complete, and Embase, that measured the status of micronutrients in DFU patients was performed.

Results: Thirty-seven studies were considered, of which thirty were included for meta-analysis. These studies reported levels of 11 micronutrients: vitamins B9, B12, C, D, E, calcium, magnesium, iron, selenium, copper, and zinc. DFU, compared to healthy controls (HC) had significantly lower vitamin D (MD: -10.82 14 ng/ml, 95% CI: -20.47, -1.16), magnesium (MD: -0.45 mg/dL, 95% CI: -0.78, -0.12) and selenium (MD: -0.33 µmol/L, 95% CI: -0.34, -0.32) levels. DFU, compared to DM patients without DFU, had significantly lower vitamin D (MD: -5.41 ng/ml, 95% CI: -8.06, -2.76), and magnesium (MD: -0.20 mg/dL, 95% CI: -0.25, -0.15) levels. The overall analysis showed lower levels of vitamin D [15.55ng/ml (95% CI:13.44, 17.65)], vitamin C [4.99µmol/L (95% CI:3.16, 6.83)], magnesium [1.53mg/dL (95% CI:1.28, 1.78)] and selenium [0.54µmol/L (95% CI:0.45, 0.64)].

Conclusion: This review provides evidence that micronutrient levels significantly differ in DFU patients, suggesting an association between micronutrient status and risk of DFU. Therefore, routine monitoring and supplementations are warranted in DFU patients. We suggest that personalized nutrition therapy may be considered in the DFU management guidelines.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=259817, identifier CRD42021259817.

KEYWORDS

diabetic foot ulcers, micronutrients, vitamins, minerals, risk

1 Introduction

Chronic wound infections pose a significant health concern, especially diabetic foot ulcers (DFU) with maximum severity. It is estimated that foot ulcer complications account for 24.4% of healthcare costs among diabetics (1). The rising prevalence of diabetes projects DFU as a growing health concern that accounts for maximum non-traumatic amputation globally. Prevalence of DFU among diabetics has risen from 15 - 25% to 19 - 35% (2). The global prevalence of DFU is 6.3%, higher in males and type 2 diabetes mellitus (DM) than in females and type 1 DM (3). A recent study reported the one-, two -, and five-year survival rates in DFU patients as 81%, 69%, and 29%, indicating the robust association with mortality (4). Foot ulcers are less likely to heal in diabetics because of disorders in the intrinsic wound-healing process, such as compromised collagen cross-linking, altered functioning of matrix metalloproteinases, and immunological reasons (5). Management strategies include patient education, wound dressings, debridement, adequate offloading, blood sugar control, infection management, revascularisation, and advanced therapies (6, 7).

Nutrient deficiencies are among the major risk factors in DFU development and healing. Nutrient deficiencies modify the physiological responses to infection by diminishing the immune response, predisposing the skin to become thin and flaky, thereby developing a wound. The deficiencies also decrease subcutaneous fat at pressure points, together exacerbating the vulnerability to pressure wounds. Nutrient deficiencies also reduce the collagen synthesis required for wound healing and promote immobility due to diminished energy reserves (8). Malnutrition adversely affects the complex wound-healing process.

Hyperglycaemia and glucose-lowering drugs alter nutrient absorption in DM patients, resulting in nutritional deficiencies (9). Oxidative stress from glucose metabolism in DM depletes the natural antioxidant reserves of vitamins A, C, and E (9). Persistent hyperglycaemia and open wounds push the body into a catabolic state. As a result of insulin deprivation, negative nitrogen balance develops from gluconeogenesis from protein breakdown. Altered nutritional status and systemic deficiencies impair fibroblast, protein, and collagen synthesis (5).

Micronutrients affect wound healing comprehensively, *via* antioxidant and anti-inflammatory action, collagen stabilization, cell growth regulation, and differentiation. A closer monitoring of micronutrient status in DFU is warranted, as nutrient status is an easily modifiable factor as compared to non-modifiable factors such as age, DM duration, metabolic factors, and micro-, and macro-vascular disorders. The focus of this study was to systematically review the literature and provide the nature of nutritional deficiencies in DFU patients as compared to DM and non-diabetic healthy controls (HC). This would help identify the primary micronutrient deficiencies in DFU patients and initiate supplementations accordingly. Therefore, we have collated and analysed multiple data related to micronutrient status in patients with DFU, DM, and healthy controls (HC).

2 Methods

This systematic review appraises the association between micronutrient status and the risk of DFU. We have followed the preferred reporting items for systematic review and meta-analysis (PRISMA) 2020 guidelines and developed the research question using the PECOS format: The original research articles (study design) among DFU patients (participants), micronutrient status (exposure) as a risk for foot ulcers (outcome) compared to the control groups (comparator). The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), identification number CRD42021259817 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=259817).

2.1 Search strategy

Initial search was performed in July 2021 and updated on 21st October 2021. We systematically searched and identified relevant studies from the following databases: PubMed, Web of Science, Scopus, CINAHL Complete, and Embase. The references cited by the included articles were examined to identify more articles. We

used the following search terms: 'micronutrient*', 'nutrient*', 'nutritional status', 'trace element*', 'vitamin*', 'provitamin*', 'mineral', 'diabetic foot ulcer*', 'DFU', 'diabetic foot infection*', 'diabetic foot osteomyelitis', 'diabetic foot', 'diabetic feet' combined using 'AND' and 'OR', without restrictions on date of publication and language.

2.2 Eligibility and study selection

The study titles and abstracts were initially screened, and full texts were examined for potential eligibility. We included studies published in English and all original research studies (RCTs and observational studies) that measured micronutrient status in DFU without date restrictions. Only baseline data regarding the demographics and micronutrient levels in DFU patients were retrieved from RCTs. We excluded animal studies, editorials, case reports, case series, abstract-only papers, conference proceedings, and publications that did not measure micronutrient levels. After the initial search, all references were downloaded to Endnote X9.3.3 software. Further, SJK and RB independently assessed the title and abstracts to check for eligibility based on inclusion and exclusion criteria. Disagreements were resolved by SSM.

2.3 Data extraction and quality assessment

Data from the included studies were extracted into a pre-framed data extraction sheet. The following variables were extracted: author name(s), year of publication, place of study, study design, patient demographic characteristics, number of patients in cases/control, sample size, DFU classification, and micronutrient assessed and status of micronutrient. SJK performed primary data extraction, which was cross-checked for accuracy by TB and RB. Disagreements were resolved by discussion/consultation with SSM. For RCTs, only the baseline micronutrient levels were extracted.

We used Cochrane risk-of-bias tool to assess the quality of RCTs, the Newcastle-Ottawa Scale (NOS) for observational studies (e.g., case-control and cohort studies), and Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies. SJK and TB independently performed the quality assessment, and disagreements between reviewers were settled through consensus/discussion with SSM.

2.4 Statistical analysis

From extracted data, we developed a narrative synthesis structured around micronutrient status, findings are presented in tabular form. We employed RevMan 5.4.1 software to perform meta-analysis of selected studies with quantitative estimation.

All data were systematically collected and converted to standard units to maintain uniformity of data using conversion tools (10). We used the statistics toolkit (STATTOOLS) developed by The Department of Obstetrics and Gynaecology of the Chinese University of Hong Kong (11) to combine the mean and standard deviation (SD), where cases or controls were categorized into multiple groups. The formula $SE = SD \div \sqrt{sample\ \ size}$ was used to convert SD to standard error (SE) and vice versa as per Cochrane guideline (12).

Studies reporting vitamin E were excluded from the meta-analysis because we could not convert multiple units of measurement into a standardized uniform unit. Similarly, zinc values from Momen-Heravi et al. study were excluded from the meta-analysis (13). Unit mismatches could be due to the differences in analytical methods. We excluded vitamin D levels reported by Qasim et al. from the review because it had the lowest score in quality assessment (14). We also excluded vitamin D levels reported by Greenhagen et al. from meta-analysis because SD values were not mentioned (15).

The I^2 statistic was used to identify the heterogeneity among studies. A random-effects meta-analyses model was conducted because there was significant heterogeneity (I^2>50%; P<0.01) in all the analyses performed. Subgroup analysis was carried out based on the geographical location, but not age and gender because of insufficient data.

2.5 Publication bias and sensitivity analysis

The publication bias was assessed using funnel plots. Based on the risk assessment scores, sensitivity analysis was performed to ensure the robustness of the data.

3 Results

We identified 1312 records from the databases listed. We identified four more relevant studies by manually searching literature references. We removed 553 duplicate records. The remaining 763 were screened based on title and abstract, of which 67 were selected for retrieval. Finally, a total of 46 articles were assessed for eligibility based on criteria, of which 9 were excluded as some were abstract only (n=3), baseline micronutrient levels were not reported (n=3), a specific micronutrient assessment was not made (n=1), low-quality assessment score (n=1), and an article was not in English. 37 were included in the review and 30 for meta-analysis. Figure 1: The PRISMA flow chart of study selection.

3.1 Study characteristics

A total of 37 articles were retrieved after a systematic literature search. Nine were RCTs (13, 16–23), and 28 were observational studies (15, 24–50) (12 cross-sectional, seven cohort, and nine case-control studies).

Nine (24.32%) each were reported from India (18, 25, 26, 30, 40, 47–50), and Iran (13, 16, 20–22, 24, 34, 39, 45), three (8.10%) from Turkey (27, 36, 43), two (5.40%) each from China (33, 37) and Nigeria (41, 42), and one (2.70%) each from Italy (19), Bulgaria (31), Greece (32), Pakistan (28), Bahrain (29), USA (15), Germany (38), Australia (35), Spain (44), Mexico (46), Denmark (17), and Slovakia (23). Number of DFU patients (men and women) ranged

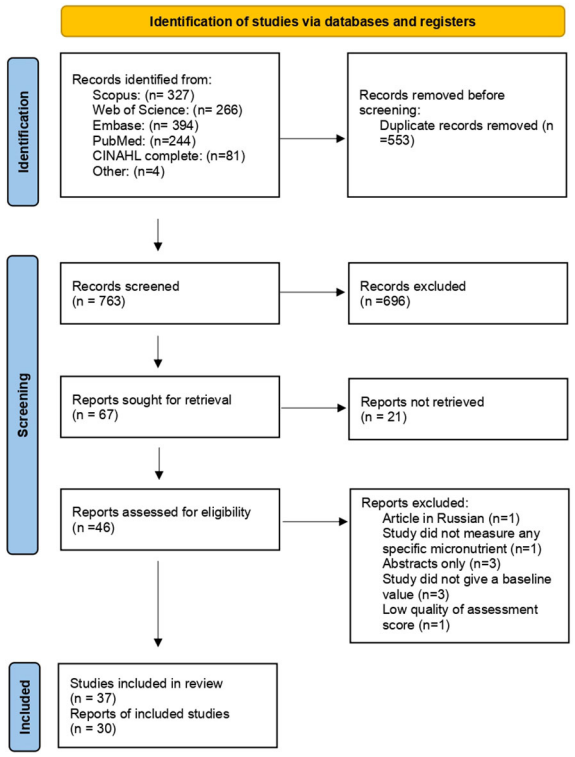

FIGURE 1
The PRISMA flow chart of screening and study selection.

from 19 to 387. Multiple classification systems were used for DFU assessment such as University of Texas Wound Classification System, Wagner's grading system, International Working Group on the Diabetic Foot (IWGDF) guideline 2019, and Armstrong classification of chronic wounds, and some were based on the clinical characteristics of the wound. These studies reported levels of 11 nutrients: vitamins B9, B12, C, D, E, calcium, magnesium, iron, selenium, copper, and zinc. Table 1 provides the study characteristics.

3.2 Quality assessment

We employed the Cochrane risk-of-bias tool to assess the quality of RCTs. Case-control and cohort studies were assessed using the NOS. The overall NOS scores for the cohort and case-control studies were 5 to 7, and 6 to 8, respectively, indicating moderate quality. We used JBI checklist for cross-sectional studies. The highest and lowest scores were 8, and 2. Qasim et al. (lowest score) was excluded (14). Table 2 lists the Quality assessment scores of all included studies.

3.3 Meta-analysis

Micronutrient levels of DFU patients were compared against those with DM [Figure 2A] and HC [Figure 2B] and are reported in

TABLE 1 Study Characteristics.

Sl. no	Year, study title, place	Participants included	Micronutrients assessed	DFU assessment	Major findings
1.	2017 Momen-Heravi et al., Iran (12)	DFU- 60	Zinc	Wagner's grading system	Zinc supplementation significantly improved wound status and various biochemical markers.
2.	2019 Greenhagen et al., USA (14)	DFU-54 DM- 46	Vitamin D	NA	Significant VDD was identified in patients with various lower extremity complications, with and without ulcers.
3.	2019 Afzali et al., Iran (15)	DFU- 57	Magnesium	Wagner's grading system	Evident decrease in magnesium levels in DFU. Magnesium and vitamin E supplementation significantly improved wound healing and biochemical markers.
4.	2021 Halschou-Jensen et al., Denmark (16)	DFU- 48	Vitamin D	Based on clinical characteristics of the wound	VDD was markedly prevalent in DFU. High-dose vitamin D (6800IU/day) with standard care achieved a 100% median wound reduction.
5.	2020 Kamble et al., India (17)	DFU- 60	Vitamin D	Wagner's grading system	VDD was markedly prevalent in DFU. Vitamin D supplementation provided positive outcomes in wound healing and biochemical markers.
6.	2014 Maggi et al., Italy (18)	DFU- 30	Vitamin D	NA	VDD was markedly prevalent in the study population.

(Continued)

TABLE 1 Continued

Sl. no	Year, study title, place	Participants included	Micronutrients assessed	DFU assessment	Major findings
7.	2018 Razzaghi et al., Iran (19)	DFU- 70	Magnesium	Wagner's grading system	Magnesium supplementation significantly improved wound status and various biochemical markers.
8.	2017 Razzaghi et al., Iran (20)	DFU- 60	Vitamin D	Wagner's grading system	VDD was markedly prevalent in the study population. Positive outcomes in wound healing and biochemical markers upon vitamin D supplementation.
9.	2016 Mozaffari-Khosravi et al., Iran (21)	DFU- 27	Vitamin D	Wagner's grading system	Both 150,000 and 300,000 IU of vitamin D improved ulcer characteristics, inflammatory, glycemic, and vitamin D status in DFU. 300,000 IU was found more effective than 150,000IU.
10.	2010 Palacka et al., Slovakia (22)	DFU- 59	Vitamin E	Wagner's grading system	Administration of polarised light along with antioxidant nutrients enhances outcomes in diabetic complications.
11.	2016 Afarideh et al., Iran (23)	DFU- 30 DM- 30 HC- 28	Vitamin D	University of Texas Wound Classification System	Serum 25(OH)D was higher in DFU than in DM and HC. Positive correlation between higher vitamin D levels and the risk of DFU.
12.	2019 Darlington et al., India (24)	DFU- 88 DM- 88	Vitamin D	Wagner's grading system	Vitamin D was less than 30ng/ml in 59.18% with a graft or achieved wound healing and in 97.44% of patients who either died or needed an amputation. 78.9% with healed wounds within six months had normal levels.
13.	2016 Gupta et al., India (25)	DFU- 50 DM- 50 HC- 25	Vitamin D	NA	Serum vitamin D levels were significantly lower in DFU than in controls. Vitamin D augments phagocytosis by macrophages and thereby enhances the innate immune response.
14.	2013 Keskek et al., Turkey (26)	DFU- 49 DM- 49 HC- 49	Magnesium	Based on clinical characteristics of the wound	A robust association between serum magnesium and incidence of DFU. Significantly lower magnesium in DFU compared to DM and HC.
15.	2020 Shaikh et al., Pakistan (27)	DFU- 387	Calcium	Wagner's grading system	Mini-nutritional assessment scores were correlated to DFU severity. No correlation between calcium levels and foot ulcers.
16.	2019 Smart et al., Bahrain (28)	DFU- 80	Vitamin D	Wagner's grading system	85% of study participants had <20ng/ml vitamin D. VDD to be included among the modifiable DFU aggravating factors.
17.	2012 Swain et al., India (29)	DFU- 74	Vitamin D Calcium	NA	Serum vitamin D < 20ng/ml; risk of vascular calcification higher with levels <10ng/ml.
18.	2020 Todorova et al., Bulgaria (30)	DFU- 73 DM- 169	Vitamin D	International Working Group on the Diabetic Foot guideline 2019	VDD significant in DFU. No significant difference in vitamin D levels between infected and uninfected ulcers.
19.	2020 Tsitsou et al., Greece (31)	DFU- 33 DM- 35 HC- 28	Vitamin D Calcium	Based on clinical characteristics of the wound	Significant VDD in diabetic patients with and without ulcers compared to HC

(Continued)

TABLE 1 Continued

Sl. no	Year, study title, place	Participants included	Micronutrients assessed	DFU assessment	Major findings
20.	2020 Xiao et al., China (32)	DFU- 245 DM- 4039	Vitamin D	NA	Significant VDD in DFU patients.
21.	2021 Yarahmadi et al., Iran (33)	DFU- 32	Vitamin D	NA	Increased hs-CRP, prooxidant-antioxidant balance, and decreased vitamin D levels could affect the pathogenesis of DFU.
22.	2020 Brookes et al., Australia (34)	DFU- 48	Vitamin D Iron Zinc Selenium Vit C Vitamin B12	NA	More than 50% of participants had VDD and vitamin C deficiency. The risk of amputation is associated with lower levels of vitamin C, albumin, and hemoglobin. The duration of the ulcer is unaffected by nutritional markers.
23.	2018 Caglar et al., Turkey (35)	DFU- 58 DM- 47	Vitamin D	Wagner's grading system	Vitamin D significantly decreased in DFU; vitamin D supplements might avoid untoward immunological responses.
24.	2020 Dai et al., China (36)	DFU- 21 DM-30	Vitamin D	University of Texas Wound Classification System	VDD is a risk factor for DFU. A cut-off value of 13.68 ng/ml of 25 (OH) vitamin D as the threshold for DFU risk.
25.	2018 Feldkamp et al., Germany (37)	DFU- 104 DM- 103 HC- 99	Vitamin D	Armstrong classification of chronic wounds	Significant VDD in DFU patients; severe VDD in more than half, indicating DFU patients to be at risk for VDD.
26.	2019 Najafpour et al., Iran (38)	DFU- 35 DM- 35 HC- 35	Vitamin D	Wagner's grading system	Significant VDD in DFU patients. VDD is a risk factor for the development and formation of ulcers in DM.
27.	2013 Zubair et al., India (39)	DFU- 90162 DM- 162	Vitamin D	University of Texas Wound Classification System	Median vitamin D levels are lower in foot ulcer group than in controls. Multivariate analysis showed that low vitamin D predicted foot ulcers.
28.	2016 Bolajoko et al., Nigeria (40)	DFU- 70 HC- 50	Vitamin C Vitamin E Copper Zinc Selenium	Wagner's grading system	Vitamin C, vitamin E, and selenium are significantly lower in ulcer patients. But copper and zinc levels were similar for all participants.
29.	2012 Bosede et al., Nigeria (41)	DFU- 50 HC- 50	Selenium Vitamin C Vitamin E	Wagner's grading system	Vitamin C, vitamin E, and selenium lower in DFU than in HC.
30.	2013 Bozkurt et al., Turkey (42)	DFU- 50 DM- 50 HC- 100	Copper Zinc Magnesium	NA	Possible association between elevated zinc levels and DFU. Serum copper and zinc were higher in the DFU and DM than in HC ($P<0.001$). Serum magnesium was lower in all diabetic patients.
31.	2010 Gonz´alez et al., Spain (43)	DFU- 89 DM- 109	Folate Vitamin B12	Wagner's grading system	Vitamins folate and B12 levels were similar in both DFU and DM.
32.	2007 Larijani et al., Iran (44)	DFU- 19 DM- 20 HC- 20	Zinc	NA	Serum zinc is significantly lower in DFU; possibly contributing to the hyperactivity of polymorphonuclear leukocytes.

(Continued)

TABLE 1 Continued

Sl. no	Year, study title, place	Participants included	Micronutrients assessed	DFU assessment	Major findings
33.	2001 Rodrigues-Moran et al., Mexico (45)	DFU- 33 DM- 66	Magnesium	Based on clinical characteristics of the wound	Significantly lower serum magnesium levels among the DFU.
34.	2013 Tiwari et al., India (46)	DFU- 125 DM- 164	Vitamin D	NA	VDD was substantially more prevalent and severe in DFI than in controls. VDD is a possible risk factor. Initiating supplementation improves patient outcomes.
35.	2014 Tiwari et al., India (47)	DFU- 112 DM- 107	Vitamin D	Wagner's grading system	Severe VDD in DFI patients is also associated with increased inflammatory cytokines. A cut-off value of 10ng/ml of 25 (OH) vitamin D for immunological alterations in DM patients.
36.	2020 Yadav et al., India (48)	DFU- 32 DM- 32	Zinc, Magnesium Copper	Based on clinical characteristics of the wound	Serum zinc, copper, and magnesium levels were substantially reduced in DFU and also found to be inversely related to glycaemic parameters and directly proportional to the duration of DM.
37.	2008 Singh SK et al., India (49)	DFU- 32 DM- 15 HC- 15	Vitamin E	NA	Diabetic patients with PVD and foot ulcers had significantly lower antioxidant levels and vitamin E.

VDD, vitamin D deficiency; NA, not available; DFU, Diabetic Foot Ulcer; DFI, Diabetic Foot Infections; DM, Diabetes mellitus; HC, Healthy controls; PVD, Peripheral Vascular Disease.

mean differences (MD). Figure 3 presents the summary results of micronutrient levels in DFU patients.

3.3.1 Vitamin B

Gonzalez et al. estimated folic acid and vitamin B12 levels among DM (n= 109) and DFU (n= 89) patients (44). Serum folic acid (24.9 ± 11.51 vs 25.8 ± 16.6 nmol/L, $P = 0.67$), and vitamin B12 (392.6 ± 242 vs 453.9 ± 290.8 pmol/L, $P = 0.15$) were similar in both groups. Brookes et al. reported vitamin B12 in DFU (n= 39) patients with a mean 294.6 ± 221.8 pmol/L (35). The pooled vitamin B12 level in DFU (n= 128) patients was 346.68 pmol/L, 95% CI: 250.83, 442.53; $P<00001$; $I^2 = 80\%$.

3.3.2 Vitamin C

Two studies compared vitamin C in DFU (n=120) and HC (n= 100) patients (41, 42). Combined results showed no significant difference in vitamin C levels between the two groups (MD: -4.38 µmol/L, 95% CI: -9.47, 0.71; $P= 0.09$; $I^2 = 99\%$). A total of three studies measured vitamin C in patients with DFU (35, 41, 42). The mean vitamin C level in DFU (n= 166) patients was 4.99 µmol/L, 95% CI: 3.16, 6.83; $P<00001$; $I^2 = 96\%$.

3.3.3 Vitamin D

Thirteen studies compared vitamin D levels in DFU (n= 1136) and DM (n= 5059) patients (24–26, 31–33, 36–40, 47, 48). Combined results showed significantly lower vitamin D levels in DFU patients (MD: -5.41 ng/ml, 95% CI: -8.06, -2.76; $P<0001$; $I^2 = 92\%$). Combined results of five studies in DFU (n= 252) and HC (n= 215) (24, 26, 32, 38, 39); show significantly lower vitamin D levels in DFU (MD: -10.82 14 ng/ml, 95% CI: -20.47, -1.16; $P=0.03$; $I^2 = 96\%$). From 22 studies that measured vitamin D in patients with DFU (n= 1433) (17–19, 21, 22, 24–26, 29–40, 47, 48), mean levels in patients were 15.55ng/ml, 95% CI: 13.44, 17.65; $P<00001$; $I^2 = 97\%$. Greenhagen et al. reported 18.7ng/ml of vitamin D in 54 DFU patients compared to 23.6 ng/ml in DM (n= 46) patients without ulcers (15).

3.3.4 Vitamin E

Four studies estimated Vitamin E. Singh et al. measured vitamin E levels in DFU (n= 32) patients, DM (n= 15), and HC (n= 15) (50). Vitamin E levels were substantially lower in DFU, compared to DM (5.04 ± 1.76 vs. 9.10 ± 2.83 ng/L, $P<0.001$) and HC (10.68 ± 2.58ng/L). Bolajoko et al. found lower vitamin E levels in DFU (n= 120) vs DM (n= 50) 19.57 ± 1.01 vs 25.57 ± 0.27 µmol/L, $P= 0.0001$ (41). A study by Bosede et al. demonstrated no significant difference in vitamin E between DFU (n= 50) and HC (n=50) (0.05 ± 0.02 vs. 0.06 ± 0.005 mmol/L) (42). Palacka et al. assessed multiple baseline metabolic parameters in DFU patients, among which vitamin E was 18.48 ± 7.62 mmol/L (23).

3.3.5 Calcium

Two studies compared calcium levels in DFU (n= 106) and DM (n= 204) patients (31, 32). The combined results showed similar calcium levels in both groups (MD: -0.17 mg/dL, 95% CI: -0.60, 0.26; $P=0.43$; $I^2 = 92\%$). A total of four studies measured calcium in DFU (n=567) (28, 30–32), with mean levels of 9.10 mg/dL, 95% CI: 8.71, 9.49; $P<00001$; $I^2 = 95\%$.

3.3.6 Magnesium

Combined results from 4 studies comparing magnesium levels in DFU (n= 164) and DM (n= 197) patients (27, 43, 46, 49); showed lower magnesium levels in DFU (MD: -0.20 mg/dL, 95% CI: -0.25,

TABLE 2 Risk of bias assessment using Cochrane risk-of-bias tool for RCTs and Newcastle-Ottawa scale for observational studies, and Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies.

RCT- Cochrane risk-of-bias							
Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Momen-Heravi M_2017 (12)	Low	Unclear	Unclear	Unclear	Low	Low	Low
Afzali_2019 (15)	Low	High	Low	Low	Low	Low	Low
Halshchou-Jensen_2021 (16)	Low	Low	Unclear	Unclear	Low	Low	Low
Kamble_2020 (17)	High	High	High	High	Low	Low	Low
Maggi_2014 (18)	Low	High	Unclear	Unclear	Unclear	Low	Low
Razzaghi_2018 (19)	Low	Low	Unclear	Unclear	Low	Low	Low
Razzaghi_2017 (20)	Low	Low	Unclear	Unclear	Low	Low	Low
Mozaffari-Khosravi_2016 (21)	Low	High	Unclear	Unclear	Low	Low	Low
Palacka_2010 (22)	High	High	High	High	Unclear	Low	Unclear

Cohort study- Newcastle-Ottawa scale									
Study	Selection				Comparability	Exposure			Final Score
	Representativeness	Selection	Ascertainment	Demonstration	Comparability	Assessment	Duration	Adequacy	
Greenhagen_ 2019 (14)	0	0	1	1	2	1	0	0	5
Brookes_ 2020 (34)	1	0	1	0	2	1	0	0	5
Caglar_ 2018 (35)	1	1	1	1	1	1	0	0	6
Dai_ 2020 (36)	1	1	1	1	2	1	0	0	7
Feldkamp_ 2018 (37)	1	1	1	0	1	1	0	0	5
Najafpour_ 2019 (38)	1	1	1	0	1	1	0	0	5
Zubair_2013 (39)	1	1	1	1	2	1	0	0	7

(Continued)

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TABLE 2 Continued

Case-control study- Newcastle-Ottawa scale									
Study	Selection				Comparability	Exposure			Final Score
	Case definition	Representativeness	Selection of Controls	Definition of Controls	Comparability	Ascertainment	Method of ascertainment	Non-Response rate	
Bolajako_ 2016 (40)	1	1	1	1	2	1	0	0	7
Bosede_ 2012 (41)	1	1	0	1	2	1	1	0	7
Bozkurt_2013 (42)	0	1	0	1	2	1	1	0	6
Gonz´alez_2010 (43)	1	1	0	1	2	1	1	1	8
Larijani_2007 (44)	1	1	1	1	2	1	1	0	8
Rodrigues-Moran_ 2001 (45)	1	1	1	1	2	1	1	0	8
Tiwari_ 2013 (46)	1	1	0	1	0	1	1	1	6
Tiwari_ 2014 (47)	1	1	1	1	0	1	1	0	6
Yadav_ 2020 (48)	1	1	0	1	1	1	1	1	7
Cross-sectional study- Joanna Briggs Institute critical appraisal checklist									
	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	
Qasim_ 2020 (13)	No	Yes	Unclear	No	No	No	Yes	Unclear	exclude
Afarideh_2016 (23)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Darlington_2019 (24)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Gupta_ 2016 (25)	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Include
Kenskek_2013 (26)	No	Yes	Yes	Yes	No	No	Yes	Yes	Include
Shaikh_ 2020 (27)	Yes	Yes	Yes	Yes	No	No	No	Yes	Include

(Continued)

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TABLE 2 Continued

Smart_ 2019 (28)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Swain_ 2012 (29)	No	No	Yes	Yes	No	No	Yes	Yes	Include
Todorova_2020 (30)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Tsitsou_ 2020 (31)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Include
Xiao_ 2020 (32)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Yarahamadi_2021 (33)	No	Unclear	Yes	Yes	No	No	Yes	Yes	Include
Singh_ 2008 (49)	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	Include

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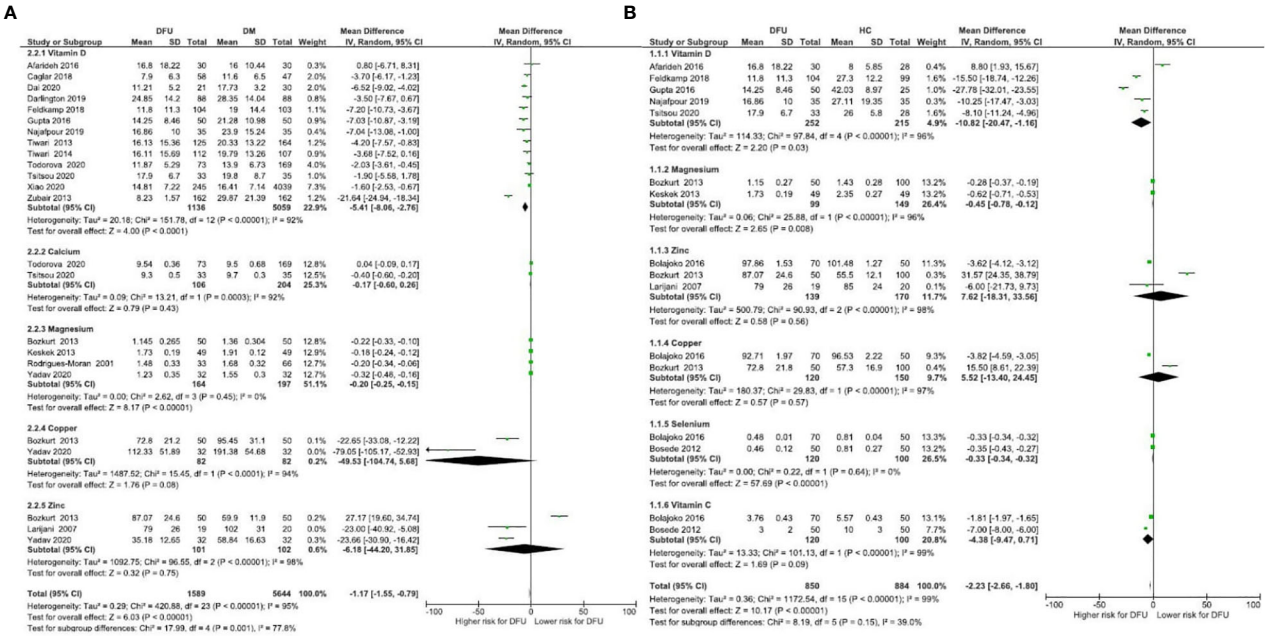

FIGURE 2
Forest plot of pooled mean difference of micronutrient status in DFU patients compared to DM and HC **(A)** Micronutrient levels of DFU patients were compared against those with DM; **(B)** Micronutrient levels of DFU patients were compared against those with HC.

-0.15; P<00001; I^2 = 0%). Combined results of two other comparison studies in DFU (n= 99) and HC (n= 149) patients (27, 43); showed lower magnesium levels in DFU patients (MD: -0.45 mg/dL, 95% CI: -0.78, -0.12; P=0.008; I^2 = 96%). From total of six studies (16, 20, 27, 43, 46, 49], pooled magnesium level was 1.53mg/dL, 95% CI: 1.28, 1.78; P<00001; I^2 = 99% in DFU (n= 291).

3.3.7 Iron

Only one study reported Iron levels. A retrospective analysis by Brookes et al. reported mean iron levels of 8.4 ± 5.9 µmol/L in 29 DFU patients (35).

3.3.8 Selenium

Combined results of two studies comparing selenium in DFU (n=120) and HC (n=100) (41, 42); showed significant difference in selenium levels between both groups (MD: -0.33 µmol/L, 95% CI: -0.34, -0.32; P< 0.00001; I^2 = 0%). A total of three studies measuring selenium in DFU (n=123) (35, 41, 42), reported mean levels of 0.54 µmol/L, 95% CI: 0.45, 0.64; P<00001; I^2 = 93%.

3.3.9 Copper

Combined results of two studies comparing copper levels in DFU (n=82) and DM (n=82) (43, 49) showed similar copper levels in both groups (MD: -49.53 µg/dL, 95% CI: -104.74, 5.68; P= 0.08; I^2 = 94%). Combined results of two studies comparing copper levels in DFU (n= 120) and HC (n= 150) (41, 43); showed similar levels in both groups (MD: 5.52 µg/dL, 95% CI: -13.40, 24.45; P=0.57; I^2 = 97%). Three studies measuring copper in DFU (n= 152) (41, 43, 49), reported mean levels of 90.67 µg/dL, 95% CI: 74.07, 107.26; P<00001; I^2 = 96%.

3.3.10 Zinc

Combined results of three studies comparing zinc levels in DFU (n=101) and DM (n= 102) patients (43, 45, 49) showed similar levels in both groups (MD: -6.18 µg/dL, 95% CI: -44.20, 31.85; P=0.75; I^2 = 98%). Combined results of three studies comparing zinc levels in DFU (n= 139) and HC (n=170) (41, 43, 45); showed similar levels in both groups (MD: 7.62 µg/dL, 95% CI: -18.31, 33.56; P= 0.56; I^2 = 98%). A total of five studies measuring zinc in patients with DFU (n= 180) (35, 41, 43, 45, 49) reported overall level of 73.67 µg/dL, 95% CI: 43.98, 103.36; P<00001; I^2 = 100%. One RCT by Momen-Heravi et al. on the effect of zinc supplements in DFU patients reported the baseline zinc level as 77 ± 9.60 mg/dL (13).

3.4 Subgroup analysis, sensitivity analysis, and publication bias

Due to insufficient data, subgroup analysis (based on geographic location) was conducted only for vitamin D, zinc, and calcium. The mean vitamin D levels [(Figure 4A] were not significantly different across Middle East, Europe, and Asia/Pacific regions (P=0.96). Mean zinc levels [(Figure 4B] significantly differed between Middle East, Asia/Pacific, and African regions (P<0.0001). The mean calcium levels [(Figure 4C] differed significantly between Europe and Asia/Pacific regions (P=0.006).

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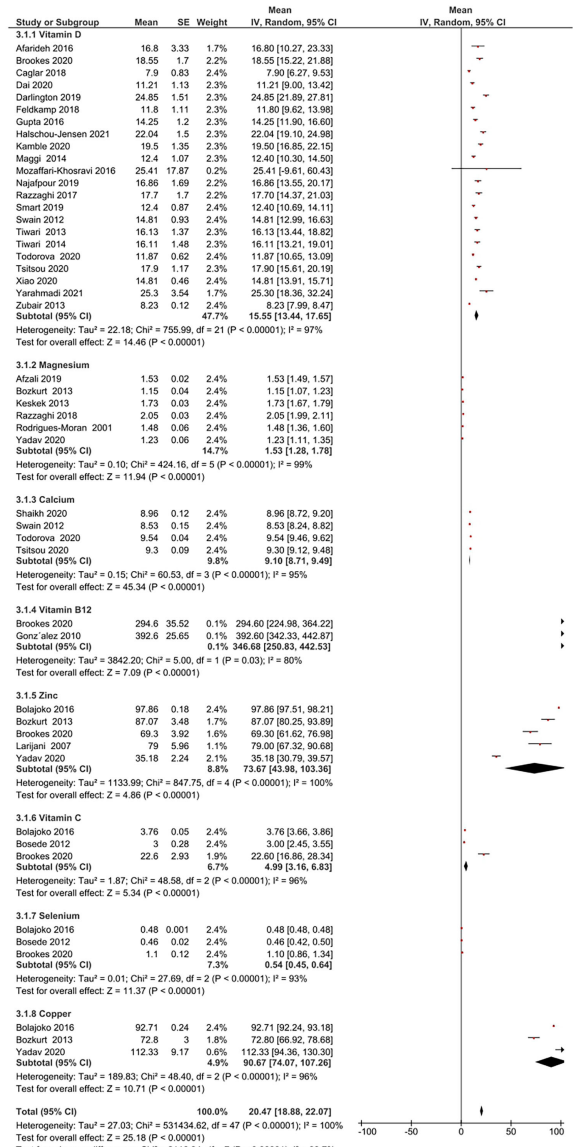

FIGURE 3
Summary of micronutrient levels in DFU patients. Forest plot of mean micronutrient status in DFU patients.

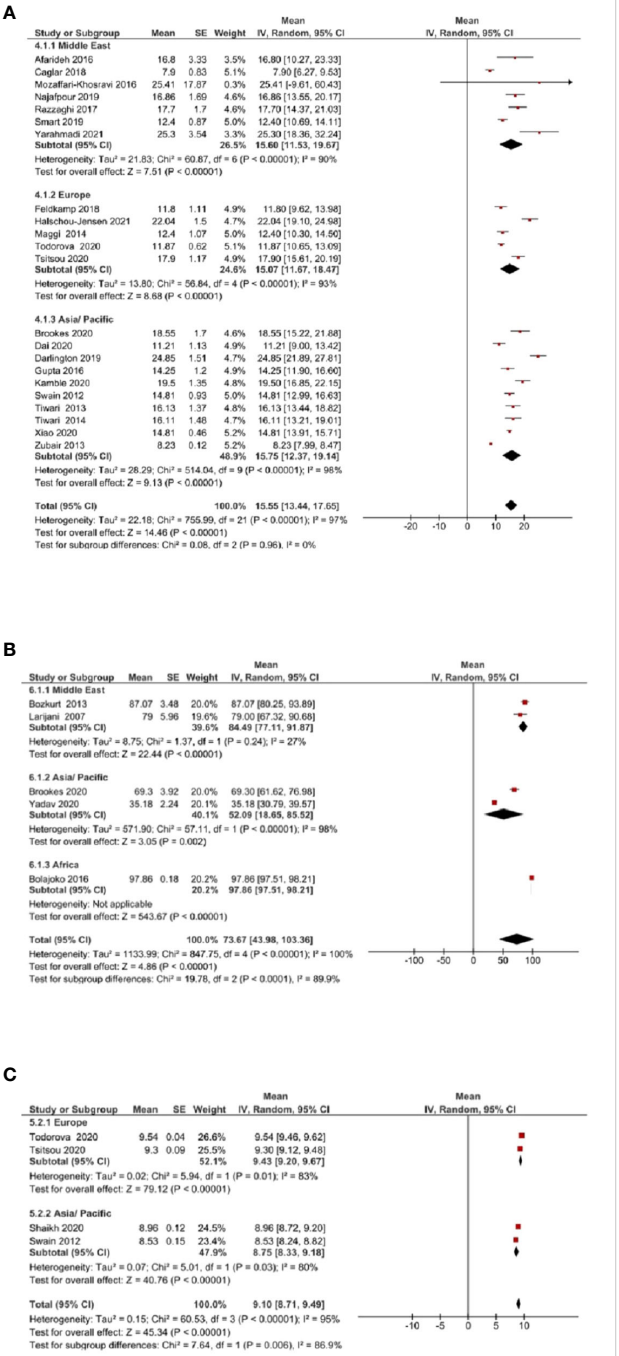

FIGURE 4
Subgroup analysis based on geographic location was assessed for vitamin D, zinc, and calcium. **(A)** Mean vitamin D levels across Middle East, Europe, and Asia/Pacific regions. **(B)** Mean zinc levels across Middle East, Asia/Pacific, and African regions. **(C)** Mean calcium levels across Europe and Asia/Pacific regions.

The sensitivity analysis by removing two studies (Swain et al. and Yarahmadi et al.) (30, 34) with the lowest risk assessment scores, does not alter the original results (mean = 20.53, 95% CI: 18.90, 22.15). The result of the sensitivity analysis is depicted in Figure 5.

The apparent asymmetry in the funnel plot (Figure 6) suggests possible publication bias.

4 Discussion

Identifying and managing chronic wounds is a critical healthcare objective. DFU generally starts with minor injuries that go unnoticed because of diabetic neuropathy (altered sensitivity and nerve damage). Convergence of immunological, vascular, nutritional, glycaemic, and infectious conditions influences wound healing. The present meta-analysis has revealed significantly lower circulating levels of vitamin D, vitamin C, magnesium, and selenium among patients with DFU than in control groups. However, other micronutrients did not differ significantly between DFU patients and controls.

Nutritional deficiencies impede normal stages of wound healing, a complex four-step process involving hemostasis,

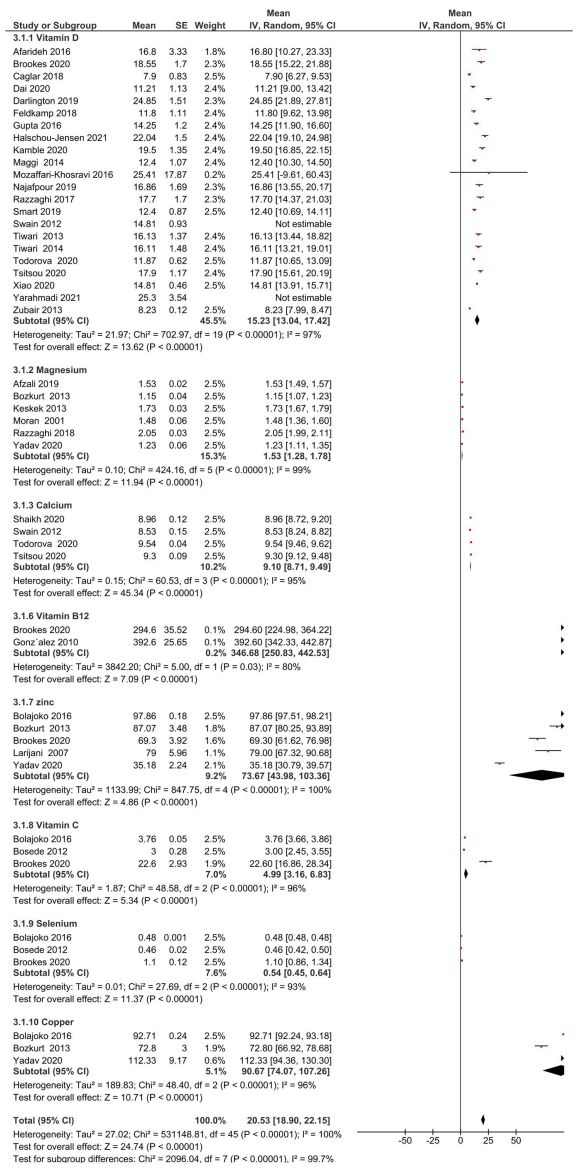

FIGURE 5
Forest plot for the sensitivity analysis. Sensitivity analysis was performed by eliminating results of two studies with the lowest risk assessment scores.

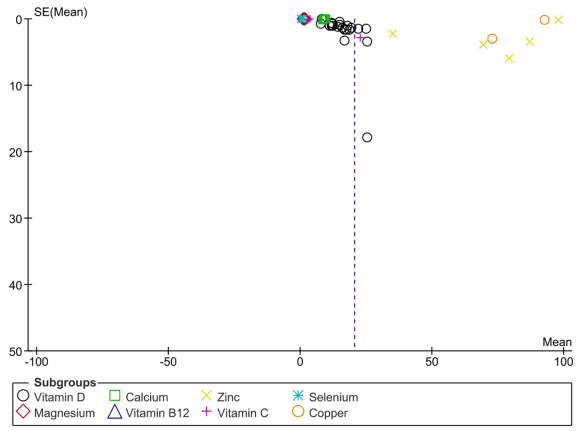

FIGURE 6
Funnel plot asymmetry test to assess publication bias.

inflammation, proliferation, and tissue remodelling (51). Chronic wounds generally get stalled at the inflammatory phase stage due to the continuous recruitment of neutrophils to the healing site, producing various alterations at systemic and molecular levels. Malnutrition also prolongs the inflammatory phase by decreasing fibroblast proliferation, and collagen formation, in addition to altering its tensile strength and angiogenesis. Malnutrition can increase the risk for infection by reducing T-cell function, phagocytic activity, complement, and antibody levels (52). Nutrients can aid wound healing by minimizing free radicals (neutrophils can release reactive oxygen species) and oxidative stress parameters by balancing the oxidant-antioxidant defenses (53). The higher proportion of nutrient insufficiencies in DFU could disturb glycaemic control, which in turn delays wound healing (49).

Vitamin D is well known for its pleiotropy. Vitamin D deficiency (VDD) is associated with impaired beta-cell function, insulin resistance (54), and micro and macro-vascular complications of DM progression. A recent systematic review and meta-analysis of 1115 patients reported that severe VDD increased DFU risk by 3.2 times (55). Interestingly, Darlington et al. observed similar vitamin D levels between DM and DFU patients but with poor DFU outcomes (25). Pena et al. identified VDD to be dominantly prevalent (55.7%) among DFU patients (6). Dai et al. proposed vitamin D levels below 13.68 ng/ml as the threshold for DFU risk (37).

Vitamin D positively improves immunological, neurological, and vascular conditions associated with DFU. Vitamin D is also an immunomodulator that facilitates T and B cell activation by macrophages. Gupta B and Singh SK showed that macrophages treated with vitamin D3, *in vitro*, enhanced phagocytosis in DFU setting (26). Vitamin D inhibits T-helper cells-1 (Th1) that promote cell-mediated inflammatory response while stimulating Th2 cells that aid wound healing (56). Tiwari et al. suggest 10ng/ml of 25-hydroxy vitamin D [25 (OH)D] as the threshold for immunological alterations in DM. Reports suggest that VDD is associated with an increased release of inflammatory cytokines (TNF-α, IL-1β, IL-6) in DFU patients (48). Vitamin D induces the transcription of cathelicidin and defensins that aid in phagocytosis, thereby enhancing the antimicrobial innate immune system (57).

Asian DM patients with VDD are at 1.22 times greater risk for developing peripheral neuropathy than those with normal vitamin D levels (58). Basit et al. showed that 600,000 IU of vitamin D, over 20 weeks, offered significant pain relief in painful diabetic neuropathy (59). VDD may also be associated with increased sensitivity to pain (60). Swain et al. reported that nearly 52% of DFU patients with vascular calcification (VC) had severe VDD (30). Their subgroup analyses showed that the risk for VC was 2.4 times

higher in patients with vitamin D levels < 10 ng/ml. Sugden et al. demonstrated that a single high dose of vitamin D supplementation can improve the flow-mediated vasodilation of the brachial artery by 2.3% (61).

Most studies have focused on the significant role of vitamin D in DFU compared to other nutrients. We need more clinical and molecular studies to explain the results. We identified four clinical trials that estimated 25 (OH) D levels and studied the effects of vitamin D supplementation on DFU outcomes. Kamble et al. and Razzaghi et al. investigated the effect of 60,000 IU and 50,000 IU of vitamin D, respectively, for 12 weeks, in DFU healing (18, 21) and reported that supplements improved wound healing and biochemical parameters. Halschou-Jensen et al. showed that two daily doses (170 µg and 20 µg) of vitamin D supplements in chronic DFU (17) delivered a median ulcer reduction of 100% (high dose) and 57% (low dose). Mozaffari-Khosravi et al. demonstrated that a single dose of 300,000 IU of vitamin D improved DFU outcomes compared to 150,000 IU (22).

Magnesium is an essential element with a pivotal role in human physiology, especially as a cofactor for enzymatic and metabolic pathways (62). Magnesium, essential for collagen formation and tissue development, is altered in DM (63). Hypomagnesemia in DM could result from enhanced renal excretion associated with insulin resistance, glycosuria, and hyperglycemia. Diabetic autonomic neuropathy alters intestinal absorption (27) and reduces dietary intake of magnesium. Improving insulin metabolism can potentially delay vascular complications in DFU. Magnesium plays a role in the formation of malonyl-COA and inhibits voltage-dependent calcium channels that facilitate insulin secretion (20). Hypomagnesemia has been associated with abnormal platelet activity and can induce a proinflammatory response that activates systemic inflammation (64). Hypomagnesemia has also been linked with neuronal damage and diabetic peripheral neuropathy in DM patients (65, 66). Further magnesium supplementation was found to promote peripheral nerve regeneration (67).

Yadav et al. observed an inverse relationship between DM duration and serum magnesium, copper, and zinc levels (49). Rodrigues-Moran et al. provided the first evidence for hypomagnesemia as a risk factor for DFU (OR: 2.9, 95% CI: 1.7-6.8; P = 0.01) (46). Interestingly, Moon et al. have reported that hypermagnesemia is a risk factor for amputation in hospitalized DFU patients (OR:2.480; P= 0.043), which could be attributed to the association between renal disorder and hypermagnesemia (68).

Two studies have investigated the role of magnesium supplementation in DFU patients. Razzaghi et al. found that 250 mg of magnesium for 12 weeks improved the ulcer area, glycaemic parameters, and other antioxidant and anti-inflammatory parameters (20). Afzali et al. showed that 250mg magnesium plus 400 IU vitamin E can improve ulcer area, glycaemic parameters, lipid profile, and other antioxidant and anti-inflammatory parameters (16). Coger et al. have suggested magnesium supplements during the late-inflammatory and mid-proliferative phases (69).

A population-based cohort study (25,639 participants; 8-12 years) demonstrated an inverse association between vitamin C levels and incidence of DM (70). Vitamin C is a strong antioxidant, a vital co-factor in several enzymatic reactions, and promotes anti-inflammatory and pro-resolution effects in macrophages, together alleviating pro-inflammatory responses (71). Vitamin C deficiency in DM has been established, and its impact on serum malondialdehyde suggests increased oxidative stress, aggravating micro- and macro-vascular complications in DM (72).

A meta-analysis of RCTs shows that vitamin C supplements significantly improved endothelial function in DM. Vitamin C is a direct antioxidant that scavenges reactive oxygen species and enhances the bioavailability of nitric oxide (NO) (73). In 2021, an RCT (n= 16) of vitamin C supplements showed benefits on foot ulcers (74). Inadequate vitamin C supplements can cause stagnation in the proliferative and maturation phases of wound healing, thereby prolonging wound healing time (71). Vitamin C facilitates the synthesis and cross-linking of collagen, enhancing vascular integrity and capillary bed strength (75). Pena et al. identified 73% of DFU patients with suboptimal levels of vitamin C (6). An RCT by Yarahmadi et al. showed that a combination of platelet-rich plasma, fibrin glue dressing, and vitamins E and C improved wound healing of DFU by alleviating oxidative stress (76).

Dixit et al. reported a significant difference between selenium levels in patients with chronic non-healing wounds and HC (77). An *in vivo* study on diabetic mice demonstrated an antioxidant role for selenium (restoring normal antioxidant status), and as an insulin mimetic in normalizing glucose levels. Selenium can also downregulate connexin expression, which promotes anti-inflammatory and anti-apoptotic signals, in addition to enhancing angiogenesis (78). Macrophages treated with selenium promote peroxisome proliferator-activated receptor (PPAR)-γ- dependent switch from M1 to M2 phenotype in the presence of IL-4 (79), suggesting selenium's wound healing potential.

Currently, available evidence suggests that immune-endocrine effects and antioxidant properties of selenium benefit infections in DM (80). Although we did not identify any interventional studies on the effect of selenium in DFU, selenium levels were markedly different in DFU patients *vis-a-vis* HC and DM (35, 41, 42).

The strength of the current study: This is the first systematic review with meta-analysis comparing micronutrient status in DFU between HC and DM. The limitations are First: relatively small sample size in some studies. Second: most study designs were retrospective or cross-sectional, limiting the possibility of establishing a causal relationship between the micronutrients and DFU. Third: marked publication bias was observed. Fourth: cannot rule out the possibility of ecology and environment as confounders. Nevertheless, the existing challenge is to articulate the effect of these supplementations in the patient population as the number of well-designed RCT's are few.

We have observed a significant association between DFU and vitamin D, vitamin C, magnesium, copper, and selenium levels. Although other micronutrients also influence multiple phases of wound healing, we did not observe a significant association. Nevertheless, we recommend assessing micronutrient levels in DFU patients and investigating their pathological correlation. Future investigations should address the effect of specific

micronutrients in DFU management, molecular mechanisms of action of micronutrients, as well as nutrigenomic studies that reveal gene-nutrient interaction and its possible effects on DFU healing. Individual genetic variants could respond differently to micronutrients, and thus directly or indirectly influence the prevention and management of DFU. Nutrigenomic approaches would deliver a holistic and personalized approach to the management of DFU.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

SK and SM formulated the research question and designed the study. SK, TB, RB, and SM were involved in carrying out the study, analyzing the data, and interpreting the findings. SK and SM wrote the manuscript. MU, MM, KS, GR, MR, and AK, critically evaluated the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Diabetic foot complications among Indigenous peoples in Canada: a scoping review through the *PROGRESS-PLUS* equity lens

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Introduction: Indigenous peoples in Canada face a disproportionate burden of diabetes-related foot complications (DRFC), such as foot ulcers, lower extremity amputations (LEA), and peripheral arterial disease. This scoping review aimed to provide a comprehensive understanding of DRFC among First Nations, Métis, and Inuit peoples in Canada, incorporating an equity lens.

Methods: A scoping review was conducted based on Arksey and O'Malley refined by the Joanna Briggs Institute. The *PROGRESS-Plus* framework was utilized to extract data and incorporate an equity lens. A critical appraisal was performed, and Indigenous stakeholders were consulted for feedback. We identified the incorporation of patient-oriented/centered research (POR).

Results: Of 5,323 records identified, 40 studies were included in the review. The majority of studies focused on First Nations (92%), while representation of the Inuit population was very limited populations (< 3% of studies). LEA was the most studied outcome (76%). Age, gender, ethnicity, and place of residence were the most commonly included variables. Patient-oriented/centered research was mainly included in recent studies (16%). The overall quality of the studies was average. Data synthesis showed a high burden of DRFC among Indigenous populations compared to non-Indigenous populations. Indigenous identity and rural/remote communities were associated with the worse outcomes, particularly major LEA.

Discussion: This study provides a comprehensive understanding of DRFC in Indigenous peoples in Canada of published studies in database. It not only incorporates an equity lens and patient-oriented/centered research but also demonstrates that we need to change our approach. More data is needed to fully understand the burden of DRFC among Indigenous peoples, particularly in the Northern region in Canada where no data are previously available. Western research methods are insufficient to understand the unique situation of Indigenous peoples and it is essential to promote culturally safe and quality healthcare.

Conclusion: Efforts have been made to manage DRFC, but continued attention and support are necessary to address this population's needs and ensure equitable prevention, access and care that embraces their ways of knowing, being and acting.

Systematic review registration: Open Science Framework https://osf.io/j9pu7, identifier j9pu7.

KEYWORDS

diabetes, foot ulcer, lower extremity amputation, indigenous peoples, diabetic neuropathy, peripheral arterial disease, health equity

1 Introduction

The estimated population of Canada is 40 million and the diabetes rate is rising (1, 2). Canada's Constitution Act (1982) recognizes three distinct groups of Indigenous peoples: First Nations, Inuit and Métis, and they account for around 5% in Canada's total population (3, 4). Approximately 58% of the Indigenous population in Canada identifies as First Nations (5). The demographic of this population is growing rapidly, and young people are more exposed to diabetes and its complications (3, 6–8). Indigenous peoples are affected by type-2 diabetes 3 to 5 times higher than the general population and this chronic disease is one of the fastest increasing health issues among this population (7). Indigenous peoples worldwide, including in Canada, are disproportionately affected by diabetes due to many factors such as genetic predisposition, new environmental exposures, poverty, scarcity of resources and many other barriers that can affect an optimal diabetes care (e.g., geographical isolation, educational status, employment disadvantage, both cultural and linguistic differences) (9, 10). From an Indigenous perspective, rooted in a holistic understanding of health, diabetes is perceived as being associated with the processes of colonization, notably through the loss of traditional ways of life and spirituality, socio-economic marginalization, socio-cultural upheaval, stress and racism (11).

Indeed, Indigenous peoples are diagnosed with diabetes at a younger age, have greater severity of diagnosis, develop higher rates of complications and experience poorer treatment outcomes (12). These outcomes are greater with remote and rural populations (13). Compared to non-First Nations, older First Nations individuals with diabetes are at greater risk of diabetes-specific hospitalization and this can be challenged in regard to ethnocultural considerations and the geographical realities (14). They are also more at-risk of experiencing diabetes-related foot complications (DRFC) such as diabetic foot ulcer (DFU), lower extremity amputations (LEA), infections, foot deformities, Charcot neuroarthropathy, peripheral arterial disease (PAD) and neuropathy (12, 15).

Up to 34% of people with diabetes will develop a DFU during their lifetime which is a significant cause of disabilities, reduces quality of life and can lead to premature death (16). Moreover, LEAs, which are an estimated potential outcome for 1 in 5 DFUs, have an estimated 5-year mortality rate of 51% after a major LEA (16, 17). Personal, societal and economic outcomes of DRFC highlight the importance of supporting prevention strategies for the at-risk population and implementing effective team management approach (18, 19). It is even more important to act towards populations facing at time multiple and intersecting oppression, such as Indigenous peoples, since ethnicity has been identified as a predictor of worse outcomes such as LEAs and health care marginalization (15, 20, 21). It is even more appropriate to talk about the colonization and oppression rather than ethnicity which has led to the worst outcomes for this population and therefore this population has particular cultural needs (22). Thereafter, we refer to indigenous identity and not to ethnicity to respect these peoples. The effect of rurality is also closely associated especially for LEAs (15, 23, 24). Some evidence is published worldwide about diabetic foot disease and DRFC among Indigenous peoples (10, 25, 26), but the specific portrayal of DRFC for Indigenous peoples in Canada is lacking. It is recognized that there are health inequities and disparities as well as poor health care experience for this population (27, 28). Therefore, the aim of this scoping review is to map the existing literature related to diabetic foot disease among Indigenous peoples in Canada based on a western systematic methodology and incorporating an equity lens.

2 Methods

The present study will follow the six-stage approach developed by *Arksey and O'Malley* (29), refined by *Levac* and *Colquhoun* (30, 31), and also described by the Joanna Briggs Institute (32). Those stages are mentioned thereafter. Reporting will be compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR) Checklist (33). The iterative nature of scoping review includes refinement of specific sections of the method as the review progresses. This project has been registered on Open Science Framework (https://osf.io/j9pu7/).

2.1 Stage 1: research questions and definitions

2.1.1 Detailed research questions of interest

Based on PICO strategy (34): What are the data regarding diabetes-related foot health outcomes (O) among Indigenous peoples in Canada (P), whether compared to the general population or not (C), for all types of health interventions including epidemiological surveillance data (I). Specific questions were:

- What is the available data on DRFC such as DFU, LEA, diabetic foot infection (DFI) experienced by Indigenous peoples in Canada?
- What is the available data on diabetes foot disease risk factors such as foot deformities, Charcot neuroarthropathy, PAD and neuropathy in Indigenous peoples in Canada?
- What is the available data on diabetic foot disease and DFRC on quality of life and mortality?
- What are other relevant variables such as patient-related outcomes and patient-related experiences related to this topic in Indigenous peoples in Canada?
- Does the reported data on this topic include demographic and equity factors based on the *PROGRESS-Plus* framework (35)?
- Do the included studies report any collaborations and/or partnerships with Indigenous peoples and/or community related to patient-oriented/centered research (36)?

The *PROGRESS-Plus* framework was developed for describing and assessing equity related to the social determinants of health within and across populations (37). Patient-oriented/centered research (POR) can support equity-focused health care research with Indigenous peoples, as the research findings are based on their needs, perspective and context as active stakeholders in the process (36, 38).

2.1.2 Definitions

The broad concept of interest in this study was to identify the burdens of diabetic foot disease/DFRC experienced by Indigenous peoples in Canada. Diabetic foot disease/DFRC were mostly defined by the International Working Group on the Diabetic Foot (IWGDF) criteria and definitions (39). The "diabetic foot ulcer (DFU) "is defined as a break of the skin of the foot, that involves as a minimum the epidermis and part of the dermis, in a person with currently or previously diagnosed with diabetes and usually accompanied by neuropathy and/or peripheral arterial disease within the lower extremity; "neuropathy" is defined as the presence of symptoms or signs of nerve dysfunction in a person (a history of) with diabetes, after the exclusion of other causes. This can also include loss of protective sensation characterized by an inability to sense light pressure (10 g Semmes-Weinstein monofilament); "Peripheral artery disease" (PAD) is defined as an obstructive atherosclerotic vascular disease with clinical symptoms, signs, or abnormalities on non-invasive or invasive vascular assessment, resulting in disturbed or impaired circulation in one or more extremities. This can cause claudication and rest pain. "Infection" is defined as a pathological state caused by invasion and multiplication of microorganisms in host tissues accompanied by tissue destruction and/or a host inflammatory response; "lower extremity amputations (LEA)" is defined as a resection of a segment of a limb through a bone or through a joint; Charcot neuroarthropathy (Charcot foot) is a non-infectious destruction of bone(s) and joint(s) associated with neuropathy, which, in the acute phase, is associated with signs of inflammation (39). "Foot deformities" are defined as structural and functional foot deformities occurring with diabetes and motor neuropathy causing atrophy and muscle imbalances such as claw and hammer toes, prominent metatarsal heads, *pes cavus*, *pes equinus*, hallux *limitus* or *rigidus* and *hallux abductovalgus* (40). The Western "health-related quality of life" refers to an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the individual's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment as they relate to the DRFC context (41).

2.2 Stage 2: identifying relevant studies

The search protocol and strategies were developed by two members of the research team (VB and JP) and revised by another team member (MBF). The primary information source included systematic search from the following database: 1) MEDLINE, 2) CINAHL, 3) EMBASE, 4) Cochrane Library, 5) Native Health Database, 6) Government Health Indigenous Affairs Departments of the United States/Canada and 7) LiSSa. The secondary information source included reference lists as well as citation searches of related relevant citations. Canadian clinical guidelines from major organizations with an interest towards in diabetic population were reviewed. Grey literature was assessed through Google Scholar, Open Access Theses and Dissertations, ProQuest, ClinicalTrials.gov and Réseau Santécom. The search strategy, limited to articles in English and French, was developed for MEDLINE database (Supplement Material 1), with the assistance of a qualified librarian and involved a combination of key terms and concepts (MeSH, non-MeSH, key terms and free

vocabulary). The search strategy was adapted for other databases and identical terms translated to French were used to search in selected French-language databases. This review had searched articles from inception up to August 29th, 2022. Citations from all information sources were merged and duplicates removed using EndNote (version 20.4, Clarivate Analytics, 2022).

2.3 Stage 3: study selection and criteria

Two independent reviewers (VB and JP) initially met to clarify the following inclusion criteria:

- Population: Adult (18 years and older) Indigenous peoples in Canada with either type-1 or type-2 diabetes with any DRFC or disease;
- Intervention: Any interventions including none;
- Comparator(s)/control: Other populations or none;
- Outcomes: Results pertaining or describing data about DRFC on DFU, LEA, DFI, quality of life, mortality, foot deformities, Charcot foot, PAD, neuropathy or other relevant data about DRFC (e.g., DFU recurrence, genetics, etc.);
- Settings: Any clinical settings or community;
- Languages: English or French

Exclusion criteria were:

- Publication/study design: Conference or meeting abstracts, commentaries, letters and correspondences, Editor's response, protocol descriptions;
- Population: Individuals who were not considered as Indigenous in Canada (e.g., native from other countries); gestational diabetes; wounds, amputation or death in the absence of a diagnosis of either type-1 or type-2 diabetes.

The search strategy was completed by one of the authors (VB). Two arms of reviewers (VB/JP and VB/SL) have independently screened titles and abstracts using eligibility criteria. Then, relevant papers were read entirely, and eligibility criteria were systematically applied. Disagreement was settled using a consensus approach between reviewers and a third person intervened if required (MBF). Eligibility criteria were clarified following a training exercise on the first 300 citations and inter-rater agreement (kappa statistic) was greater than k=0.70, signifying substantial agreement, and then selection was completed (42).

2.4 Stage 4: charting the data

A Microsoft Excel (Microsoft Corporation) spreadsheet served as the data extraction form developed by the two reviewers (VB and AML) and updated by an iterative manner during the full article revision process. The data-charting form includes the PICO elements, "*PROGRESS-PLUS*" factors (place of residence, race/ethnicity/identity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) including age and disabilities for the equity lens, year of publication, authors, study location, study design, type of data, sample sizes, aims of study and important results extracted from selected articles (35). We also identified whether a patient-oriented research strategy was integrated or not. The extraction of all information was conducted by one reviewer (VB) and double-checked by one of two reviewers (JP and SL).

2.5 Stage 5: collating, summarizing and reporting results

A visual flow diagram (PRISMA) outlined the decision-making in the study selection process (33). Frequency measures such as numbers and their percentages numerical summary for the overall study characteristics and a narrative synthesis was conducted, centered on every variable aimed to answer our research sub-questions on Indigenous peoples in Canada. We have also aggregated the results in tables to identify the elements associated with equity, the integration of patient-oriented research, and the key findings from included studies. Risk of bias assessment is not mandatory in a scoping review, as many different study designs are included. However, two reviewers (VB and ST) conducted an appraisal based mixed methods appraisal tool (MMAT) and chose *at posteriori* according to the studies included (43).

2.6 Stage 6: consultation

Even though consultation of knowledge users (e.g., clinicians, citizens, patients and caregivers, decision makers, other researchers) is optional, it enhances the methodological rigor and the validity of the review. Thus, to gain appreciation of the review's findings, the lead reviewer (VB) approached diabetic foot disease and Indigenous stakeholders in Canada to provide voluntary insights about our review.

3 Results

3.1 Search and selection

A total of 5, 323 records were identified from bibliographic databases and 18 from additional searches. All duplicates were removed with Endnote and 2, 526 titles were screened. We retained 40 studies that reported data on diabetic foot disease for Indigenous peoples in Canada, as represented in the flow diagram (Figure 1) (44–81). Some included studies have described similar dataset/population [(75, 79) (80, 81) (48, 64) (44, 82); and (49, 78)] and therefore, they were merged and reported together for a same study design/similar outcomes or separately for significant differences (13, 52) and (50, 60) (Table 1).

3.2 General characteristics of included studies and population

General characteristics of the included studies and population are presented in the Table 1. The studies were published between

1985 and 2021. Most (51%) were published between 2000 and 2010 (52–70, 76, 82) and between 2010 and 2021 (39%) (44–51, 75, 77–79). Five percent were published between 1985 and 1990 (73, 74) and another five percent between 1991 and 2000 (71, 72). The majority of the studies were quantitative (86%), with the majority (61%) using a descriptive cross-sectional design (44, 47, 48, 50, 51, 53–57, 59–64, 66, 68–70, 72–74, 76) and the remainder (22%) using an observational cohort design (45, 46, 49, 52, 75–77, 80). There were also three qualitative studies (8%) (58, 67, 71) and two mixed-method studies (6%) (65, 81). Various types of data were reported such as administrative data (44, 46, 49, 53, 57, 59, 68, 70, 74, 75, 77, 79) and registry (58, 80, 81), self-reported data (47, 54, 55, 66), retrospective chart review data (50, 51, 61–63, 65, 69, 72–74), prospective data (e.g., physical examination, interviews, focus, questionnaires, etc.) (52, 56, 58, 60, 63–67, 71, 73, 76, 81) and data from a previous prospective study (48). The majority of studies were conducted in Indigenous population in Manitoba, followed by those living in Ontario. One study was pan-Canadian and the provinces and territories were not specified (54). No study included the Yukon, Nunavut and the Northwest Territories population. The Atlantic region was poorly represented with only three studies (but two with the same dataset) that included Newfoundland and Labrador in the overall study (51, 80, 81). The situation was similar for Saskatchewan (51, 75, 79).

Of the 40 studies included, the most published data were focused on First Nations (92%). Only one study (3%) did not distinguish specifically the identity of its population (i.e., First Nations, Métis, or Inuit) (47). Inuit were less represented, being included in only in one study (3%) (62). Métis were represented in a quarter of the studies (26%) (49, 50, 53, 60–63, 65, 67). All studies included at least 332,233 individuals from Indigenous peoples in Canada. The residential area of the community was mentioned for only 53% (19/36) of included studies from which eight studies clearly mentioned the population living on communities (i.e., on reserve) (52, 55, 56, 59, 64, 68, 77, 80, 81). Ten studies did not report demographic data about population with diabetes and/or Indigenous peoples only (47, 49, 50, 54, 62, 63, 66, 69, 70, 79). All

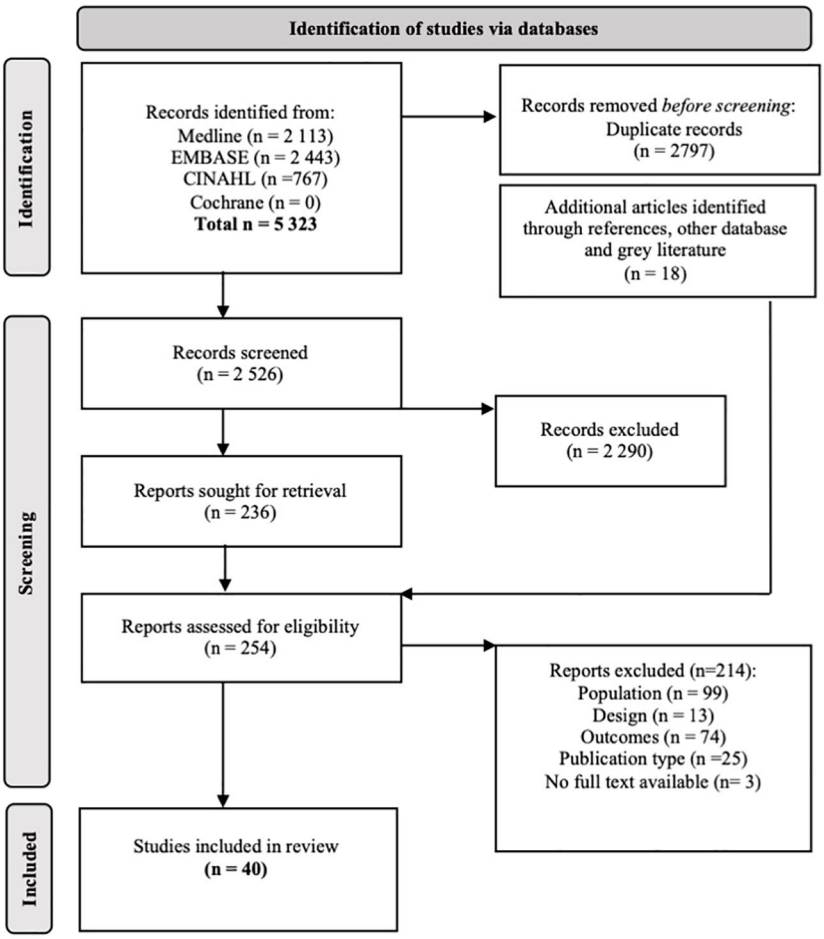

FIGURE 1
Study selection flowchart. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Open Access.

TABLE 1 Overview of included studies (n= 40).

First author	Year	Study Design	Data	Canadian Location	Indigenous people			DFU	LEA	N	PAD	FD/C	M	DFI	QoL	ORV
					FN	M	I									
Chan	2021	CS	Administrative Database	On	√				√							
Essien†	2020; 2021	CS	Administrative Database	SK	√				√		√					
Pace†	2020	CS	Registry Data	BC, AB, MB, ON, QC, NF	√					√						
Hayward†	2020	MMS	Workshops, Registry data, Chart Review	BC, AB, MB, ON, QC, NF	√					√						
Shah	2019	CSS	Administrative Database	ON	√				√		√		√			√
Loewen	2017	CS	Census and Administrative Database	ON	√				√							
Turin	2016	CS	Administrative Database	AB	√						√					
Al Sayah	2015	CSS from CS	Self-Reported (self-administered questionnaires); Administrative Database	AB	NA	NA	NA	√	√	√	√			√		
Maple-Brown†	2012	CSS	Data from Hanley 2005	ON	√			√	√	√	√					
Martens†	2010 updated in 2012; 2002	CS	Administrative Database	MB		√			√							
Reda	2012	CSS	Chart Review	MB	√	√		√	√	√	√	√				
Harris	2011	CSS	Chart Review	BC, AB, SK, MB, ON, QC, NF	√				√	√	√					√
Oster	2010	CS	Physical Examination	AB	√											√
Shah†	2010; 2011	CSS	Administrative Database	ON		√			√							√
Lovell	2009	CSS	Self-Reported (Phone survey)	NA - pancanadian	√						√					
Oster	2009	CSS	Self-Reported	AB	√			√		√						√
Bruce	2008	CSS	Physical Examination	MB	√			√	√	√						
Dannenbaum	2008	CSS	Administrative Data	QC	√			√	√	√	√					
Attawar	2006	Q	Interviews, Registry Data, Physical Examination	MB	√			√	√	√	√	√			√	
Virani	2006	CS	Questionnaire, Physical Examination, Chart Review	AB	√											√
Martens†	2007	CSS	Administrative Database	MB	√				√							
McIntyre	2007	CSS	Chart Review, Physical Examination and Interviews	MB	√	√		√	√	√	√	√	√	√		√

(Continued)

TABLE 1 Continued

First author	Year	Study Design	Data	Canadian Location	Indigenous people			DFU	LEA	N	PAD	FD/C	M	DFI	QoL	ORV
					FN	M	I									
Rose	2007	CSS	Chart Review	MB	√	√		√	√							√
Goulet	2006	CSS	Chart Review	MB	√	√	√		√		√					√
Reid	2006	CSS	Interview, Physical Examination, Chart Review	MB	√	√		√	√	√	√	√				√
Hanley	2005	CSS	Physical Examination, Laboratory Analysis, Questionnaire	ON	√					√	√					
Meatherall	2005	MMS	Chart Review and Questionnaire	MB	√	√			√						√	
Pollex	2005	CSS	Physical Examination, Self-Reported, and Laboratory	ON	√						√					
Iwasaki	2004	Q	Focus Groups	MB	√	√										
Légaré	2004	CSS	Administrative Database, Registery	QC	√				√							
Thommasen	2004	CSS	Chart Review	BC	√					√	√					
Jin	2002	CSS	Administrative Database	BC	√					√						
Hernandez	1999	Q	Interview	ON	√				√				√			
Brassard	1995	CSS	Chart Review	QC	√					√	√					√
Macaulay	1988	CSS	Chart Review, Interview and Physical Examination	QC	√				√	√	√					
Young	1985	CSS	Administrative Database and Charts Review	MB, ON	√					√						

†Similar population/dataset (Essien 2020 and 2021; Pace 2020 and Hayward, 2020; Mapple-Browns 2012 and Hanley 2005 ; Martens 2002, 2007, 2010 and 2012; Shah 2010 and 2011)
MMS, Mixed-method study; CSS, Cross-sectional study; Q, Qualitative study; CS, Cohort study; MB, Manitoba; QC, Québec; SK, Saskatchewan; ON, Ontario; BC, British Colombia; AB, Alberta; NF, Newfoundland and Labrador; FN, First Nation; M, Métis; I, Inuit; NA, Not available; DFU, Diabetic foot ulcer; LEA, Lower extremity amputation; N, Neuropathy; PAD, Peripheral arterial disease; FD/C, Foot deformities or Charcot; M, Mortality; DFI, Diabetic foot infection; QoL, Quality of life; ORV, Other relevant variables.
√ means that it fits the category of the colon.

details about the population are presented in Supplemental Material 2.

3.3 Diabetes foot disease and complications outcomes

Nine studies did not present clear outcomes: microvascular disease including neuropathy, retinopathy and nephropathy (80, 81), surgery for leg circulation, including LEA (77), other atherosclerosis (including gangrene and other peripheral vascular disease) and neuropathy and amyotrophy (70), PAD (including ischemic feet, LEA and claudication) (73), microvascular disease including ischemic heart disease, cerebrovascular disease and peripheral vascular disease (72), ulcers or sores on their feet and legs (55), foot or leg ulcers or infection/gangrene or LEA (47) and precise type of amputation (i.e., lower, upper, traumatic, etc.) not mentioned (51). Therefore, their data are detailed in the Supplemental Material 2. and sparsely integrated. Studies that reported results for Indigenous peoples with comparators are presented in Table 2. The main results are also summarized in the following subsections.

3.3.1 Diabetic foot ulcer

Ten studies provided data on DFUs (Table 1) (47, 48, 50, 55–58, 60, 61, 63). The prevalence of DFU ranged from 1% to 39% (47, 48, 50, 55, 57, 58, 60), and the prevalence of a history of DFU from 32% to 75% (58, 60). Only one person had a history of DFU in a population of 483 First Nations people (56). Six to fifteen percent of individuals had a history of DFU or had active DFU (13, 63).

3.3.2 Lower extremity amputation

Twenty-four studies provided data about LEAs, and thus it is the most studied outcome (44, 46–51, 53, 56–63, 65, 68, 71, 73, 75, 77–79). The incidence of LEA varied among communities and was estimated to range between 1.19 à 6.16 per 1,000 persons, and rates of LEA were inversely related to the access to specialists (59). The prevalence was estimated between 0 and 36% in this population (48,

TABLE 2 Major findings concerning diabetic foot outcomes for Indigenous peoples[†].

Author, Year	Trends for the Indigenous peoples	Comparator
Essien, 2020;2021[‡]	↑: Overall LEA rate*; Primary LEA*; Subsequent LEA*; Major LEA*; Minor LEA* ↑: Post-operative acute care length of stay* Age-adjusted ↑: LEA rate for people aged of 50 years and over for both population; LEA rate* Sex-Adjusted ↑: LEA rate for males in both population Indigenous female almost twice likely to have a LEA* Indigenous male at higher risk*	Non-Indigenous Population with or without diabetes; Population with LEA
Shah, 2019	Number of revascularization procedures are comparable, but PAD may be underdiagnosed. ↑: LEAs are 3-5 times higher; For people aged of ≤ 44 years: LEA are 6 times more frequent; LEA rates associated with increased age and rurality. Remote community is associated with LEA in both populations. ↑: LEAs in Indigenous female* than non-indigenous female*; LEAs in Male* ↑: 15% of mortality* Disparity associated with poor access to care, specialized services for wounds care and rehabilitation	Non-Indigenous population
Loewen, 2017	LEA rate is 7 times the provincial rate* Rate for major LEA (below-knee amputation) is 3 times higher* at a lower age	Non-Indigenous population with diabetes data available
Turin, 2016	↓: PAD (0.2% vs. 0.6%)	Non-Indigenous population
Maple-Brown, 2012	↑: Neuropathy*	Other Indigenous population (Australia)
Martens, 2010;2012[‡];2002	↑: LEA rate*, but similar risk of LEAs with controlled age, sex, income, geographic area, mental and physical comorbidities, continuity of care ↑ similar LEA risk for males, older, living in neighborhood income areas and for those with comorbidities for both population ↓: LEA rate when seeing the same physician for a 2-year periods for both population* ↓: LEA risk associated with continuity of care* 2002: twice ↑ LEA rate for Metis* compared to other Indigenous population and 30 times the non-Indigenous population	Non-Indigenous population with diabetes; Other Indigenous population
Shah, 2010	LEA rate (adjusted sex and age) comparable	Non-Indigenous population with diabetes
Martens, 2007	↑: LEA adjusted sex/age rate* and even more ↑ in some community (Dakota Ojibway Tribal Council) * LEA rate is inversely proportional to specialist access	Non-Indigenous population with diabetes; between the indigenous communities of Manitoba
McIntyre, 2007	Absent Dorsalis Pedis pulse* ↑: History of DFU*, Charcot Foot*, mean number of DFU*, DFU with prior osteomyelitis* ↑: Number of LEA* Reason for inadequate foot care: financial cost, lack of family support, language barrier Risks associated with mortality for both population: number of DFU in the patient history, the proportion of patients with either: an absent dorsalis pedis pulse, prior myocardial infarction, LEA, prior angiogram, not performing a daily foot inspection, occluded vessel detected by angiography	Non-Indigenous population (Caucasians, Filipinos, Asians, east Indians, Blacks)
Rose, 2007	↓: Time from initial visit to major LEA*; also correlated with living in rural or remote communities* Survival time without LEA: risk factors associated with indigenous ethnicity, non-urban residence, and PAD Indigenous ethnicity is not associated with risk factors for poor DFU outcomes Indigenous patients with a DFU had a LEA approximately 12 weeks earlier than in non-indigenous patient with a DFU	Non-Indigenous population (Caucasians)
Goulet, 2006[‡]	↑ Indigenous people with PAD and diabetes required revascularization bybass*, risk factors are lower age* and end-stage renal disease* Indications for bypass procedure: rest pain*, claudication*, gangrene*, non-healing DFU*, acute ischemia ↑ LEA (at the revascularization procedure): at least one toe*, forefoot* Complications after revascularization are not significant (limb loss, wound infection, death)	Non-Indigenous population
Pollex, 2005[‡]	No significant association between MTHFR genotype and intermittent claudication ↑ PAD: Gene MTHFR 677T carriers (677T allele*)	Other Indigenous population (without the gene)
Jin, 2002[‡]	Trends to ↑ neuropathy, amyotrophy, hospitalization, atherosclerosis (including gangrene and PAD)	Non-Indigenous population
Macauley, 1988	↑ PAD (including ischemic foot, amputation, claudication)* Low rate of neuropathy	Indigenous population without diabetes (Mohawks)

[†]Studies without comparative groups/data were excluded (n=10) ; Studies with not clear outcomes were excluded (n= 4).
[‡]Not specific data for the population with diabetes type 2 only and/or indigenous people only (n = 10).
*Statistically significant.
↑, Augmentation/Increase.
↓, Diminution/Decrease.
LEA, Lower Extremity amputation; PAD, Peripheral Arterial Disease; DFU, Diabetes Foot Ulcer.

49, 51, 57, 60). Studies have estimated that the prevalence of LEA was 7 to 49 times higher than the Indigenous population with diabetes than in the non-Indigenous population without diabetes (46, 49, 58, 78). A study identified that LEA's frequency was 3 to 5 times higher to the non-Indigenous comparative across sex, age and location (44). Among people with diabetes, Ethnicity, or colonization, as experienced by people identifying as Indigenous would lead to a 1.7-fold increase in the risk of having LEA (75). Specifically, in the Métis population, the sex- and age-standardized LEA rate was equivalent to that of the entire population with diabetes (82). Their risk of LEA was similar compared to other Manitobans after controlling sex, age, income, geographic area, mental and physical comorbidities and continuity of care (49). However, a higher risk of LEA was identified in Métis male *vs.* female (59).

The risk factors for LEAs, similarly to non-Indigenous peoples, were male sex, living in low-income area, living with comorbidities, and being older. A protective factor was to see the same physician for at least one half of their visit over the two-year period (49, 75). Among those aged 44 years or younger, the frequency of LEA was six times higher and living in a remote community was a high-risk factor for LEA (44). The first major LEA on Indigenous peoples occurred at a younger age (65), Indigenous peoples had a shorter average time from initial clinic visits to major LEA compared to non-Indigenous population which also correlated with living on rural or on reserve (61). When controlling the effect of the place of residence (i.e., rurality and on reserve), Indigenous identity was not associated with poorer outcomes such as LEA and death, but early LEA was associated with non-urban residence, identity and arterial insufficiency (61). Indigenous patients with DFU are at-risk of LEA approximately 12 weeks earlier than non-Indigenous patients (61). A study has reported that on average, Indigenous peoples had less phantom limb pain (65). A study related to diabetes has observed seven hospitalizations, totalizing 81 days of hospitalization over a 5-year period related to five cases of amputations (68). Finally, LEA trends (i.e., overall LEA rate, primary LEA, subsequent LEA) increased over a 13-year period by about 5% over this period compared to the trend in the non-Indigenous population which was more stable or declining (75).

3.3.3 Neuropathy

Eighteen studies provided data about neuropathy (13, 47, 48, 50, 51, 56, 58, 63, 64, 69, 70, 72–74, 80, 81). The prevalence of neuropathy ranged from 5% to 94% (47, 56, 58, 60, 63, 64, 72–74). Prevalence of neuropathy was reported higher in Indigenous peoples in Canada compared to the one from Australia (48). Among Indigenous peoples, the likelihood of developing neuropathy was 2.7 times higher for women than for men and 3 times higher for those who had completed less education than for those who had completed grade 9 or higher. The risk of neuropathy was twice as high for a person with a glycated hemoglobin level of 9% compared to 6%, and 3 times higher for heavy smokers (56).

3.3.4 Peripheral arterial disease

Eighteen studies provided data about PAD (44, 45, 47, 48, 50, 51, 54, 57, 58, 60, 62–64, 66, 69, 72, 73, 75). PAD prevalence was estimated between 0.2% to 23.0% (47, 48, 51, 57, 64, 69, 75). A genetic mutation that may be present particularly in Indigenous peoples is significantly associated with an increased risk of PAD (66). It was found that 92% of Indigenous peoples with diabetes and PAD required more bypass revascularization compared with 42% in the non-Indigenous population (62). Indigenous peoples also had a greater burden of PAD symptoms (i.e., claudication, rest pain, gangrene and acute ischemia) than the non-Indigenous (62).

3.3.5 Foot deformities and charcot neuroarthropathy

Four studies provided data related to foot deformities and Charcot neuroarthropathy (50, 58, 60, 63). Foot deformities were estimated to be between 16% and 51% in Indigenous peoples and included hallux valgus, claw toes, hallux rigidus, flat feet, cavus feet, long second toe, ankle deformity, heel pad atrophy, dorsal exostosis (58, 63). There was more Charcot neuroarthropathy in the Indigenous group with end-stage renal disease than in a similar non-Indigenous group (60). In a study, Charcot neuroarthropathy was a very rare condition estimated at less than 1% of the population (63).

3.3.6 Mortality

Three studies provided data related to mortality and DRFC (44, 60, 71). Mortality (age- and sex- adjusted) after LEAs was 15% higher in Indigenous peoples than in non-Indigenous peoples, with a median survival of 3.5 years compared to 4.1 (44). First Nations people with diabetes were very concerned about the loss of freedom, mortality and LEA (71). Risk factors for mortality were the same for the Indigenous and comparative populations i.e. mean number of prior DFU, the proportion of patients with either an absent dorsalis pedis pulse, prior myocardial infarction, LEA, prior angiogram, not performing a daily foot inspection, occluded vessels detected by angiography (60).

3.3.7 Diabetic foot infection

Two studies provided data related diabetic foot infections (47, 60). In patients with diabetes and end-stage renal disease, DFUs had significantly greater prior osteomyelitis amongst Indigenous peoples compared to their non-Indigenous counterparts (60).

3.3.8 Quality of life

Three studies provided data related to diabetic foot disease and quality of life (58, 65, 67). Indigenous peoples reported having suffered from LEA for the rest of their life and living in fear of the future (for themselves and their families). They realized that they have to live with these DRFC on a daily basis and were stressed about living another 20 years because they realized that it may get worse (67). There was no difference between Indigenous and non-Indigenous peoples in their feelings of distress related to DRFC. They expressed feelings of regret, self-blame, and guilt about their general health, diabetes, and LEA (65). Many Indigenous peoples reported chronic and persistent foot pain, which affected their quality of life. LEA has changed their lives as it restricted their ability to participate meaningfully in their community (58).

3.3.9 Other relevant data

There were 11 studies that provided insights about other relevant data detailed in Supplemental Material 2. Over a 7-year period, for 169 people with 498 DRFC, this resulted in 18% emergency room visits, 16% hospitalizations, 11% elective transfers and 6% emergency transfers (63). Progression of poor clinical outcomes in this population is associated with referral with a lesion, age greater than 60 years, prior LEA or vascularization, PAD, more than one lesion at presentation, longer duration of diabetes, higher grade of DFU on the Wagner classification (61). The reasons for inadequate foot care are associated with financial cost, lack of family support, and language barriers (60). Despite interventions to achieve the recommended practice guidelines and recommendations, there is still limited foot screening in this population (76, 81). Foot abnormalities are more common in Indigenous men (52), and unspecified diabetic foot disease was estimated to 35% of the population from 19 different Indigenous communities (51). The revascularization rate (age and sex adjusted) is equivalent to the non-Indigenous and Indigenous populations with diabetes (82), and the Indigenous population presented worsen symptoms before revascularization (62). Health disparity related to DRFC in Indigenous population may be driven in part by poor access to health care, particularly specialized services for wound care and rehabilitation and especially because of their residency in remote communities (82). Indigenous identity is associated with prolonged postoperative acute care length of stay after a LEA (79).

3.4 Equity lens and patient-oriented research

We have listed the different factors of the *PROGRESS-Plus* framework in Table 3 for the included studies. The most frequently included factors in ascending order were place of residence, sex, race and age. One study included all factors (58). Education, income, and social per capita were minimally included in the included studies. There was little data on the occupation of the Indigenous population. Religion and spirituality were not discussed in any study. Patient-oriented research has been clearly mentioned in six studies representing 17% of included studies (49, 51, 58, 75, 77–79, 81), and it was particularly favored in the last decade. Details about the integration of patient-oriented research are also displayed in Table 3. None of those studies has used the *GRIPP-2* tool to reported patient and public involvement in research (83).

3.5 Bias

We conducted a critical quality appraisal of the included studies, and the results are presented in Figure 2. All three qualitative studies were of good quality. One of the mixed-method studies was good (81). The quality of the non-randomized qualitative and descriptive studies was variable but mostly of average quality. It was highlighted by the consultation that there is substantial bias in that the bulk, if not all, studies included were led by non-Indigenous people using non-Indigenous methodology.

3.6 Consultation

Six stakeholders from the Indigenous peoples and/or working very closely with them were consulted about this review: a citizen, a patient with DRFC, a caregiver, a clinician, a decision-maker and a researcher. These people chosen from our networks are from different communities and representing three different provinces. Their feedback was incorporated into this review.

4 Discussion

Our objective was to map the existing literature published in database related to diabetic foot disease among Indigenous peoples in Canada based on a systematic methodology and incorporating an equity lens. Thus, Indigenous peoples experience a heavy burden of diabetic foot disease compared to the non-Indigenous population. LEA, the most reported complications, are higher in Indigenous peoples. Very little is reported on patient-reported experience and outcomes related to DRFC. Besides, studies mainly report on First Nations and Métis data, with very little representation for Inuit people. Data on Inuit living with diabetes in Northern communities in Canada is limited, as they represent the least populated group in the Indigenous population (3). Their voices are still less represented in diabetes research which is coherent with our results (85). We examined our results from three perspectives: trends in DRFC, the equity lens, and POR.

4.1 Trends in diabetes-related foot complications and diseases

The trends identified in this study confirm a high level of DRFC in this population, but it may be only the tips of the iceberg. DRFCs affect more Indigenous men than Indigenous women and both sexes are at higher risk for LEA at a younger age than non-Indigenous people. In addition, there is a significant effect of the place of residence where rural and remote communities are associated with increased numbers of LEA. These trends are consistent with those demonstrated previously (10, 86, 87). Indigenous identity is associated with LEA in Indigenous peoples of Australia (88). Recent studies in the United States on race and rurality have identified their association resulting in more LEA events, both major and minor (24, 89). Indeed, deficiencies of specialized care and the effect of rurality on LEA was also demonstrated similarly as highlighted in our review (24). LEAs are amplified by race, particularly in ethnic minorities groups of a population (24). In general, LEAs are also more prevalent among men (90), and this trend was also identified amongst the Indigenous population in Canada. Similarly, the same trend was identified with respect to age, with the mean age of first LEA being younger among

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TABLE 3 PROGRESS-Plus Factors and Patient-Oriented Research Data in the Included Studies.

Author, Year	P	R	O	G	R	E	S1	S2	+	Details *plus* factors	POR	Comments regarding POR
Chan, 2021	■	■		■				■	■	Age	■	Data planification and collection; Consent of the leader of the community to publish data.
Essien, 2020;2021		■		■			■		■	Age	■	Multidisciplinary patient-oriented research team comprised of people with amputation, caregivers, researchers, educators, and health care providers. Not stated if people from Indigenous communities.
Pace, 2020	■	■		■					■	Age		Not reported
Hayward, 2020	■	■		■				■	■	Age	■	Integrated community as partners in developing culturally relevant innovations and improved care/access. FORGE-AHEAD is co-designed.
Shah, 2019	■	■		■					■	Age		Not reported
Loewen, 2017		■		■					■	Age		Not reported
Turin, 2016	■	■		■			■		■	Age		Not reported
Al Sayah, 2015	■	■		■		■	■		■	Age		Not reported
Maple-Brown, 2012		■		■					■	Age		Not reported
Martens, 2010;2012; 2002	■	■		■			■		■	Age	■	Wellness-lens approach and partnership; Culturally coherent; Holistic approach to knowledge translation
Reda, 2012									■	Disability: hemodialysis/ end-stage renal disease		Not reported
Harris, 2011	■	■		■					■	Age	■	Community participation after community consultations (data collection)
Oster, 2010	■	■		■					■	Age		Uncertain. SLICK program is in collaboration with First nations.
Shah, 2010	■	■					■					Not reported
Lovell, 2009		■										Not reported
Oster, 2009	■	■		■					■	Age		Uncertain. SLICK program is in collaboration with First nations.
Bruce, 2008	■	■	■	■				■	■	Age		Not reported
Dannenbaum, 2008	■	■		■				■	■	Age		Not reported
Attawar, 2006	■	■	■	■	■	■	■	■	■	Age	■	Integrating fundamental principles of community-based participatory research, collaboration, equity, community development, and action); conducted in collaboration with First Nation communities in Manitoba and supported by community diabetes research working group.
Virani, 2006	■	■		■				■	■	Age		Uncertain. SLICK program is in collaboration with First nations.
Martens, 2007	■	■		■			■	■	■	Age		Not reported
McIntyre, 2007	■	■	■	■					■	Age; Disability: hemodialysis/ end-stage renal disease		Not reported
Rose, 2007	■	■	■	■					■	Age		Not reported
Goulet, 2006		■							■	Age; Disability: need revascularization		Not reported

(Continued)

TABLE 3 Continued

Author, Year	P	R	O	G	R	E	S1	S2	+	Details *plus* factors	POR	Comments regarding POR
Reid, 2006	■	■		■					■	Age		Not reported
Hanley, 2005	■	■		■					■	Age		Not reported
Meatherall, 2005	■	■	■	■		■			■	Age; not receiving dialysis		Not reported
Pollex, 2005	■	■		■					■	Age; Disability: genetic predisposition PAD		Not reported
Iwasaki, 2004		■	■	■		■	■		■	Age		Not reported
Légaré, 2004	■	■		■					■	Age		Not reported
Thommasen, 2004	■	■										Not reported
Jin, 2002									■	Age		Not reported
Hernandez, 1999	■	■		■					■	Age		Not reported
Brassard, 1995		■		■					■	Age		Not reported
Macauley, 1988	■			■				■	■	Age		Not reported
Young, 1985	■	■		■					■	Age		Not reported

The shaded boxes indicate the presence of this factor.
P, place of residence; R, race/ethnicity/culture/language; O, occupation; G, gender/sex; R, religion; E, education; S1, socioeconomic status; S2, social capital; + , Plus Factors; POR, Patient-oriented Research

Indigenous peoples, approximately 14 years younger than in the non-Indigenous population, and LEA being more common among those under 50 years of age (10, 86). PAD appears to be underdiagnosed in Indigenous peoples, whereas revascularization procedures may be overdone compared with non-Indigenous peoples. Those trends have also been identified among marginalized groups (87, 91). There is very little Canadian data on diabetic foot infection which has been documented to be very prevalent in the Indigenous peoples of Australia (86). Indigenous identity has been associated with an increased risk of neuropathy and DFU, with a 3- to 6-fold increase in the likelihood of experiencing LEA, but our data do not permit such a precise estimate in comparison (86).

Our results support that, although this research topic is receiving more recent attention in Canada, knowledge remains limited. In fact, most of the DFRC identified seem to be underestimated including neuropathy, PAD, diabetic foot infection, when compared to those of the Indigenous population in Australia (86). Moreover, we did not identify any study reporting on mental health (e.g., depression, anxiety) and DRFC. Yet the association with DFU and LEA is well demonstrated (92, 93). This result is consistent with the fact that these data are often missing for this population related to mental health studies (94). Nevertheless, this is a difficult topic for this population given the intergenerational effects of colonization, residential schools and other trauma (95), in addition to competing health priorities.

The overall results are consistent with those of a previous study conducted 10 years ago, which identified increased biomedical risk factors for all Indigenous populations with diabetes related to LEA, neuropathy and PAD, and highlighted that complex political and social factors are also barriers to optimal health care for Indigenous peoples (10). Therefore, Indigenous identity alone does not explain all the outcomes, it is mainly the synergy of socio-historical-political conditions (and colonization) faced by Indigenous peoples that predispose them to diabetes and its complications in Canada (8). Hence the importance of considering factors related to the inequity.

4.2 Equity lens and care

This review suggests that the magnitude of the problems associated with diabetic foot disease and its complications in this population is identified but underestimated, particularly with respect to equity as their influence on DRFC remains unclear. That this review did not identify the real inequity experienced by Indigenous people regarding DRFC only highlights how problematic western methodologies are. Only minimal robust data was available, and few studies have incorporated *PROGRESS-Plus* factor perspective. When equity factors are less accounted for in research, this inevitably impacts the results. Yet the effect of equity factors is well known in the Indigenous population with diabetes (12). Strategies were suggested to address

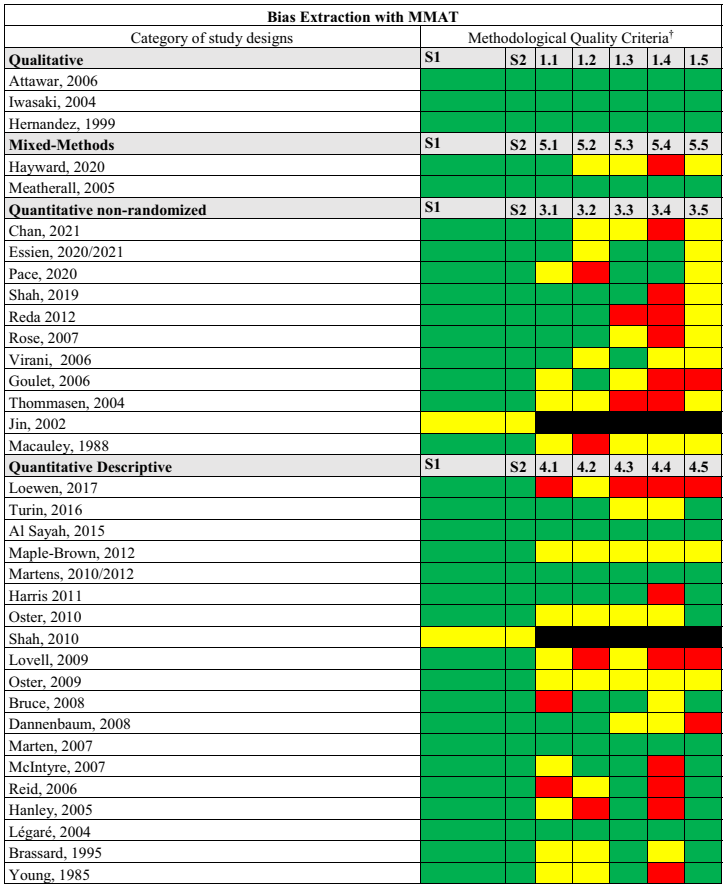

FIGURE 2
Quality Appraisal of included studies. MMAT, Mixed Methods Appraisal Tool. †Are criteria are available in MMAT (84).

social barriers and to improve outcomes, equity and cultural safety approach in Indigenous population in Canada (96). However, it takes time to set up at all levels i.e., individual, organizational, system and in research.

Social determinants of health, identified with *PROGRESS-Plus* factors may not be enough and appropriate. This must be grounded in decolonization and increasingly centering on Indigenous ways of knowing, being and doing and Indigenous health determinants (97). While our project has shown that even Western factors have been given little consideration, it is essential to also include determinants of wellness that are much more aligned with the beliefs, values and preferences of Indigenous peoples, including elements such as self-determination, identity, language and land (98). Mental, physical, spiritual and social are holistic dimensions of health for this population and specific Indigenous frameworks may better support the equity lens (99). Foot health in Indigenous peoples should be no different from the non-Indigenous population and based on prevention and management that is proven to be effective (100). However, evidence-based, trauma-informed, and culturally safe care should be inseparable in order to decrease health disparities for this population. Poor outcomes included in this review may be consistent with the limitations of the Canadian health services/system, especially when actions are not relevant to the social and cultural contexts of Indigenous peoples (12). A focus on building relationships with an Indigenous person with diabetes is important rather than a singular emphasis on achieving management targets. This also needs to be considered in research. Previous studies have shown that there is little good quality evidence to assess diabetes health outcomes in primary care or system services for Indigenous peoples in Canada with type 2 diabetes (101). In addition, the limited success in achieving evidence-based targets (e.g., glycated hemoglobin, lipid levels, physical activity levels) in this population has highlighted the limitations of health services, as the targets are not necessarily relevant to Indigenous peoples and are not aligned with the equity factor (102, 103). The access to culturally safe health care, delivered by culturally competent (allied) health professionals were seen as a contributing factor to foot and lower extremity health (102). This is also aligned with a call to action as per the Truth and Reconciliation Committee of 2015, commissioned by the Government of Canada (104).

Our results highlighted the hypothesis of disparities regarding prevention, treatments, and quality of care, particularly in rural and remote communities, and may be the direct effect of colonization.

Disparities have been well demonstrated for the management of diabetes and its complications in rurality (105). Deficiencies of specialized care and the effect of rurality on LEA was demonstrated on race and ethnicity in a previous study (24). Socio-economic conditions and risk factors for type 2 diabetes and its complication are important determinants of health and therefore culturally safe and appropriate policies, programs and services that address health equity have a preponderant role to play in preventing diabetes complications at different (from individuals to structural) levels of change (106, 107).. Appropriate screening and intervention programs and improved access to effective health care services are required to prevent a widening of the gap in DRFC between Indigenous and non-Indigenous in Canada (86), while advocating for systemic changes to address health inequities. Indigenous peoples living in Canada are among the highest-risk populations for DRFC and screening should be carried out earlier and at more frequent intervals (12). Currently, this is not the case (108), but some studies included in the review aimed to reach a better standard of care for foot health and reduce disparities (13, 50, 76, 80, 81). Thus, establishing more healthcare services that integrate Indigenous Peoples cultures and traditions could improve access to care and the course of treatment (109). Finally, engagement is a paramount component of care for DRFC. A recent study on engagement did not identify specific data on this population (110), but it is worth bearing in mind that Indigenous populations are not less "engaged" than non-Indigenous populations (111). This is also a Western perspective on their engagement. Some populations are not difficult to reach - to mobilize - but they may find it hard to trust clinicians, researchers and policymakers (27, 112). Effects of colonialism (e.g., traumatic historical relationship with the government, health care professional too prescriptive or authoritarian, racism, discrimination, stereotypes, and structural barriers to cares) may be at the root of the heavy burden of DRFC. However, our study did not set out to precisely explore this population's engagement, and this is an important avenue to explore in diabetic foot care.

4.3 Patient-oriented/centered research

It is not surprising that POR was not particularly integrated before 2020 for research with this population because we are more likely to employ Indigenous health research methodologies. In fact, actions that develop cultural safety, integrate all care spectrum and stakeholders, respect the values, customs, and traditions of Indigenous Peoples, and joint data collection to monitor progress and outcomes are a necessity in research to achieve health equity (101). There are specific methods for Indigenous population-centered research such as the use of Indigenous frameworks, western methods adapted to Indigenous context, community-based participatory research, storytelling and culture-specific methods (113). We have very little information about this in the literature reviewed, apart from community-based participatory research in recent years and the request for community permission in connection with ethical approval. Furthermore, based on our findings, it is also clear that this population needs to be more fully considered in research and health initiatives to promote culturally safe and quality health care. The predominantly western biomedical approach to health care in Canada has been identified as culturally insensitive and not inclusive of Indigenous perspectives and well-being (114). Currently, there is a lot of work being done in hospitals, but it's a long-term effort. Patient interactions and engagement in diabetes care have been influenced by personal and collective historical experiences with health care providers and contemporary exposures to culturally inappropriate and potentially harmful healthcare (27). Moreover, social determinants of wellness are drivers of health equity and community research capacity (115).

Data regarding Indigenous people's perspectives on foot health were scarce, yet critical. Thus, in order to develop culturally safe health care and promote positive change in foot health among First Nations people, it is imperative that stakeholders such as clinicians and researchers including Indigenous peoples perspectives (102). There is also a need to engage empowered Indigenous peoples in the foot health initiative. A recent call to action was issued to integrate traditional Indigenous and Western health models to improve outcomes as well as radical changes to reduce inequities and support the transformation of primary health care programs to empower Indigenous peoples and communities and improve chronic disease prevention and management (7, 116). As far as First Nations are concerned, they have the control and aim to achieve data sovereignty for data collection processes, and they want to own and control how that information can be used using the principles of ownership, control, access and possession, better known as OCAP® (117). Therefore, Indigenous peoples are empowered to act independently and address their own health issue with research including DRFC (118, 119). POR is aligned with this and the non-Indigenous and Indigenous research community can team up for the health of all Canadians. Taking over control of health, well-being and clinical care by Indigenous peoples is a desirable way forward such as in the NUKA health project (120, 121).

4.4 Strengths and limitations

There are strengths and limitations to our scoping review. First, to our knowledge, this is the first comprehensive review of DRFC using a systematic method specifically targeting this Canadian population and including an equity lens and POR data. However, the high heterogeneity of the included studies makes it very difficult to obtain comprehensive results representing the situation. For this reason, we opted for a narrative synthesis and focused on studies including comparison/control to express broad trends. The chosen methodology is also Western and focuses on research done by predominantly non-Indigenous researchers, published in the Western evidence base and therefore Indigenous ways of knowing, being and acting based on their teachings and medicines are lacking. In addition, the overall quality of the evidence reported is dependent on the quality level of evidence of included studies. The use of the MMAT quality assessment tool (43) is a strength of our work as this is not mandatory with this research

design but highlights the average quality of observational studies. Therefore, this is an area that needs improvement.

Second, although our database search strategy was robust and validated by an academic librarian, we may have missed data from the grey literature and specific communities. However, grey literature is rarely peer-reviewed and difficult to identify, but our attempt is a plus value to portray the overall situation. Otherwise, we minimized bias by testing our selection strategy with a two-arm independent reviewer pilot, and agreements were strong (Cohen's kappa > 80%) (122). Due to a selection performed by two groups of reviewers, this may lead to differences in selection and extraction. We attempted to reduce this disparity by involving the lead reviewer in both arms.

Third, this review followed the recorded protocol, but was modified to improve the robustness of the methodology based on the progress of the study and evidence. This study was initiated in November 2020. The adjustment concerned the research questions on equity and POR, and the choice of the scoping design, being less restrictive, allowed this malleability. We wanted to provide a concrete analysis of the evidence regarding equity and POR to also contribute to the improvement of research in this area. Finally, although the initial research question emanated from a clinical setting dealing with Indigenous peoples and wanted to identify the overall burden of the diabetic foot disease, no patient or citizen were included in the research process as co-investigators. On the other hand, consultation with stakeholders was our way of involving them and was undoubtedly a great addition as we have conducted inclusive research, used culturally acceptable language, and discussed the results in concert with what is important for them.

4.5 Futures directions

With these strengths and limitations in mind, we emphasized the urgent need for robust research in Canada with Indigenous peoples, particularly integrating all factors related to equity and to consider specific socio-historical-political conditions and risk factors to worse outcomes identified in this review such as rurality/remote locations, age, sex, health care accessibility (123, 124). We highlight the catastrophic effects of limb loss on this growing population, without even considering what happens to young people (≤18 years old), but knowing that the youth is increasingly affected by diabetes (125). Indigenous peoples have different identities, cultures, and contexts in the society, but data on their specific characteristics are scarce in terms of their diversity and DRFCs. There are reportedly over 630 different First Nations communities in Canada, representing more than 50 Nations and speaking more than 50 Indigenous languages, in addition to Inuit and Métis (3). We have presented our results as one group, but each subgroup (i.e., First Nations, Métis and Inuit) need to be considered independently as they have a unique situation. Precise population definition can support a better portrayal of the situation, on the one hand, and the development of adapted interventions on the other. It is well known that user-based interventions in patient-centered research are developed and implemented more easily (126). We also strongly suggest that future studies apply national and international validated standards, recommendations and definitions for DRFC research on this population (39, 127). In addition, outcomes research needs to be more inclusive with nationally representative populations by including Indigenous peoples to better inform the national burden of this disease in Canada.

Finally, it appears from all the literature reviewed that less attention has been paid to diabetic foot disease from a preventive perspective and the major focus was related to LEAs. Although these results support previous findings (10, 86), more data are needed to better understand the burden of DFU, PAD, neuropathy, and foot deformities in Indigenous in Canada, particularly in those with additional vulnerability factors such as end-stage renal disease and/or frailty (128, 129). Researchers need to embrace Indigenous methods and co-research with two eyed seeing. The Inuit peoples of the provinces and territories, who are still poorly integrated in the knowledge of the burden of diabetic foot disease, deserves special attention in further research. While efforts have been made in recent years to identify and manage DFRCs, particularly in collaboration with the community, it is imperative that Indigenous communities and peoples be considered as partners in the promotion of quality and culturally safe health and social services for limb preservation within the research. Knowledge development with this population should move in this direction regardless of the type of study and resources and ensure adequate transfer.

5 Conclusion

Indigenous peoples in Canada experience a high burden of foot disease and DRFC, however since the data and high-quality studies are limited and heterogeneous, the extent of the situation may be underestimated. Even if Indigenous identity shows trends for worst health outcomes related to DRFC, it is also the synergy of socio-historical-political conditions (and colonialism) faced by Indigenous peoples that predispose them to diabetes and its complications. We have done a comprehensive review that specifically included an equity lens and POR, but this review highlights the problem of our western method. This knowledge is only the tip of the iceberg in terms of truly supporting this population through concrete and concerted action with, not for, Indigenous peoples. Social services and health care must be improved using Indigenous ways of knowing, being and acting to reach equity, especially for those living in rural and remote communities in Canada. Potential solutions lie with them. Although these results corroborate previous findings for other populations, additional data are needed to better understand the impacts of DRFC considering culture, beliefs, traditional medicine, and lifestyle of Indigenous peoples. The Indigenous peoples should be given further consideration in research and initiatives aimed at promoting culturally safe and quality health care and access. It is crucial to recognize the specific needs and prioritize prevention strategies to reduce the burden of diabetic foot disease among this at-risk population.

Author contributions

The project was conceptualized by VB, JP, and A-ML. Data acquisition, including selection, review, and extraction was performed by VB, ST, JP, MB-F, and SL. VB performed most of the analysis with JP and ST. VB conducted the consultation. VB drafted the manuscript and was mentored and advised by DA and M-CT. All authors contributed equally to the revision of the manuscript and its final approval. All authors take full responsibility for its content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1177020/full#supplementary-material

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Current status and progress in research on dressing management for diabetic foot ulcer

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Diabetic foot ulcer (DFU) is a major complication of diabetes and is associated with a high risk of lower limb amputation and mortality. During their lifetime, 19%–34% of patients with diabetes can develop DFU. It is estimated that 61% of DFU become infected and 15% of those with DFU require amputation. Furthermore, developing a DFU increases the risk of mortality by 50%–68% at 5 years, higher than some cancers. Current standard management of DFU includes surgical debridement, the use of topical dressings and wound decompression, vascular assessment, and glycemic control. Among these methods, local treatment with dressings builds a protective physical barrier, maintains a moist environment, and drains the exudate from DFU wounds. This review summarizes the development, pathophysiology, and healing mechanisms of DFU. The latest research progress and the main application of dressings in laboratory and clinical stage are also summarized. The dressings discussed in this review include traditional dressings (gauze, oil yarn, traditional Chinese medicine, and others), basic dressings (hydrogel, hydrocolloid, sponge, foam, film agents, and others), bacteriostatic dressings, composite dressings (collagen, nanomaterials, chitosan dressings, and others), bioactive dressings (scaffold dressings with stem cells, decellularized wound matrix, autologous platelet enrichment plasma, and others), and dressings that use modern technology (3D bioprinting, photothermal effects, bioelectric dressings, microneedle dressings, smart bandages, orthopedic prosthetics and regenerative medicine). The dressing management challenges and limitations are also summarized. The purpose of this review is to help readers understand the pathogenesis and healing mechanism of DFU, help physicians select dressings correctly, provide an updated overview of the potential of biomaterials and devices and their application in DFU management, and provide ideas for further exploration and development of dressings. Proper use of dressings can promote DFU healing, reduce the cost of treating DFU, and reduce patient pain.

KEYWORDS

diabetic foot ulcer, dressing, biomaterial, wound healing, progress

1 Introduction

Patients with diabetes are prone to complications of the kidney, retina and nervous system, and approximately 34% of patients have diabetic foot ulcer (DFU). A DFU is defined as a break of the epidermis and at least part of the dermis in a person with diabetes (1). DFU is associated with numerous risk factors and has complex mechanisms and insignificant clinical manifestations. Its pathogenesis is roughly categorized into peripheral neuropathy, Peripheral arterial disease and infection. The pathophysiology of ulcers is also categorized into pre-ulcer, ulcer phase, and ulcer recurrence based on the chronological order of their appearance. DFU is often not detected until it has progressed to an irreversible ulcer. There are about 4 million new DFU patients in China every year, and according to statistics, there is one amputation due to DFU every 30 seconds, accounting for 68% of the non-traumatic amputation population. Moreover, DFU is often accompanied by severe infection, resulting in long-term wound nonhealing, and approximately half of patients with DFU experience lower limb amputation (2). Patients with DFU have a higher risk of death compared to diabetic patients without comorbid DFU (3). The shortened lifespan of DFU patients places a heavy burden on public health and on health care systems. Progress in the development of modern dressings for DFU continues to be driven by the seriousness and urgency of the above situation as well as by extensive clinical and laboratory experience.

The concept of moist wound healing has been accepted by clinical researchers since the 1970s. A humid environment promotes autolytic debridement, stimulates collagen production, promotes the migration of keratinocytes to the wound surface, and supports the function of growth factors in the wound microenvironment, thereby reducing pain, inflammation, necrosis, and scarring. This has led to the rapid development of a variety of wet dressings, including hydrogels, hydrocolloids, films, alginates, and foams (4, 5). Clinical practice has become increasingly reliant on wet dressings, and wet dressings are gradually replacing dry dressings such as gauze and bandages. Second, based on the poor prognosis of DFU after multiple microbial infections, the progress of antibacterial dressings will also be reviewed separately. Moreover, wet dressings are becoming increasingly microscopic and have begun to integrate the modern technology used in drug delivery systems.

Nanodressings, microneedle dressings, bioactive dressings, and dressings produced by 3D printing and photoelectric effects have been developed. Furthermore, modern dressings focus on the monitoring and response of wounds in real time rather than simply on therapy. In fact, prior to the advent of wet dressings, early forms of bioactive dressings such as allografts and xenografts were used. We classify dressings according to their active ingredients (Figure 1).

2 Pathogenesis of DFU

There are many risk factors for DFU, and its pathogenesis is very complex. Its pathogenesis can be divided into three categories: peripheral neuropathy, peripheral arterial disease, and infection (6) (Figure 2).

2.1 Peripheral neuropathy

Diabetic peripheral neuropathy (DPN) is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes (7). Neurological disorders associated with diabetes can be classified as sensory, motor or autonomic neuropathy (8). In diseased nerve cells, high

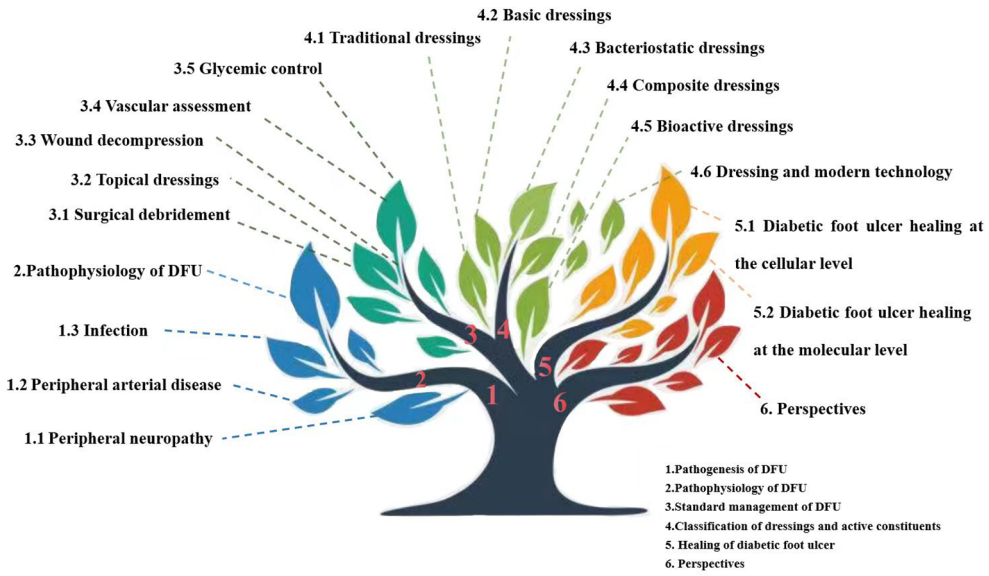

FIGURE 1
Diagram showing the structure of this review.

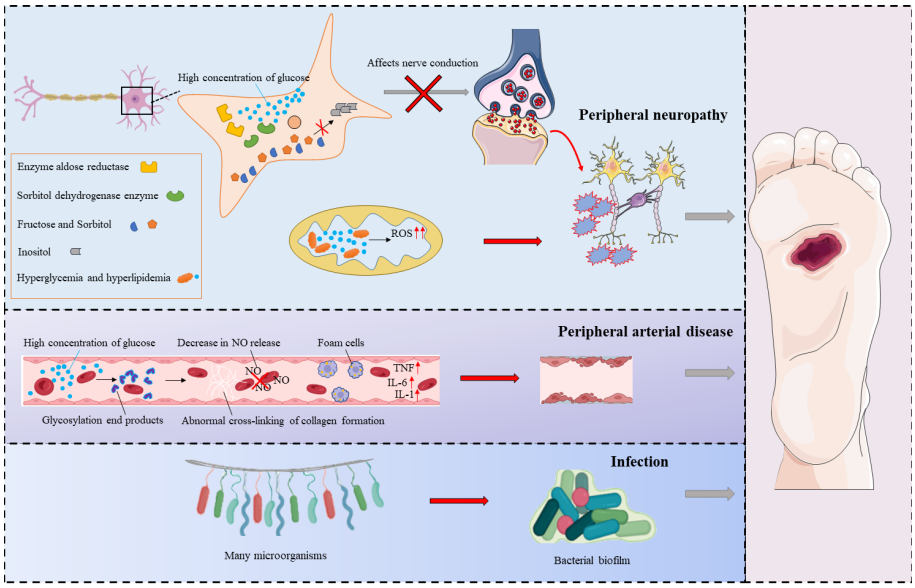

FIGURE 2
The mechanism of DFU.

concentrations of glucose increase the activities of aldose reductase and sorbitol dehydrogenase, leading to intracellular conversion of glucose to sorbitol and fructose, compounds that affect nerve conduction (9). At the same time, conditions such as hyperglycemia, dyslipidemia and insulin resistance lead to dysregulation of metabolic pathways, and this in turn leads to an imbalance in mitochondrial redox status that results in excessive formation of reactive oxygen species in mitochondria and in the cytoplasm. These conditions lead to loss of axon energy storage and axonal damage, and this aggravates peripheral nerve lesions and causes damage to the nerves in the foot (10). As a result of neuropathy, damage to the lower extremity is often not felt in time, and the lesion remains subject to repeated stress (including prolonged walking or loading). Moreover, neuropathy leads to imbalances in the muscle tissue and to muscle atrophy in the feet of patients with diabetes. Over time, foot deformities such as foot drop, claw foot, and equinus deformity may occur, leading to or aggravating DFU. Autonomic neuropathy affects perspiration and causes abnormal blood circulation in the foot. With the decrease in foot perspiration and the dysfunction of sebaceous glands, the skin becomes dry and keratinized and is more likely to become cracked, leading to infection (11).

2.2 Peripheral arterial disease

The high blood glucose concentrations that occur in individuals with diabetes lead to increased oxidative stress responses, increased matrix protein glycosylation, and accumulation of advanced glycation end products (AGEs). With the accumulation of AGEs, protein structure and function change, leading to microvascular and macrovascular disease (12). Studies have confirmed that AGEs cause collagen to form abnormal crosslinks; this leads to vascular stiffness and decreased nitric oxide release from endothelial cells, and the modification of lipoproteins leads to the formation of foam cells. The formation of AGE/AGER (AGE receptor) complexes in endothelial cells induces the production of nuclear factor κB (NF-KB). Thus, the expression of vascular cell adhesion protein 1 (VCAM-1) and proinflammatory cytokines increases. Eventually, endothelial cell function is disrupted, affecting the normal constriction of blood vessels and causing platelet aggregation, endothelial cell proliferation, and atherosclerosis. Vascular lesions affect the supply of blood and oxygen to tissues. Ischemic hypoxia can lead to poor wound healing, worsening of the condition, ulceration, and, in severe cases, avascular necrosis and even amputation (13).

2.3 Infection

DFU occurs when normal barrier function is lost and there is an increased risk of foot infection. The bacteria most often associated with DFU include not only gram-positive bacteria such as *S. aureus* (MSSA—methicillin-susceptible *Staphylococcus aureus*, and MRSA—methicillin-resistant *Staphylococcus aureus*), *Streptococcus β-hemolytic* and *C. striatum* but also gram-negative bacteria such as *P. aeruginosa*, *E. coli*, *A. baumannii*, *Proteus* spp., and *Enterobacter* spp. and some anaerobic bacteria that reside more deeply in the wounds, such as *Bacteroides* spp., *Prevotella* spp., *Clostridium* spp., and *Peptostreptococcus* spp (14). Microorganisms gather in specific areas within DFU wounds, where they and grow and multiply, wrapping themselves with extracellular polymers containing polysaccharides and lipids. The polymeric substances (EPS) secreted by the cells embedded in the ulcer include proteins, lipids, nucleic acids, polysaccharides and other components that aggregate with microorganisms to form biofilms. These films give bacteria the ability to adhere to both biotic and abiotic surfaces.

Because biofilms are resistant to antimicrobial agents and to immune and chemical attacks, they delay wound healing and cause chronic inflammation and repeated infections (15). Hyperglycemia reduces leukocyte function, most notably the function of neutrophils, and this is reflected in reduced production of chemokines, increased production of reactive oxygen species, and reduced phagocytosis and migration of cells caused by complement system dysfunction (16). At the same time, keratinocyte migration in DFU wounds is impaired, and this is one of the reasons for slow wound healing (17).

3 Pathophysiology of DFU

According to the sequence of appearance of diabetic foot ulcers, their pathophysiology can be roughly divided into pre-ulcer, ulcer phase, and recurrent ulcer phase (18). First, abnormal blood glucose levels in diabetic patients can cause sensory, motor or autonomic neuropathy. The clinical manifestations are loss of sensation, muscle atrophy and deformation, and dry skin. This period is the preliminary stage of foot ulcer development and is also an extremely dangerous period, which can very easily lead to the development of diabetic foot ulcers if not managed properly (e.g., improper patient education). Entering the second stage, ulcers develop due to the loss of self-protection of the patient's foot and peripheral vascular lesions caused by abnormal blood glucose concentrations, in the presence of a large number of repeated traumas and injuries. The clinical manifestation is the development of foot ulcers, which are very prone to wound infection. Therefore, management during this period is particularly important, and the choice of appropriate adjuvant and surgical approach is a key factor in determining the patient's prognosis. Finally, as the ulcer heals, the clinical manifestations resolve, but diabetic patients are at an extremely high risk of recurrence. Although surgical or pharmacological treatment can improve the blood supply to the trauma, a complete level of control cannot be achieved for the most fundamental causative factors such as neuropathy, peripheral vascular lesions, and infection. Consequently, diabetic patients in this stage often relapse and develop chronic wounds that do not heal over time. And the correct use of appropriate adjuvants can reduce the recurrence rate and improve the quality of life of patients.

4 Standard management of DFU

The ultimate goal of DFU therapy is to bring about wound healing and prevent wound infection, amputation, and decreased quality of life. The standard management of DFU primarily involves surgical debridement, topical dressings, wound decompression, vascular assessment, and glycemic control, among others.

4.1 Surgical debridement

Surgical debridement is the surgical removal of nonviable or necrotic tissue from the wound bed and drainage of abscesses, if present. In addition to surgery, there are other methods of debridement such as mechanical debridement, enzymatic debridement and biological debridement, with surgical debridement being the effective and preferred method. Surgical debridement promotes wound healing by accelerating granulation tissue formation and re-epithelialization. Surgical debridement also plays an important role in infection control because necrotic tissue provides a breeding ground for bacterial proliferation. The experts made two recommendations: (a) Patients with diabetes-related foot ulcers should not be sent to the operating room for unnecessary surgical debridement if appropriate sharp debridement can be performed on an outpatient basis, as this is more expensive and resource-intensive, and may actually delay debridement if it can be performed chair-side. (b) Patients with diabetes-related foot ulcers with limb- or life-threatening features (e.g. extensive necrosis, oozing fluid or gas infection) must always be referred urgently for expert surgical opinion to assess the need for surgical intervention to avoid the risk of further deterioration and worsening prognosis (19). Surgical debridement is very commonly used in clinical practice. However, due to the complexity of the pathomechanisms of DFU, monotherapy strategies will result in very low levels of recovery, and combination therapy is more effective. A case report states that a 63-year-old male patient with a DFU was treated and managed with a combination of surgical debridement, maggot therapy, negative pressure wound therapy, and a combination of silver foam dressings. After 3 months and 10 days, the patient's ulcer had completely healed and was discharged from the hospital in good and stable condition (20).

4.2 Topical dressings

Dressings are an integral part of the DFU treatment process. Traditional optimal dressings should have the ability to help relieve symptoms, protect DFU wounds and promote wound healing. A currently accepted wound dressing should also (i) have the ability to promote the tissue reconstruction process by providing thermal insulation, gas exchange, increased drainage, and debris removal; (ii) be biocompatible and not cause allergic or immune reactions; (iii) prevent secondary wound infection; and (iv) be easily removable without causing trauma (21). Because there are different types of wounds and the characteristics of each phase of wound healing differ, there is no single dressing that meets all requirements for use with DFU and can be effectively applied in all cases. There are different types of dressings, and each has its own characteristics. Appropriate application of dressings increases the rate of DFU healing, thereby reducing hospitalization and healing time, and reducing the cost of treating DFU (22). Wound type, patient requirements, and cost should be considered when selecting a dressing. Presently available dressings for DFU can be divided into two categories: traditional dressings and current dressings. Table 1 presents a comparison of the dressings in these two categories.

TABLE 1 Comparison of traditional and current dressings.

Traditional dressings	Current dressings
Easy access to the raw materials needed for preparation	Excellent insulation ability
Simple preparation process	Promote rapid wound healing
Low cost	Reduce reactive oxygen species in wounds
Fast replacement frequency Prone to tissue adhesion	Slow replacement frequency, long-lasting effect Less prone to tissue adhesion
Extremely likely to carry pathogens Absorption of wound exudate affects the efficacy of the treatment, and exudate leaks rapidly from the dressing Slow deposition of granulation tissue Less effective in relieving pain Local dryness, unable to maintain a humid microenvironment Tends to damage the wound and aggravate pain during replacement Slow onset of action, longer treatment course	Excellent antibacterial effect, can reduce bacterial infections High ability to absorb wound exudate Rapid deposition of granulation tissue Effective in relieving wound pain Excellent moisturizing ability Improves microcirculation and shrinks wounds Rapid onset of action and shortened course of treatment

4.3 Wound decompression

The most common pathway to DFUs is the application of excessive mechanical pressure to the non-sensory foot. If the mechanical stress is excessive, it can lead to inflammation, DFU development, and prolonged DFU healing time, which in turn increases the risk of infection, hospitalization, and amputation. Reducing excessive mechanical stress using offloading interventions is a major goal and important prerequisite for promoting healing outcomes and preventing ulceration (23). This process involves reducing the load on the affected areas of the foot by redistributing additional pressure to other areas. Bed rest, wheelchairs, crutches to assist with gait, surgical decompression, total contact casts (TCCs), removable cast walkers (RCWs), and offloading shoes are all common methods. Strong evidence supports the use of non-removable knee-high offloading devices (either TCC or non-removable walker) as the first-choice offloading intervention for healing plantar neuropathic forefoot and midfoot ulcers (24). Despite being the gold standard offloading treatment for plantar DFU, these devices remain underutilized in clinical practice.

4.4 Vascular assessment

Up to 50% of patients with diabetes and foot ulcers have coexisting peripheral artery disease (PAD), which leads to a significantly higher risk of adverse limb events and cardiovascular disease (25). Early identification of PAD in patients with diabetic foot ulcers (DFUs) is important because the presence of PAD is associated with an increased risk of nonhealing ulcers, infections, and major limb amputations, as well as cardiovascular complications and increased overall mortality. Assessment of PAD by palpation of the pedal pulse or ankle-brachial index (ABI) is recommended for patients with DFU. An ABI below 0.7 is associated with some degree of arterial insufficiency, and patients with an ABI below 0.4 have severe PAD (26). Patients with noncompressible vessels should undergo additional tests, including toe systolic blood pressure, pulse volume recording, transcutaneous oximetry, or dual-function ultrasound. Abnormalities on any of these secondary tests reliably confirm the diagnosis of PAD.

4.5 Glycemic control

The close relationship between blood glucose levels and the progression of diabetic complications has been widely reported in the literature. It has been reported that enhanced glycemic control in patients with diabetes mellitus delays the onset of retinopathy, peripheral neuropathy and nephropathy, which are the major risk factors for DFU, and is therefore positively associated with wound healing (23). It has been shown that proper glycemic control will aid in wound healing during the treatment of diabetic foot ulcers. The study by Xiang et al. suggests that reasonable glycated hemoglobin (HbA1c) targets (ranging from 7.0% to 8.0% during treatment) can promote ulcer healing in patients with DFUs without increasing mortality, especially in patients with better glycemic control on admission (27).

5 Classification and active ingredients of dressings

5.1 Traditional dressings

Traditional dressings, also known as inert dressings, such as gauze, cotton pads and bandages. It is the most widely used dressing in clinical practice due to its low cost and simple manufacturing process (28). As one of the earliest systems used in the treatment of DFU wounds, traditional dressings provide cushioning that reduces pressure, prevents abrasion, protects the wound, and absorbs small amounts of exudate.

Traditional dressings such as dry gauze, oil gauze, cotton gauze and bandages have played a landmark role in the history of dressing development as effective topical treatments (29–31). These dressings are mainly used to prevent direct contact between the wound and contaminants and to absorb exudate, but they do not directly promote wound healing. In addition, dry dressings tend to

adhere to the wound, causing secondary damage to the wound when the dressing is replaced and extending the healing time (30, 32, 33). However, as one of the basic dressings, traditional dressings are still widely used in clinical practice.

Traditional dressings are of great significance, and there would be no advancement in modern dressings without the most basic of dressings. Although traditional dressings do not provide effective healing of the wound. However, it can be used to control diabetic foot infections and to prevent diabetic foot ulcers from continuing to develop. It is the most basic treatment and deserves to be emphasized by primary care doctors, especially for remote and poor areas. So we list three of the most basic and representative dressings, dry gauze, oil gauze and traditional Chinese medicine. And they are described in detail.

5.1.1 Dry gauze

In the treatment of DFU wounds, dry gauze has the effect of covering the wound and isolating it from microorganisms, but it has no antimicrobial activity and does not significantly promote wound healing (34). In addition, dry dressings may cause secondary injury to wounds, and current research in this area tends to focus on the use of multidrug combination therapy to reduce the negative impact of dry dressings on wounds. It is more effective for superficial clean ulcerated wounds.

Studies report that it has been possible to compensate for the shortcomings of dry dressings by functionalizing gauze in ways that give it moisturizing and antibacterial properties. For example, carboxymethylated chitosan that exhibits water solubility, biocompatibility and antimicrobial activity has been synthesized by direct alkylation. Calcium alginate and modified chitosan have also been used as hygroscopic polymerizing agents. The two polymers were applied to the surface of cotton gauze, woven with 40s Ne cotton thread using a mat drying method (35). Studies have also shown that application of a mixture of deacetylated chitosan and petrolatum to sterile gauze followed by drying can be used to prepare chitosan-vaseline gauze (CVG) dressings. CVG dressings are soluble, noncytotoxic and antimicrobial. CVG dressing therapy also increases angiogenesis and the microvascular density of wounds and is therefore a highly promising dressing for wound treatment (36). Thus, the comprehensive function and superior performance of dry gauze play an important role in the treatment of DFU.

5.1.2 Oil yarn

Compared with dry gauze, oil gauze has a unique advantage in that it does not adhere to the wound during the healing process. Dong et al. randomly assigned 22 patients with diabetes to a silver ion dressing group and an oil gauze-silver group. The dressings were changed twice weekly until the DFU healed. The healing outcomes and speed of healing were used as clinical therapeutic indices. The results showed that compared with silver ion dressings, silver-gauze dressings showed better clinical efficacy in the treatment of DFU, especially with respect to ulcer healing speed (37).

Oil yarn has a degree of moisturising power and isolates bacteria and promotes wound healing. However, if it is too thick, it can restrict the exchange function of the skin. This prevents the excretion of metabolic waste, prevents the skin from absorbing oxygen and hinders the skin's metabolism, which then prevents the wound from healing. Moreover, oil yarn is ineffective in preventing wound infection and has certain limitations related to its ability to manage osmotic fluid leakage.

5.1.3 Traditional Chinese medicine

Traditional Chinese medicine (TCM) foot baths have a long history in the treatment of wounds and are widely used to treat surgical wounds, especially infected wounds. Chinese medicine tonics, which are the essence of TCM, have unique advantages over Western medicine in that they affect multiple targets and have significant clinical efficacy and fewer adverse effects (38). The foot bath decoction (FBD), which is designed for used in a foot bath, is one of the TCM formulas. Its main ingredients are raw rhubarb (Shengdahuang), Coptidis Rhizoma (Huanglian), Fructus Forsythia (Lianqiao), aluminum potassium sulfate (Kufan), and Pseudobulbus Cremastrae Seu Pleiones (Shancigu). All of these TCM have a wide range of pharmacological activities that include anti-inflammatory, antibacterial, and metabolism-promoting activity and improvement of the microcirculation (39). At the same time, certain other TCM adjuvant treatments such as external application, acupuncture, massage, acupoint injection, fumigation and moxibustion also have a certain therapeutic potential for DFU (28). Recent progress in research on TCM-assisted treatment of DFU is summarized in Table 2.

In summary, traditional dressings are mainly used to control diabetic foot infections and thus prevent the development of diabetic foot ulcers. Based on previous studies, we conclude that these dressings are suitable for patients with Wagner classification of 2 and 3. The Wagner system assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades: grade 0 (pre- or postulcerative lesion), grade 1 (partial/full thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene), and grade 5 (whole foot gangrene) (39).

5.2 Basic dressings

To overcome some of the shortcomings of traditional dressings, basic dressings have been developed. Basic dressings are made of polymers crosslinked to form a compound with a certain structure. It has better biocompatibility, degradability, and moisture retention and a dressing with strong exudate absorption. As mentioned earlier, dressings with a certain spatial structure facilitate the maintenance of a relatively constant local temperature and humidity in the wound, providing conditions similar to the internal environment of the body (45). Interestingly, basic dressings may avoid re-injury of new granulation tissue due to scar formation and promote cell proliferation, differentiation and epithelial cell migration. In particular, they may play a role in

TABLE 2 Overview of DFU-assisted therapy with traditional Chinese medicine.

Type	Active ingredient	Mechanism of action	Clinical application
Massage (40)	Administered at specific locations	Changes nerve conduction velocity	Adjunctive therapy for diabetic peripheral neuropathy (DPN) and early DFU.
External application (41, 42)	Compound Phellodendron liquid, ARCC [*Angelica sinensis* (A), Radix Rehmanniae (R), calcined gypsum (C), and calamine (C)]	Upregulates VEGF and PDGF expression in wound tissues to promote angiogenesis, cell proliferation and inhibition of local inflammatory responses	Compound Phellodendron liquid, ARCC
Acupuncture (43)	Acupoint stimulating control	Promotes cell proliferation and angiogenesis, induces extracellular matrix remodeling and reduces inflammation	Encircling needling, Bangci (focal center-side needling), auricular acupuncture, pestle needling therapy, and traditional acupuncture
Moxibustion (44)	Smoke and heat	Promotes the formation of collagen fibers, granulation tissue and capillaries and inhibits inflammation	Moxibustion treatment

avoiding wound contact with external bacteria and effectively preventing cross-infection (46). Basic dressings have a strong ability to absorb exudate. In addition, they are insulating and impermeable to water and bacteria, making them more comfortable to wear. Moreover, basic dressings do not stick to wounds, making it possible to avoid secondary damage to the wounds during dressing changes and reducing pain. Basic dressings also require fewer changes than conventional dressings (47). Basic dressings include hydrogel dressings, alginate dressings, films (permeable films and membrane dressings), hydrocolloid dressings, sponge foam dressings, capillary-action dressings, and odor-absorbing dressings (48). All of these dressings are widely used and effective in DFU treatment. One of the most widely used basic dressings is hydrogel. We describe it in detail and give a brief overview of other basic dressings.

5.2.1 Hydrogel dressings

As a new biomaterial, hydrogels are essentially insoluble hydrophilic polyurethane polymers. They are widely used in the treatment of DFU wounds because of their moisturizing properties, biocompatibility and similarity to living tissue, properties that allow hydrogels to produce the best wound healing effect. The hydrophilicity of a hydrogel, which is a three-dimensional (3D) network structure with high water content, depends on the degree of crosslinking of its polar functional groups. The hydrogel is in direct contact with the wound surface, and its three-dimensional network structure promotes the absorption and retention of water. This long-term moistening of the wound environment helps maintain gas exchange, cell migration and tissue regeneration within the wound and promotes wound healing (49–52). At the same time, hydrogels do not adhere to wounds, are easy to apply and remove without secondary damage and are considered ideal DFU dressings (53–56) (Figure 3). Moreover, based on the special structure of hydrogels, precise regulation of the DFU wound microenvironment can be achieved by adding functional polymers or bioactive substances, and these modifications can help accelerate wound healing and promote the healing of difficult-to-heal wounds (57). When used as drug delivery systems, hydrogels can improve the efficiency of drug delivery while minimizing the toxic damage to wounds that is sometimes caused by drugs (58). However, the drug delivery systems that can be created using hydrogels are also somewhat flawed. If only a single extracellular matrix (ECM) component (gelatin, collagen, or hyaluronic acid) is present in the gel, the potential to provide the optimal microenvironment for the wound is limited.Existing hydrogel dressings cannot meet all the requirements for DFU wound treatment; therefore, different drugs must be used at various stages of wound healing (59, 60). The functional hydrogels were designed by simulating the ECM microenvironment. According to the characteristics of functional hydrogels, functional hydrogels can be divided into anti-inflammatory hydrogels, antioxidant hydrogels (AOH), antibacterial hydrogels (ABH), and proangiogenic hydrogels. According to the meta-analysis, early treatment with AOH followed by ABH a week later could be an advanced strategy for future DFU treatment. This information is important for researchers and/or physicians considering the alternative application of hydrogel dressings (61).

It is well known that the inflammatory response is an important obstacle to the healing of DFU wounds. Hydrogels can be classified as those that contain anti-inflammatory agents, those that are based on anti-inflammatory materials and those that contain anti-inflammatory biological components (62, 63). For example, hydrogels containing ibuprofen (IBU), a nonsteroidal anti-inflammatory drug (NSAID) that acts as an anti-inflammatory agent by inhibiting immune cell aggregation and platelet aggregation, have been widely used (64). Research shows that sacran hydrogel membranes can improve skin barrier function, regulate the production of anti-inflammatory cytokines, and achieve anti-inflammatory effects and that they therefore have potential value in promoting wound healing (65–67). Hydrogels that contain biological components, such as fibrin hydrogels, counteract the inflammatory response by forming porous fibrous network scaffolds through fibrin crosslinking; these scaffolds promote infiltration by and aggregation of anti-inflammatory macrophages (68).

The paragraph above discussed the use of anti-inflammatory hydrogel dressings in the treatment of chronic wounds. The following paragraph discusses the application of AOH dressings and proangiogenic hydrogels to chronic wounds. Some researchers have designed functional hydrogels that simulate the ECM microenvironment. As functional hydrogels, antioxidant

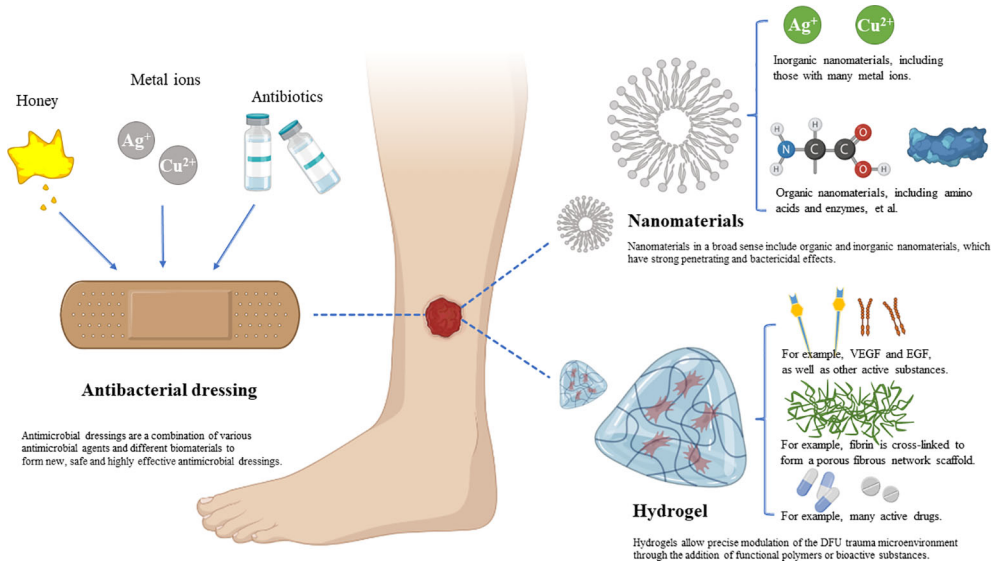

FIGURE 3
Schematic diagram showing antibacterial dressings, nanodressings and hydrogel dressings.

hydrogels exert antioxidant effects through the presence of curcumin (an antioxidant drug) or other bioactive substances within the hydrogel (69). Vascularized hydrogels that contain bioactive components such as epidermal growth factor or vascular endothelial growth factor can promote the regeneration of blood vessels and subsequently promote the healing of DFU (70). In addition, the three-dimensional network structure of the extracellular matrix simulated by hydrogels can provide shelter for stem cells in the inflammatory microenvironment and maintain the survival and vitality of stem cells in DFU wounds. Compared to treatment with mesenchymal stem cells (MSCs) grown under standard conditions, wounds treated with MSC-seeded hydrogels showed significantly accelerated healing and a return of skin appendages (71). Interestingly, some drugs can also be released by hydrogels as gases. Junpeng Chen et al. developed an all-in-one CO gas therapy-based versatile hydrogel dressing (ICOQF) that produces CO by rapidly removing reactive oxygen from wounds. CO causes oxidative stress, inhibits the synthesis of adenosine triphosphate, exerts antimicrobial effects, inhibits phagocyte proliferation, promotes M1-to-M2 phenotype polarization, and produces anti-inflammatory effects. ICOQF hydrogel is a nonantibiotic antimicrobial dressing that is of great significance considering that global antibiotic resistance is increasing yearly (72). A new study has developed hydrogels based on chitosan (CHT) and the polymer of β cyclodextrin (PCD). Cinnamaldehyde (CN) can be delivered locally at DFU. Antibacterial and antibiofilm activity (*Staphylococcus aureus* and *Pseudomonas aeruginosa*) were evaluated. It was found that the bacteria were reduced by about 99.99% (73).

The hydrogel is hydrophobic, biocompatible, similar to living tissue and does not adhere to the wound. It maintains a moist wound environment and can be used in conjunction with secondary dressings. The precise regulation of the DFU wound microenvironment can be achieved by adding functional polymers or bioactive substances. The addition of antimicrobial components allows it to inhibit bacterial growth and accelerate wound healing. These make hydrogel dressings very versatile and effective for most types of DFU. However, it has some limitations, with its low absorption capacity, poor bacterial barrier and sometimes poor mechanical stability. And it can lead to the accumulation of exudate can lead to wound maceration and bacterial proliferation, requiring the use of different medications at different stages of wound healing, which is more costly. By reviewing the relevant research literature, we learned that hydrogel-based dressings are indicated for patients with Wagner grade 2, 3 or 4 DFU lasting at least 4 weeks. Patients with other high-risk factors were excluded (74).

5.2.2 Other types of basic dressings

Due to their strong ability to resist infection and promote local tissue and cell growth, multifunctional combination dressings are now commonly used clinically (75, 76). Basic dressings other than hydrogels, such as alginate dressings, films (permeable films and membrane dressings), hydrocolloid dressings, sponge foam dressings, capillary-action dressings, and odor-absorbent dressings, are shown in Table 3.

5.3 Bacteriostatic dressings

For the DFU, an infection would be a catastrophe. Eighty percent of DFU patients have a poor prognosis due to concurrent infection (18). Furthermore, microorganisms infecting DFU wounds are becoming increasingly complex and often resistant to drugs, such as MRSA, which poses a huge challenge to the clinical treatment of DFU. Biofilm formation in a variety of microbial infections protects bacteria from antimicrobial agents and immune responses and is a cause of wound healing failure. It can lead to

TABLE 3 Other types of basic dressings.

Type of dressing	Constituents	Experimental model	Mechanism of action	Clinical effects
Hydrocolloid (77–79)	Semipermeable membranes, foam materials, or nonwoven polyester fibers and hydrophilic biocompatible gel proteins or polysaccharides	Randomized controlled clinical trials involving 535 subjects	Absorbs wound exudate, creates a wet local environment, has a buffer effect	Easy to use, conducive to wound debridement, long maintenance time
Alginate with chlorhexidine hexametaphosphate (CHX-HMP) (80, 81)	CHX-HMP	Wound pathogens were evaluated *in vitro* in terms of total viable count (TVC) and an agar diffusion zone of inhibition (ZOI) model	Absorbs a large amount of wound exudate, prevents leakage, and provides a moist healing environment for the wound surface	At baseline, silver alginate was more effective than CHX-HMP alginate in the TVC test, but CHX-HMP alginate was more effective in the ZOI test
Rubidium-containing calcium alginate hydrogel (82)	Rubidium, calcium alginate hydrogels	*In vitro* experiments on human umbilical vein endothelial cells (HUVECs) and *in vivo* experiments on male SD rats with type II diabetes mellitus were conducted	Kills and inhibits the growth of bacteria, increases the secretion of vascular endothelial growth factor and improves activation of the nuclear factor (erythroid-derived 2)-like 2 (NRF2)/heme-oxygenase-1 (HO-1) signaling pathway	Promotes the migration of fibroblasts and keratinocytes, accelerates neovascularization and epithelial reformation, and improves collagen deposition
Fibracol collagen-alginate wound dressing (83)	Fibracol collagen, calcium alginate	Seventy-five patients with foot ulcers participated in a clinical trial	Absorbs the wound exudate to form a local wet environment and prevents leakage	Collagen-alginate wound dressing is more effective and safer than gauze dressing
Sponge foam (84–86)	Various types of polymers and foam plastics	Clinical trials were conducted on six patients with venous leg ulcers	The sponge foam is pressed by the bandage to achieve even and optimal pressure on the wound bed	Mainly used for mild or high- consumption wounds; can protect and integrate into the skin
Silver-releasing foam dressings (87–89)	Silver	Adult patients diagnosed with type 2 diabetes were selected	Anti-inflammatory and antibacterial	Silver-releasing dressings can significantly reduce the ulcer area in patients with lower limb ulcers and improve the cure rate
Films (48, 90, 91)	Film inclusions (commonly used preservatives such as silver-based compounds, gentamicin sulfate, and other compounds)	Preliminary tests were performed using microspheres with a diameter of 0.71 microns	The inclusion kills bacteria and prevents systemic infection	Single films are only suitable for wounds with a small amount of exudate; the clinical efficacy of combined films is better

wound enlargement requiring surgical intervention or even life-threatening. Therefore, there is an urgent need for dressings with anti-infective properties to address this dilemma (92).

To promote wound healing, several drugs (or bioactive agents) are added to the matrix of the dressing preparation, most commonly antimicrobials (93). This has driven the research and application of Bacteriostatic dressings. Combining different antibacterial agents and biological materials to make new antibacterial dressings is currently an active area of research in modern skin tissue engineering. Honey, antibiotics, metals, and metal oxides are the most common pharmaceutical ingredients with antibacterial properties. Biomaterials come in many forms and structures, including thin films, hydrogels, sponges, nanofibers, and other types of structures (94).

In a meta-analysis of 767 patients, patients treated with honey dressings were better than the control group in terms of complete healing rate (RR=1.32, 95% CI: 1.10-1.57, P=0.003), bacterial complete clearance (RR=2.56, 95% CI: 1.33-4.92, P=0.005), mean healing time (SMD=-1.12, 95%CI: -2.06~-0.19, P=0.02). No serious adverse effects were observed (95). Clinical trials have shown that honey contains active enzymes such as glucose oxidase, which produces hydrogen peroxide and inhibits microbial growth (96). Compared to conventional dressing techniques such as iodine voltammetry, honey dressing treatment can significantly better than the control group in terms of pain score, wound pH reduction, antibacterial effect and other aspects (P<0.05), and does not cause blood glucose fluctuations. Clinical confirmation: In the control group, 50 patients with DFU were treated with routine dressing changes. In the treatment group, 50 patients added topical application of honey to this basis. On the 20th day of dressing change, 25 cases of infection occurred in the control group and 18 cases in the treatment group (P<0.05) (97). Therefore, honey dressings can be used clinically as effective and safe antibacterial dressings. The use of a combination of debridement and silver ion hydrogel dressings is another representative anti-infective therapy. Clinically, both nonmechanical (autolysis, enzymatic) and mechanical methods (sharps surgery, wet-to-dry debridement, water-based hyperbaric lavage, ultrasound, negative pressure

wound therapy (NPWT), and biosurgery/maggot debridement therapy) are used to debride wounds (98). In NPWT, negative pressure is applied to the wound tissue; this reduces the area of wound exposure and accelerates wound healing by promoting adhesion to the surrounding tissue. The filler used with NPWT is also important; silver ion hydrogel dressings have significantly higher antimicrobial activity than gauze and foam dressings (99). The antimicrobial mechanism of silver ion dressings may be related to their degradation of bacterial cell walls and the promotion of bacterial content outflow. Silver ions also affect the metabolic activity of bacteria by altering the structure of their cell membranes, leading to the death of bacteria that are in an active but nonculturable state (100). Despite this, the use of silver ion dressings for long periods often results in local irritation and decreased compliance among patients. It is therefore necessary to optimize silver nanoparticles (SNPs) for use in wound dressings. The researchers found that sericin- and chitosan-capped silver nanoparticle (S/C-SNP)-loaded hydrogel were more acceptable to patients, and the antimicrobial activity and wound closure exhibited by S/C-SRP were confirmed by histopathological results (101).

The development of antimicrobial dressings based on active polymeric biomaterials has produced unexpected effects. Injectable adhesion-thermosensitive polysaccharide-based dressings (FEPs) deliver exosomes from adipose stromal cells and thereby promote the repair of DFU wounds. The antimicrobial activity of FEP dressings is one of their primary functional properties, especially in cases in which drug-resistant bacteria are present in wounds (102). In addition, a copper (Cu)-containing bioactive glass nanocoating with uniform nanostructure that continuously releases copper ions was prepared on a natural eggshell membrane using pulsed laser deposition (PLD) technology. Copper ions significantly inhibit the survival of bacteria, especially methicillin-resistant *Staphylococcus* and *E. coli*. The presence of copper ions effectively slows the process of bacterial infection (103). A dressing that can be used to rapidly sterilize wounds has also been described in the literature. It contains Ag/Ag@AgCl/ZnO heterogeneous nanostructures embedded in a hydrogel. Exposure of this hydrogel system to simulated visible light kills 95.95% of *E. coli* and 98.49% of *S. aureus* within 20 minutes. In this system, the production of reactive oxygen species is enhanced by exposure to visible light, allowing the Ag/Ag@AgCl nanostructure to enhance the photocatalytic and antibacterial activity of ZnO. The slow release of Ag+ and Zn^{2+} stimulates the immune system, resulting in the production of large numbers of white blood cells and neutrophils. It also produces synergistic antibacterial effects and accelerates wound healing (104). Cross-linked double-network hydrogel biodressings consisting of polyethylene glycol diacrylate (PEGDA) and sodium alginate (ALG) have potent antimicrobial activity and promote healing without any biological agents or drugs. In this innovative dressing design, biomaterials rather than biologics provide antimicrobial activity (105). In summary, the development of antibacterial dressings is aimed at designing and producing safer and more efficient antibacterials.

Typical antibacterial dressings are mainly honey dressings and silver ionomer dressings. The weak acidity of honey inhibits the growth of pathogenic bacteria, thus acting as a cleansing and anti-infective agent, and it also has a strong ability to promote ulcer healing (22). In recent years the use of honey dressings has become more widespread and has proven to be effective. There are many different types of honey and its complex composition needs to be further explored in the future to better guide its clinical application. Silver ion dressing improves wound hygiene and has antibacterial activity. It may cause silver staining on wounds, and silver allergy in some patients limits its use.

5.4 Composite dressings

Composite dressing refers to the improvement on the basic dressing by adding polysaccharides, proteins, polymers and other bioactive substances to make the dressing function more perfect. Crosslinking polysaccharides and proteins on top of the base dressing (hydrogel, alginate, film) can form a porous structure. It has many advantages, such as allowing oxygen, drugs, nutrients and metabolic wastes to move in and out of the cell (106). It provides better quality conditions for the healing of DFU. We list the three most commonly used materials for composite dressings and describe them in detail.

5.4.1 Collagen dressings

Normal human skin contains a large amount of collagen, which gives it a tight, intact structure. However, the skin tissue of diabetic individuals contains elevated levels of human matrix metalloproteinases (MMPs) and lysine oxidase (LOX). And the collagen it contains is sparse, disorganized, and prone to breakage. Consequently, the dermal collagen structure is compromised, and the skin appears rough. This abnormal collagen microenvironment may be a risk factor for DFU (107). Therefore, based on the pathological alterations, the development of direct collagen dressings or dressings that promote normal collagen synthesis has great prospective clinical value. In the study, a multifunctional nano and collagen-based materials was designed and applied to animal models of diabetes. When applied to wounds, the antimicrobial nanoparticles first form a layer that prevents bacterial proliferation and eliminates biofilms. After it has been applied, the thermosensitive collagen matrix is plasticized so that it conforms to the wound shape and adheres closely to the wound surface (108). The tensile strength, porosity, and biocompatibility of collagen and its ability to support cell proliferation can be increased using electrochemical deposition methods. Exposure of wounds to thermosensitive collagen increases granulation tissue, epidermal thickness, and reconstruction of tissue. All of these effectively promote wound repair, regardless of whether it binds to adipose-derived mesenchymal stem cells (109). In addition, a porous dressing is made from novel collagen (COL-SPG). In that study, the *in vivo* evaluation of the COL-SPG 3D sponge exhibited with enhanced collagen synthesis and aids in faster reepithelialization (110). In a new study, a bionic, double-layer antibacterial collagen scaffold is reported. It consists of an epidermal anti-bacterial collagen used to prevent wound infections combined with a dermal collagen-glycosaminoglycan scaffold. The dressing exhibits a structure similar to that of natural skin, successfully inhibiting

bacterial growth and promoting angiogenesis. This dressing is an excellent candidate for enhancing diabetic wound healing (111).

Collagen is a biocompatible structural protein that is biodegradable and biomimetic, making it an ideal source of biomaterials for tissue engineering and regenerative medicine. Collagen dressings significantly improve wound closure, positively affect unhealed DFU, highly promote angiogenesis and rapid re-epithelialisation (112). There is insufficient evidence to demonstrate the superiority of specific collagen biological sources or combinations. Wound dressings containing collagen appear to have some benefit in the treatment of diabetic foot ulcers and should be carefully considered by the clinician managing the wound.

5.4.2 Chitosan dressings

Chitosan (CS) has received a lot of attention in the field of medical research because of its antibacterial activity, antioxidant activity, high safety, biodegradability, and biocompatibility. CS exists in many forms, such as gels, thin films, and nanoparticles (113, 114). After modification or coupling to other substances, chitosan becomes a wound dressing and a drug delivery system when loaded with active substances (115, 116). The value of chitosan in the treatment of DFU is closely related to its anti-infective and antioxidative properties. For example, hydrogels prepared from chitosan and agarose have pore sizes (90-400 μm) that are compatible with cell internalization and proliferation. Hydrogels containing more than 188 μg/mL chitosan exhibit strong antibacterial properties (50). The antibacterial activities of two types of antimicrobial composite films (CH_2CuO-CH and CH_2Cu-CH) made of nanocopper oxide or encapsulated in nanocopper and covered with chitosan (CH) were compared. The results showed that both inhibits the growth of *Escherichia coli* and *Bacillus.* The CH2CuO-CH suppression circle values were 1.0 cm and 0.75 cm, respectively. The suppression circle values of CH2Cu-CH were 0.6 cm and 0.5 cm, respectively. Thus, the nanocomposite CH_2CuO-CH film shows stronger antimicrobial activity and can be used in antimicrobial applications (117). However, the biological effectiveness of chitosan requires its solubility in water or other solutions, and this limits its widespread use. Ways in which chitosan can be modified to avoid these limiting conditions and enhance its original activity is a focal area of current research. For example, a new family of cationic hydrogels based on arginine-based poly (ester urea urethane) (Arg-PEUU) and glycidyl methacrylate-modified chitosan (CS-GMA) is currently being developed. This modified chitosan dressing accelerates the healing of infected wounds by activating RAW 264.7 macrophages and causing them to increase their release of NO and TNF-α (118). A novel antibacterial hydrogel dressing made of poly(aminoethyl)-modified chitosan (PAEMCS) has also been reported. In antibacterial experiments on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella*, PAEMCS had higher antibacterial activity than CS at the same concentrations. Experiments have shown that the increase in the number of amino groups increases the antibacterial activity of CS (119). An injectable chitosan-based POSS-PEG hybrid hydrogel has been reported. It contains polyhedral oligosilsesquioxane (POSS), a nanoparticle with excellent stability and biocompatibility. In addition, the effect of hydrogel as a wound repair material in diabetic mice was systematically and comprehensively evaluated by histomorphological analysis using a full-thickness diabetic wound model. The results showed that the hydrogel-treated wound showed faster epithelial tissue regeneration, fewer inflammatory cells, more collagen deposition and higher VEGF expression levels (120). In one study, a novel supramolecular photothermal nanoparticles (MCC/CS NPs) were reported. It consists of mono-carboxyl corrole (MCC) and CS. MCC molecules have good photothermal properties and achieve a photothermal conversion efficiency of 66.4%. Under near-infrared laser irradiation, diabetic wound models of bacterial infection confirmed that MCC/CS NPs can effectively kill drug-resistant bacteria, accelerate wound healing and angiogenesis, and exhibit good biocompatibility (121). Chitosan dressings play an important role in the antimicrobial treatment of DFU.

5.4.3 Nanodressings

Nanomaterials are materials at least one dimension of which (in three-dimensional space) is between 1 and 100 nm in size; this is approximately equivalent to the scale of 10~1000 atoms closely aligned together. Nanoparticles have the property of penetrating the barrier with a small particle size and a high specific surface area. Nanoparticles can interact with biological constituents and infiltrate wound sites. Nanomaterials possess the ability to effectively transport and deliver various pharmacological agents, such as nucleic acids, growth factors, antioxidants, and antibiotics, to specific tissues (122). Specific nanodrug delivery systems can enter the cytoplasmic space or activate specific transport mechanisms, improving drug retention. The incorporation of bioactive molecules prevents drug degradation and enhances therapeutic effects. By using biocompatible and biodegradable nanomaterials, drug delivery systems can be designed to enhance wound healing and provide sustained drug release. Furthermore, nanomaterials can be tailored to meet specific requirements for wound healing, such as enhanced cellular and tissue penetration, antibacterial properties, and controlled mechanical properties. In addition, appropriate antimicrobial action can be achieved by controlling the size and shape of nanopreparations. In wound healing, nanomaterials have shown the potential to promote cell proliferation, migration, angiogenesis, and extracellular matrix remodeling and prevent infections (123). Therefore, nanoparticles are more suitable for many purposes than macroscopic materials.

Nano silver, nano copper, nano copper oxide, nano zinc oxide and nano gold have been widely used in research (124). With the advancement of nanotechnology, it is possible to produce nanoscale sterling silver particles. Silver nanoparticles (AgNPs) is non-toxic to eukaryotic cells but highly toxic to prokaryotic cells. This allows nanosilver to show powerful antibacterial activity. In addition, the antibacterial activity of copper nanoparticles is similar to that of silver nanoparticles. The antibacterial activity of ZnNPs is generally lower than that of AgNPs and Copper NPs. AuNPs have been found to be effective against gram-negative bacteria but less effective

against gram-positive bacteria. In a groundbreaking study, the AgNPs were incorporated into carrageenan to develop nanosilver acticoat. *In vivo*, *in vitro* and in silico three-mode studies were carried out. *In vivo* studies showed that dressing with Carrageenan silver nanoparticles (CAgNPs) acticoat promoted wound healing and had good reepithelialization and dense collagen deposition capabilities. *In vitro* experiments were tested against *Escherichia coli* and *Staphylococcus aureus*. Computer analysis provides information about the drug similarity of the dressing and predictions related to human health hazards. The application potential of this dressing in DFU was emphasized (125). Compared with ordinary silver dressing, nano-silver dressing has a larger contact surface and stronger bactericidal effect. In a clinical observation of 160 patients, the patients were randomly divided into groups that received treatment with either epidermal growth factor, a nanosilver dressing, a nanosilver dressing combined with epidermal growth factor, or saline alone, and the time required for wound repair to each healing stage was recorded. The results showed that the wound repair time of the combined nanosilver and epidermal growth factor group was shorter than the repair times of the epidermal growth factor group and the control group, and the differences were statistically significant (126).

Another category of nanomaterials is represented by organic nanomaterials such as self-assembled peptide (SAP) hydrogels made from natural amino acids. SAP hydrogels can be used to create extracellular matrix (ECM)-like nanostructures that mimic the human cellular microenvironment and improve the local lesion state of DFU (127). In the section in which we reviewed collagen dressings, we stated that elevated levels of MMPs in diabetes lead to abnormal collagen deposition. To address this problem, a 3D polycaprolactone (PCL)/collagen (PC) nanofiber dressing (3D-PC) was created that contained the MMP inhibitor doxycycline hydrochloride (DCH) and the antibacterial agent cefadroxiride (CEX). MMPs inhibitors can limit the overexpression of MMPs in DFU wounds to avoid delayed wound healing (128). Multiplex nanoenzymes are another important organic nanomaterial. However, research has been slow due to the incompatible reaction microenvironments of these nanoenzymes and the unsuitability of conventional assembly strategies. Notably, a recent study reported that a fiber-based compartmentalization strategy could be used to provide the preferred microenvironment for each nanozyme. The development of this integrated platform promotes the use of multiplexed nanozymes in DFU therapy (129). Furthermore, a bilayer nanofiber scaffold has been developed (130). The first layer of the multifunctional bilayer nanofiber scaffold (DLS) consists of mupirocin and lidocaine hydrochloride uniformly doped into PCL; the function of this layer is to provide an initial "burst" release of lidocaine hydrochloride followed by slow release of mupirocin. The second layer consists of chitosan. DLS nanofibers are thermally stable, have high antibacterial activity and are nontoxic to fibroblasts (131). In addition to chemicals, herbal extracts have shown unique advantages for use in nanodressings. A study reported the incorporation of *Calendula officinalis* extracts into an electrospun fiber scaffold. The electrospun fiber scaffold consisted of poly(ϵ-caprolactone) (PCL), maize alcoholic protein (Zein), and gum arabic (GA). It exhibits desirable mechanical properties and degradability suitable for skin tissue engineering (132).

Clinical response to wound infections is still dominated by antibiotic therapy. Antibiotic treatment increases microbial resistance over time and often leads to a poor prognosis. It is worth mentioning that nanofiber dressings that do not use antibiotic therapy as a means of treatment are gradually gaining attention. For example, electrospun hyaluronic acid/polyvinyl alcohol/polyethylene oxide blends encapsulated with new ZnO NPs/cinnamon essential oil (CEO) have demonstrated advantages such as good antimicrobial effects, promotion of rapid healing of traumatic injuries, and high safety (133). The remaining inorganic and organic nanodressings are summarized in tabular form in Tables 4, 5.

In conclusion, nanomaterials have the following advantages. High surface/volume ratio allows for small filler size and inter-fill distance. Improved mechanical properties, high strength. Resistance to scratches. In addition, metal ion nanomaterials can be repeatedly sterilised to better control wound infection and promote wound healing. However, current nano dressings also have certain shortcomings that need to be further optimized. It still suffers from high resistance to cell infiltration and multiple dressing changes. Insufficient understanding of formulation properties. Structural relationship, need for easier exfoliation of particles, and dispersion. Cost-efficiency (123).

5.5 Bioactive dressings

Bioactive materials are biomaterials that cause a specific biological or chemical reaction by the surface of the material that promotes or influences the connection between the tissue and the material, induces cellular activity or regenerates new tissue. Natural biomaterials derived from cells, cytokines, and even plants and their biological derivatives (e.g. exosomes) have particular advantages in biomedical applications. Most of them can, for example, by activating the immune system, also exhibit specific tissue and organ tropisms. And for some living cells (e.g. stem cells) have a strong ability to penetrate tissue and biological barriers. These properties provide an opportunity to construct large molecule drug carriers that can cross physiological barriers and have good efficacy against DFU (148). While smart nanomaterials cause changes in the bacterial cell membrane in wounds by regulating different particle shapes, compositions, sizes and surface charges. It includes compositional changes and reactive oxygen species (ROS) production, lipid peroxidation, loss of respiratory activity, etc. This ultimately allows biofilm disruption and promotes healing of the DFU (149).

We enumerate the use of cells, cytokines, enzymes and inhibitors, outer membrane vesicles, and smart nanomaterials in DFU dressings.

5.5.1 Scaffold dressings with stem cells

Individuals with DFU have usually been in a state of hyperglycemia for a long time, and the affected blood vessels and

TABLE 4 Summary of other inorganic nanodressings.

Inorganic nanotype	Mean particle size (nm)	Synthesis method	Carrier	Microbial species affected
Polydopamine-assisted silver nanoparticles (134)	300-500	Chemical reduction	Sericin (SS)/AGAR composite membrane	*E. coli* and *Staphylococcus aureus*
Silver nanoparticles (AgNPs) (135)	35-65	*In situ* synthesis	Polydopamine-coated sericin/ polyvinyl alcohol (PVA) composite film	*E. coli* and *Staphylococcus aureus*
Silver nanoparticles (AgNPs) (136)	——	*In situ* synthesis	Sericin/polyvinyl alcohol (PVA) blend film	*E. coli* and *Staphylococcus aureus*
Copper oxide nanoparticles (CuONPs) (137)	88-97	Electrospinning	Polycaprolactone (PCL) film	*Pseudomonas aeruginosa, Klebsiella acidogenes* and *Staphylococcus aureus*
4,6-diamino-2-pyrimidine mercaptan functionalized gold nanoparticles (138)	2.44	Chemical reduction	Fibroin (SF) mixed matrix membrane	MDR *E. coli*
4,6-diamino-2-pyrimidine mercaptan (DAPT) gold nanoparticles (139)	——	——	Bacterial cellulose	*E. coli* and *Pseudomonas aeruginosa*
Zinc oxide nanoparticles (ZnO (NPs) (140)	60-120	Polydopamine (PDA) helps modify	Sericin (SS)/polyvinyl alcohol (PVA)	*E. coli* and *Staphylococcus aureus*
Zinc oxide nanoparticles (ZnO (NPs) (141)	——	Electrospinning technology	Chitosan-polyvinyl alcohol (PVA) nanofibers	*E. coli, Pseudomonas aeruginosa, Bacillus subtilis* and *Staphylococcus aureus*

tissue cells produce different degrees of lesions. A number of animal experiments have shown that stem cell transplantation is effective in promoting hemodynamic reconstruction and regeneration as well as in regulating the secretion of inflammatory factors, growth factors, and immunomodulatory factors. These effects, which are due to the unique paracrine properties of stem cells, give the method great clinical potential for the treatment of DFU. Conventional stem cell transplantation techniques such as systemic intravenous or local intradermal injection have resulted in low cell survival rates. Intravenously injected cells are also rarely effective because they do not target the lesion (150). If stem cells are inoculated into biomaterials such as nanomaterial scaffolds and collagen scaffolds, cell survival and therapeutic potential can be improved, and targeted delivery can be achieved (151). Therefore, the scaffold delivery method plays a key role in determining the efficacy of cell therapies. These material delivery systems can be used to build *in vivo* cell banks that gradually release stem cells that fill defects and participate in the regeneration of vascular networks (152). Overall, stem cells (SCs) have many advantages. It can express many cytokines and a variety of nerve growth factors that

TABLE 5 Summary of other organic nanodressings.

Active ingredient	Fiber diameter (nm)	Synthesis method	Carrier	Effect
Curcumin (CUR) and tetracycline hydrochloride (TCH) (142)	360-770	Electrospinning technology	Poly-ϵ-caprolactone (PCL)/AV hybrid nanofiber scaffold	Promotes fibroblast proliferation; antibacterial, nontoxic
Aloe vera (AV) (143)	131.6 ± 27.5	Double-nozzle electrospinning technology	Gelatin (gel) and poly (ϵ-caprolactone) (PCL) mixed scaffold	Improves cell activity, sterilizes; nontoxic
Polyurethane and propolis ethanol extract (PU/EEP) (144)	237.3 ± 65.1	Electrospinning technology	Polycaprolactone/gelatin (PCL/gel) nanofiber scaffold	Promotes collagen deposition, inhibits the growth of *Staphylococcus epidermidis*, *Staphylococcus aureus*, and other species
Propolis ethanol extract (EEP) (145)	——	Electrospinning technology	Polyurethane-hyaluronic acid (PU-HA) nanofiber wound dressing	Improves dermal development and collagen deposition; antibacterial
Cinnamon essential oil (CEO) and nano cerium dioxide (nCeO2) (146)	178.5 ± 34.3	Double-spinneret electrospinning technique	Polyurethane (PU) and polyvinyl alcohol-gelatin (PVA/gel) nanofiber scaffolds	Improves cell count; antibacterial
ZM essential oil (147)	218 ± 58	Glutaraldehyde vapor chemical crosslinking	Polyvinyl alcohol-based nanofiber pad	Inhibits the growth of *Staphylococcus aureus, Pseudomonas aeruginosa* and *Candida albicans*

modulate immune function in wounds. It can also accelerate DFU healing by promoting angiogenesis, cell proliferation and nerve growth as well as modulating the inflammatory response. SCs are promising for research as they can solve the problem of low stem cell viability and accelerate wound healing by scaffolding drug delivery systems. Many types of SCs are used in the treatment of skin wounds, such as bone marrow mesenchymal SCs (BMMSCs), umbilical cord mesenchymal SCs (UCMSCs), peripheral blood SCs (PBSCs), adipose-derived mesenchymal SCs (AMSCs), placenta-derived mesenchymal SCs (PMSCs), human amniotic fluid-derived stem cells (AFMSCs), and human gingival-derived mesenchymal SCs (GMSCs). Currently, BMMSCs are the most frequently used type (153). These pluripotent stem cells could differentiate into several types of fibroblasts, osteoblasts, chondrocytes, adipocytes, vascular endothelial cells, epithelial cells.

The process by which these useful cells promote DFU healing is also very interesting. Significantly, these cells can promote endogenous angiogenesis through microenvironmental regulation and expression of vascular hemophilic factor (vWF) and vascular endothelial growth factor (VEGF). At the same time, they stimulate epithelial stem cell recruitment through the secretion of tumor necrosis factor-α (TNF-α) and reduce lymphocyte function and interferon gamma (IFN-γ) activity in the inflammatory response (154). Secondly, these cells promote the production of cytokines such as IGF-1, EGF, MMP-2, MMP-9, and the tissue inhibitors of the extracellular receptor kinase (Erk) signaling pathway, metalloproteinase (TIMP)-1 and -2, by human keratinocytes (155). Moreover, they secrete mitogens that stimulate the proliferation of keratin-forming cells, dermal fibroblasts and epithelial cells *in vitro* (156).

Dressings in which stem cells are used as active therapeutic substances have been extensively reported. For example, on the treatment of diabetic rabbit ear ulcers, circulating angiogenic cells (CACs) were isolated from the peripheral blood mononuclear cell fraction. Osteopontin is a stromal cell protein involved in wound healing and acts as a scaffold for the delivery of CACs. This design increases the angiogenic potential of CACs (150). It has also been reported that incorporation of allogeneic nondiabetic bone marrow-derived mesenchymal stromal cells (MSCs) into collagen scaffolds promotes the healing of diabetic rabbit ear ulcers. The efficacy of this dressing is related to the amount of MSCs in the dressing. If a collagen dressing containing 1,000,000 MSCs is used for treatment, a total neovascular length of 270731 ± 146549 mm can be observed. However, collagen dressings containing 100,000 or 50,000 MSCs were used for treatment, and the total length of neovascularization was only 231849 ± 90588mm and 250521 ± 80213mm, respectively. At the same time, the radial diffusion distance of nutrients from capillaries to damaged tissue was significantly shortened to about 5.4 ± 0.7 μm (157). In a study of the tissue-engineered skin substitutes, a three-dimensional bionic scaffold of collagen-chitosan sponge carrying bone marrow-derived mesenchymal stem cells (BM-MSCs) was designed. BM-MSCs secrete collagen and upregulate the expression of proangiogenic factors such as HIF-1α, VEGF and PDGF. These combined effects promoted ulcer healing in diabetic rats (158).

Other stem cell dressings are summarized in tabular form according to the types of delivery scaffolds they employ (Table 6).

SCs express many cytokines and a variety of nerve growth factors and regulate immune function in wounds and may accelerate DFU healing by promoting angiogenesis, cell proliferation and nerve growth as well as modulating inflammatory responses. These investigations have demonstrated that stem cell dressings are unique and that they have better efficacy than other dressings. At this point in time, most stem cell dressings are still being evaluated in animal experiments and have not been directly applied in clinical practice. Research on stem cell dressings has provided clinical experience and potential for the treatment of DFU. It is expected that stem cell dressings will benefit patients in the clinic over time.

5.5.2 Cytokine dressings

Cytokines (CK) are low molecular weight soluble proteins induced by immunogens, mitogens, or other stimulants to be produced by a wide range of cells, and have a variety of functions, including regulation of intrinsic and adaptive immunity, hematopoiesis, cell growth, APSC pluripotency, and repair of damaged tissues. Cytokines suggested to be effective in DFU dressings are Basic Fibroblast Growth Factor (bFGF), Vascular Endothelial Growth Factor (VEGF), and Platelet−Derived Growth Factor (PDGF), among others (164).

Basic fibroblast growth factor (bFGF) can be involved in many biological processes such as angiogenesis, wound healing, neurogenesis, cellular differentiation and migration, and it can bind to all receptors (165). It has been found that the prepared bFGF-gel dressing effectively promotes wound healing in rats. Through histological and immunohistochemical analyses, it was found that bFGF-gel dressing could promote the proliferation of traumatic cells, reduce traumatic inflammation and enhance capillarization (166). It suggests that basic fibroblast factor can be applied to DFU excipients.

The vascular endothelial growth factor (VEGF) family is an important family of growth factors that are key players in the process of angiogenesis. In recent years, VEGF has also been found to have neuroprotective and trophic roles and to be an important signaling molecule for nerve repair and regeneration (167). One study showed that decreased VEGF expression was associated with poor wound healing and an increased ratio of matrix metalloproteinase-9 to tissue inhibitor of metalloproteinase-1 in infected DFUs, thus suggesting that VEGF could be applied to DFU dressing disease to promote wound healing (168).

5.5.3 Exosomes dressings

Exosomes are nanoscale lipid bilayer-enclosed structures carrying proteins, lipids, RNAs, metabolites, growth factors, and cytokines that can play key roles in mediating intercellular communication both locally and systemically (169). A study showed that the application of autologous mesenchymal stem cell exosomes to treat high glucose-induced HUVECs or DFU mice revealed that mmu_circ_0001052, an exosome of Adipose-derived stem cells (ADSC), had a better effect in promoting wound healing

TABLE 6 Summary of cell dressings created using various delivery scaffolds.

Type of bracket	Type of cell	Animal model	Mechanism of action	Curative effect
Type 1 collagen scaffold (159)	Mouse BM-MSCs and AD-MSCs	Diabetic C57BL/6 mice induced by STZ	Promotes new blood vessel formation and reepithelialization; effectively accelerates wound healing. Notch signaling is upregulated. Increased concentration of macrophages in the wound.	Mouse ADSC can enhance diabetic wound healing, and the therapeutic effect is similar to that of BMSC.
Silk fibroin (SF)/chitosan (CS) scaffold (160)	Rat adipose stem cells (ADSCs)	Stz-induced diabetic Sprague –Dawley rats	Secretes EGF, fibroblast growth factor, insulin-like growth factor and other important cytokines that repair keratinocytes. ADSCs participate in the establishment of a neovascularization bed.	The wound closure rate of treated animals was significantly improved.
Gellan gel - hyaluronic acid (GG-HA) scaffold (161)	Human adipose stem cells (hASC)	Diabetic CD1-ICR mice induced by STZ	Reduces the number of macrophages at the wound site and promotes healing from the inflammatory stage to the proliferative stage. Promotes the re-epithelialization of keratinocytes.	Accelerates wound closure. Increases the thickness of new epidermis.
Type 1 collagen rolling scaffold (162)	MSC of mouse bone marrow origin	Diabetic C57BL/6 mice induced by STZ	The hypoxic core environment of the rolling scaffold activates MSCs to promote cell survival and produce VEGF. Enhances wound angiogenesis.	Cell proliferation increases. Enhanced wound healing.
N-carboxyethyl chitosan and diacylhydrazine adipate crosslinked scaffold with hyaluronate aldehyde (163)	Bone marrow mesenchymal stem cells (BM-MSCs)	Stz-induced SD rats	BM-MSCs secrete growth factors, inhibit the expression of M1 macrophages and promote the expression of M2 macrophages. Promotes granulation tissue formation, collagen deposition, nucleated cell proliferation, and new blood vessel formation.	Promotes diabetic wound healing

and improving wound area. And the mechanism of action of mmu_circ_0001052-miR-106a-5p-FGF4 mRNA network in DFU angiogenesis was verified (170). Another study showed that exosomes isolated from platelet-rich plasma (PRP-exos) had a promising therapeutic effect on DFU wounds and verified the involvement of MALAT1-mediated signaling in the treatment of DFU wound healing by PRP-exos. This may help to identify the best targets and effective therapies for DFU treatment (171).

In conclusion, exosomes have a high targeting capacity, which improves the efficiency of drug use and reduces the frequency of drug use. It also has the advantages of high drug-carrying capacity and high loading efficiency. And it can promote low immunogenicity and reduce body clearance. It has high temporal stability and can produce combined and synergistic therapeutic effects (172).

5.5.4 Autologous platelet-rich plasma dressings

In recent years, an increasing number of studies have demonstrated the unique clinical advantages of autologous platelet-rich plasma (PRP) dressings (173–175). It has been confirmed that autologous platelets are enriched with more than 1100 different protein types and contain more than 1500 protein-based bioactive factors (176). The most abundant proteins in platelets are signaling proteins, including growth factors (epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), chemokines and other cytokines (interleukin-1β, platelet basic protein, platelet factor 4, and C-C chemokine ligand 5), adhesion proteins (vitamin d-binding proteins, fibrinogen, fibrinogen, fibronectin, and vitreous connecting proteins), proteases, and antiproteases (177). On the other hand, platelets contain amino acids, hormones (insulin, estradiol, adrenocorticotropic hormone, androgens, estrogen, progesterone, and human growth hormone), corticosteroids, thyroxine, serotonin, adrenaline, histamine, enzymes, vitamins, organic acids, pigments, ions, dissolved gases, nutrient molecules, and metabolic products (178). Wound healing can be accelerated and supplied with substances through Autologous platelet-rich plasma dressings due to the many active ingredients enriched in platelets.

In one study, 90 patients with DFU were randomly divided into a local injection of PRP supplemented by hydrogel coverage group (Group A), a PRP gel and hydrogel dressing coverage wound group (Group B), and a hydrogel dressing covering wound group (Group C). The wound healing rate in Group A was 93.2% ± 0.8%, approximately 41.1% and 71.9% higher than the healing rates in Group B and Group C, respectively. The mean duration of hospitalization for Group A patients was 40.5 ± 1.8 days, approximately 21 days and 48 days shorter than those of Groups B and C, respectively. There were significant differences both in wound healing rate and in duration of hospitalization (179). The most important mechanism responsible of PRP dressings is that these dressings release growth factors in proportions that optimally promote gene expression in target cells. Thus, they increase collagen synthesis and promote cell division and proliferation. In addition, because white blood cells and platelets have similar sedimentation rates, PRP obtained by centrifugation contains a certain concentration of white blood cells, improving its local anti-infection ability. Since PRP is extracted from the patient, it is low in immunogenicity and high in safety (180). At the same time, it has

also been reported that PRP can be uniformly incorporated directly into collagen-glycosaminoglycan (collagen-gag) scaffolds. This loaded scaffold releases key growth factors that promote wound healing. It can be used to overcome the bottleneck created by collagen-gag scaffolds that rely only on local endogenous signals to promote healing (181). For the reasons discussed above, PRP dressing therapy is widely popular in the clinic and can greatly reduce the long-term medical burden of patients with DFU.

Platelets release growth factors, cytokines and interleukins, which have a critical impact on healing mechanisms, including angiogenesis, cell migration and proliferation and ECM protein synthesis (182). The efficacy of Autologous platelet-rich plasma dressings appears to cover a wide range of indications. The use of autologous PRP improved wound healing in a shorter period of time compared to traditional wound care. Platelet-rich plasma may be an effective and promising treatment for chronic DFU, with PRP being able to heal in a shorter period of time. However, the mechanism of action of these products has not been fully elucidated.

5.5.5 Acellular wound matrix

Decellularized extracellular matrix (dECM) is obtained from human or fish skin by decellularization technologies that include chemical methods, physical methods, enzymatic treatment, and osmotic treatment (183–186). Unlike the aforementioned collagen dressings, dECM contains approximately 75% natural collagen but also includes fibrin, fibritin, proteoglycans, glycosaminoglycans, stromal cell protein, and other proteins (187, 188). Current studies have shown that dECM not only anchors cells but also has activities that affect cell survival, proliferation and function. Various components of dECM with specific functions interact with each other to promote wound healing (188). Decellularized fish skin matrix is rich in a large number of lipids that are omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These compounds regulate wound healing processes, form bacterial defense barriers, and alter skin physiology at the cellular and molecular levels (189). Another advantage of using decellularized matrix therapy in cases of dermal trauma is that dECM is almost cell-free and weakly immunogenic. The ECM is a major component of the skin and is critical for chronic wound healing. Thus, dECM is an emerging research target for the clinical application of bioactive dressings. A randomized clinical trial showed that wound dressings containing human decellularized dermal matrix (ADM) exhibited a trend toward better wound healing and greater wound area reduction compared to conventional care in a controlled trial involving 168 DFU patients (190).

ECM compositions are emerging bioactive wound dressings due to their ability to modify cellular properties in healing wounds. Despite the excellent biological properties of conventional ECM membranes and their demonstrated efficiency in the clinical treatment of skin wounds, there are still some drawbacks that prevent their widespread use. Considering that most ECM membranes do not possess antimicrobial properties, the risk of potentially transmitting fungal, bacterial, or viral infections should be carefully addressed to avoid any unfavourable complications. In addition, due to the heterogeneity of biologically derived materials, the development of standard protocols to improve the consistency of ECM membranes is necessary for future clinical applications.

5.5.6 Smart nanomaterials dressings

Smart polymer nanomaterials are able to dynamically sense changes in environmental stimuli and respond accordingly by changing their physicochemical properties, similar to the self-regulation and adaptive ability of biological systems in nature (191). If the molecular structure is applied to the diabetic foot ulcer dressing after careful design, the dressing can respond to a variety of stimuli such as changes in ambient temperature, pH, light, ions, molecules, electric and acoustic fields, which is more conducive to the healing of DFU wounds. The most introduced smart nanomaterials are nanoemulsions and nanoparticles.

Nanoemulsions are kinetically stabilized emulsions with nanoscale droplet sizes (192). It is a widely used formulation in diabetic wound healing applications due to its excellent physicochemical properties and high patient tolerability. It was found that the synergistic effect of insulin-loaded nanoemulsion and homogenized aloe vera gel given to diabetic rats resulted in faster wound closure (193). And it proved to be an effective and promising treatment for diabetic wounds. A naringenin nanoemulsion gel enriched with tocotrienols has been formulated for the treatment of diabetic foot ulcer wounds. The droplet size, surface charge, spreadability, polydispersity index, viscosity, *in vitro* release kinetics and mucosal adhesion properties of the stabilized nanoemulsion gel were evaluated by several metrics. The results showed that an increase in polymer concentration of the nanoemulsion gel increased the mucosal adhesion properties and decreased the drug release rate (194). Thus, the use of nanoemulsion gels is a promising approach to wound management associated with diabetic complications.

Nanoparticles with small size and large surface area to volume ratio are effective in increasing penetration and biological interactions at the wound site. It triggers cell proliferation, cell signalling, cell-cell interactions, vascularisation and epithelialization (195). Therefore, it is ideal for topical drug delivery applications. It has been reported that gelatin nanoparticles were constructed to test the therapeutic effect on diabetic foot ulcers by *in vitro* model human endothelial cells and *in vivo* model diabetic foot ulcer rats. It was found that the nanoparticles showed higher wound healing rate, cell proliferation, blood vessel formation and epithelialization (196).

In summary, nanomaterials, especially smart nanomaterials, have outstanding performance and great research prospects in diabetic foot ulcer treatment. In the future, smart nanomaterials will appear in diabetic foot ulcer dressings with outstanding performance.

5.6 Dressings and modern technology

Current academic research on the development of dressings for chronic wounds is not limited to the simple mixing of various biological materials. Current designs are more individualized and

are based on the wounds of the patient. Dressings that are based on the specific wound morphology and the condition of the lesion eliminate the mismatch between the wound and the dressing size and improve the patient's fitness. Moreover, this multidisciplinary approach integrates physics, zoology, and intelligent technology. Functions such as real-time dynamic monitoring and wound response can be added to the treatment.

5.6.1 3D bioprinting technology

3D printing (3DP) is a technology that uses a digital model file as the basis for constructing an object by printing layer by layer using a bondable material such as powdered metal or plastic. For the medical field, it is undoubtedly a great boon. the maturity of 3DP technology has largely inspired the rapid development of reconstructive bionics. Especially for chronic wounds such as DFU, its emergence has given hope to diabetic foot ulcer patients. Currently, the most established 3DP technology is Drop-on-demand (DOD), which offers the advantages of low cost, fast printing speed, high resolution, and the ability to change the concentration gradient (197). However, there are drawbacks such as low inoculum density and impaired cell viability and function due to cross-linking and gelation processes. The study reports the use of 3D bioprinting to fabricate implantable multilayer vascularized bioengineered skin grafts. The graft is formed using one bioink containing human foreskin dermal fibroblasts (FBs), human endothelial cells (ECs) derived from cord blood human endothelial colony-forming cells (HECFCs), and human placental pericytes (PCs) suspended in rat tail type I collagen to form a dermis followed by printing with a second bioink containing human foreskin keratinocytes (KCs) to form an epidermis. *In vitro*, it has biological and morphological functions comparable to those of natural human skin (198). Provide solid evidence for the use of 3DP technology in DFU. The current research hotspot is more inclined on how to design innovative, individualized and versatile 3DP technology and apply it with diabetic foot ulcer wounds. For innovative technologies, the design of novel 3D printed biomaterials with mechanical, rheological and biological properties that match those of the target tissue is a key factor. In the case of individualized techniques, each patient's condition and physical functioning is different. In the future, precision medicine will be a big trend. The 3D bioprinting technology converts the raw material for preparing a variety of dressings into a bio-ink, which can then quickly seal skin defects according to the contours of the wound. Specifically, when diabetic foot ulcers occur, the wound site is scanned to prepare an accurate 3D model for 3D printing. Once the 3D model is obtained, it is transferred to a printer with the corresponding bioink and converted to a 3D printed toolpath. The printed scaffold is then crosslinked and applied to the wound site. The design of personalized adjuncts based on the size and shape of the wound in diabetic foot ulcer patients adapts to the patient's unique wound topology to ensure complete wound coverage and better aesthetics after healing (199, 200).

Acellular dermal matrix (ADM) and gelatin methacrylamide (GelMA) bioinks with shear-thinning properties print simulated full-layered skin. This not only enhances cell viability and proliferation but also supports *in vitro* epidermal reconstruction and improves wound healing quality (201). Another report describes a digital light processing (DLP)-based 3D printing technique that prints functional living skin (FLS). It used gelatin methacrylate (GelMA), hyaluronic acid (HA-NB), and photoinitiator phenyl lithium-2,4,6-trimethylbenzoyl phosphite (LAP) as bioink. This method allows precise targeting of human skin fibroblast (HSF) and human umbilical vein endothelial cell (HUVEC) clusters with high cell viability and thereby promotes skin regeneration and neointima formation (202). Research has designed a biomaterial that can be 3D printed. It contains functionalized sodium alginate (FSA), biomineralized silica, and DNA from salmon sperm. And investigated the chronic wound healing ability of DNA-bSi30@FSA dressings in mouse models of diabetes. On the 6th day of local wound monitoring, the residual wound in the DNA-bSi30@FSA dressing group was significantly reduced (50.5%). The wound area in the control group, FSA, DNA@FSA and Si30@FSA dressing groups was still 89.7%, 87.3%, 66.8% and 61.9%, respectively. Finally, on day 15, the wounds treated with the DNA-bSi30@FSA, Si30@FSA, and DNA@FSA dressing groups showed faster healing than those of the saline and FSA dressing groups. Thus, the 3D-printed DNA-bSi30@FSA dressing could significantly enhance wound healing in a chronic wound in diabetic mice by enhancing the synergistic bioactive functions of DNA and biomineralized silica nanotherapeutics (203).

3D oprinting has emerged as a promising technology designed to rapidly close skin defects according to their contours. The 3D bioprinted skin substitute has a strictly layered structure with controlled cell type and density localisation, enhancing homology with natural human skin. It also offers better cost and time efficiency. However, 3D bioprinting still has some limitations and requires long-term evaluation studies in large animal models to confirm its future clinical potential. Its precise molecular mechanisms have not yet been elucidated.

5.6.2 Light, heat and electrical effects

Scholars have focused considerable attention on the auxiliary effects of light, heat, and electricity in dressing applications in recent years (204). Multicolor light irradiation in the near infrared region (NIR) is most commonly reported. Physical stimulation and photoactivation can increase the biological effects of a variety of materials (205). Photothermal therapy (PTT) mainly destroys bacterial cell membranes and biofilms by light-induced heat generation. NIR laser irradiation also has a bactericidal effect through its effects on ROS levels, ATP levels, lipid peroxidation, glutathione and adenosine triphosphate accumulation, and bacterial membrane disruption; through these mechanisms, it appears to assist in eradicating multidrug resistant bacteria and accelerating wound healing in MRSA-infected diabetic models (206–208). In DFU treatment, PTT can be combined with chemobacteriological therapy to form a synergistic antibacterial strategy. At present, metal nanoparticles, non-metallic nanoparticles, organic dyes, etc. have been found to be used as photothermal conversion agents. Among them, black phosphorus (BP) showed high photothermal conversion efficiency. In one study,

BP modified with bismuth oxide (Bi_2O_3) and ϵ-polylysine (ϵ-PL) was reported. When BP/Bi_2O_3/ϵ-PL is infiltrated into the hydrogel, NPs@gel-2 is obtained. NIR irradiation triggers the photothermal conversion capability of BP/Bi_2O_3. ϵ-PL generates high temperatures to further damage bacterial cell membranes and lead to leakage of intracellular substances, achieving sterilization and preventing biofilm formation. In the *in vitro* antimicrobial test, NPs@gel-2+NIR was 100% inhibited against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli*. And on day 14 of the infected wound model monitoring in diabetic animals, the wound shrinkage rates of each group are sorted as follows: NPs@gel-2+NIR (98.8%) > Control (−) (refers to an uninfected wound) (94.2%) > NPs@gel-2 (88.1%) > Blank gel (81.2%) > Control (+) (71.7%) (209).

After the wound appears, the movement of ions begins to repair the wound and create an endogenous electrodynamic field. Endogenous and exogenous electric fields can provide the earliest signals needed to initiate cell proliferation, migration, and eventual wound epithelialization. Changes in the electric field then direct cells, molecules, and drive the wound healing process. The final charge and bioelectric dynamic field penetrates into several stages of wound healing, driving cells and molecules and maintaining the flow of oxygen and nutrients necessary for wound healing. Many treatments can promote wound healing by influencing electrical factors. For example, exogenous electric fields such as pulsed electromagnetic fields (PEMF), pulsed high-voltage stimulation (PHVS), and low-level laser therapy (LLLT) promote wound healing. LLLT can produce electrical action because it increases the yield of ATP, thereby improving the efficiency of the sodium-potassium pump. The potential difference between the inside and outside of the battery is guaranteed (210). Microfabricated electrodes, pH-sensitive hydrogels, and controlled electronic circuits can be added to dressings. And the release of the drug by applying a voltage to change the pH near the electrode. This results in a dressing that allows flexible stimulus-response drug delivery (211). Therefore, not only can an electrical stimulus be applied to the dressing, a low voltage can also be applied directly to the wound, providing a new treatment that accelerates wound healing. Electrodynamic fields direct the migration of fibroblasts, keratinocytes, macrophages, and epithelial cells and influence blood rheology and microcirculation to promote wound healing. For example, microbattery-impregnated bioelectric dressings (BEDS) allow an animal's wound to close completely within 4 weeks without infection or transplantation. Bioelectric dressings are therefore a promising wound dressing for DFU (210, 212). In addition, a pulsed capacitive coupled electric field (PCCEF) platform has been researched and developed. When the pulse width ≥ 10 μs, PCCEF significantly promoted the migration and proliferation of human dermal fibroblasts and HaCaT cells, enhanced M2-type polarization of macrophages, and promoted wound healing in mouse models (213).

Light, heat and electricity are excellent aids in dressing application. Physical stimulation and photoactivation can enhance the biological effects of a wide range of materials. Light stimulation of platelets has great potential for platelet activation and fibroblast stimulation. The electric field directs the migration of fibroblasts, keratinocytes, macrophages and epithelial cells, affecting blood rheology and microcirculation, thereby promoting wound healing. However, relevant studies are currently inadequate, limiting its widespread clinical use.

5.6.3 Microneedling dressings

A painless and simple drug delivery system known as microneedling (MN) has been developed since the turn of the 21st century. The MNs used in this system contain porous structures with continuous nanometer- or micron-scale pores that transport drugs or biofluids through capillary action. Changing the porosity of these structures affects the internal fluid flow, and this in turn adjusts the mechanical strength of the MN device (214). The stratum corneum (SC) is the outermost keratinizing layer of the skin, and only molecules smaller than or equal to 500 Da (dalton) in size can move freely in the skin. Microneedles can create microchannels through the SC of the skin without stimulating proprioceptive pain nerves (215). And there are numerous studies showing that MNs can successfully deliver both small and large molecule drugs (e.g., insulin, vaccines, proteins, and chemotherapeutic agents) through the skin. Compared with conventional bandages and hydrogels, MNs have the advantage of transporting drugs through deeper layers of skin and improving drug delivery efficiency (216). The chances of infection when using MN are much smaller than with traditional hypodermic needles. There is great interest in the development of MN dressings for DFU. Inspired by the structure of mosquito mouthparts, MN devices with fixed and liquid transfer parts have been developed. In addition, the dressing as a whole features an ultrafine needle tip, a personalized pattern design, and programmable needle length and can be prepared with a variety of mechanical strengths to realize intelligent painlessness (217). Inspired by the flat and sloping structure of shark teeth, MN patches are designed to provide stable adhesion. MN can also be combined with MXene electronics to provide sensitive monitoring of the motion of the dressing (218). Inspired by the highly folded structure of insect wings, the versatile three-dimensional (3D) origami MN patch features an ultrafine needle structure, microfluidic channels, and circuits. It promotes wound healing by releasing drugs in a controlled manner and monitoring exercise (219). In one study, a near-infrared (NIR)-responsive hair microneedle patch was reported. It contains hierarchical microparticle (HMP), ZnO, vascular endothelial growth factor and basic fibroblast growth factor. It delivers drugs to the extremities painlessly, accurately and controllably under NIR irradiation. Among them, hair-derived HMP exhibits the ability to clear ROS, thereby preventing damage to blood vessels. At the same time, zinc oxide (ZnO) nanoparticles confer excellent antibacterial activity on the MN patch, and the photothermal effect of HMP under near-infrared radiation can further enhance this activity. *In vivo*, it significantly raises the temperature of the fingertips of diabetic rats and promotes collagen deposition and angiogenesis during wound healing (220). In addition, the development of hydrogel dressings in the form of microneedles exhibits better sustained release of drugs, adequate mechanical properties, and better biocompatibility than traditional dressings (221, 222).

Microneedling can safely and sustainably deliver large amounts of therapeutic agents through the skin without compromising painless injections. And does not increase the risk of infection. Microneedle dressings accelerate the healing process of diabetic wounds, reduce the inflammatory response, promote collagen deposition at regenerated tissue sites, and improve glycaemic control in animals. However, once the microneedle dressing adheres to the skin, it is difficult to peel off from the skin. And there are still individual differences in side effects such as skin redness, irritation, or skin allergies. If high doses are required for treatment, the MN patch may be underloaded, so the MN patch must be used multiple times. It is effective in diabetic wound management and has great potential in the treatment of other chronic skin injuries.

5.6.4 Intelligent bandages

The smart bandage is a product of wearable technology for the treatment of DFU. With the development of the Internet of Things, and emerging biomaterials, wearable sensing and information and communication technologies are key steps in driving the transformation of health care services to a new model of connected health (CH) care (223). In the clinical diagnosis and treatment of DFU, the healing stage of the wound and the existence of complications such as infection are usually judged only by medical evaluation and by the naked eye. The use of such rough wound assessment and fixed dressing change patterns not only frequently results in missing of the optimal treatment time but also leads to unnecessary dressing changes and increased medical costs. Smart bandages solve this problem. Smart bandages based on wearable technology are mainly used for integrated wound identification, real-time dynamic monitoring of wounds in which information on important parameters is collected, and early prediction of infection. In addition to 3D printing, online wound image scanning and recognition technologies such as image recognition, computer modeling, nanomaterial fabrication and modification, combined with offline smart material manufacturing, can further promote the individualized design of wound dressings (224). Smart bandages monitor pH, sodium, potassium, calcium and uric acid levels, and wound temperature in real time to provide quantitative diagnosis (225). The basic principle on which they work is that the wound exudes fluid into the sensing area or excites the pH response current, resulting in flow analysis results through voltage changes and potential conversions (226, 227). In a pioneering study, a flexible bioelectronic system was developed. It facilitates the integration of current smart bandage technology with sensors and stimulators. This system consisting of wirelessly powered, closed-loop sensing and stimulation circuits with skin-interfacing hydrogel electrodes capable of on-demand adhesion and detachment. The system continuously monitors skin impedance and temperature and provides electrical stimulation depending on the wound environment. Across preclinical wound models, the treatment group healed ~25% more rapidly and with ~50% enhancement in dermal remodeling compared with control (228). In addition, a smart disinfection bandage based on wirelessly powered ultraviolet C (UVC) radiation has been reported. The induction coil is seamlessly hidden in a fabric bandage and coupled to the rectifier circuit. This system can effectively eradicate Gram-negative bacteria and *Pseudoalteromonas sp* (229). Nowadays, a wide variety of mobile applications are widely used worldwide in many areas of daily activities, which greatly improve the quality of human life. Meanwhile, mobile applications for DFU monitoring and care are being developed. Cassidy et al. developed the first mobile app capable of accurate DFU detection using AI and cloud-based technologies. This system was tested in a 6-mo clinical evaluation at two UK National Health Service hospital sites (Lancashire Teaching Hospitals and Salford Royal Hospital) and is currently being further developed to improve functionality and accuracy (230). The success of this type of program development also provides some guidance in the selection of dressings.

5.6.5 Orthopedic prosthetics and regenerative medicine

An orthopedic prosthesis is a medical device designed to replace missing or damaged bones and joints, thereby restoring mobility and function to individuals with musculoskeletal injuries or conditions. But improving the biocompatibility of orthopedic prostheses to promote better integration with natural tissues is an urgent problem. Regenerative medicine focuses on how to induce human tissue regeneration and identify instructive cues that direct refractory tissues down a regenerative path (231). This suggests the potential of regenerative medicine to use natural tissue repair and regeneration to improve the biocompatibility of prostheses and potentially replace lost tissue. Cells, growth factors, and biomaterials can be used to stimulate the body's natural regenerative ability to repair damaged tissue. Therefore, by using regenerative medicine techniques, we can develop orthopedic prostheses that are more compatible with natural tissues. Its application to ulcer defects in DFU patients is expected to reduce the risk of various complications (such as infection, inflammation, rejection) and improve long-term outcomes for patients. In addition, as mentioned earlier, patients with DFU have a high rate of amputation. For these patients, orthopedic prostheses are undoubtedly a huge boon. Sensory neuroprosthetic devices have been designed to provide individuals with the sensation of natural feet, enabling them to walk more confidently and controllably (232).

6 Healing of diabetic foot ulcers

The healing of DFU is complicated. At the cellular level, it is the result of multiple cells working together. At the molecular level, it can affect the activities of various cell types through the activation of many signaling pathways. With continuous improvements in science and technology, the healing process of DFU is gradually becoming clear, and this has a very significant effect on clinical treatment (Figure 4).

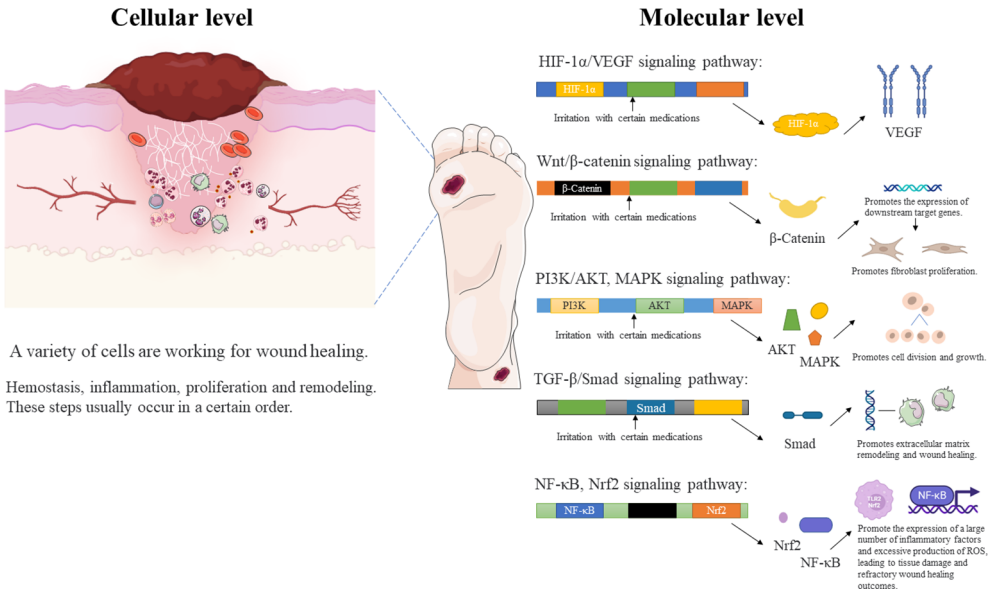

FIGURE 4
The healing mechanism of DFU.

6.1 Diabetic foot ulcer healing at the cellular level

Wound healing is normally a dynamic process. It occurs in four main stages: hemostasis, inflammation, proliferation and remodeling. These stages usually occur in a specific order. Hemostasis occurs immediately after injury; it is characterized by recruitment of platelets and circulating clotting factors to the wound site to initiate clotting. When platelet recruitment occurs, damaged cells release signaling factors that activate resident macrophages and damage-related molecular patterns. At the same time, stimulated polymorphonuclear neutrophils (PMNS) enter from the vasculature to defend against pathogens. When PMNs begin to migrate to the wound, they initiate the inflammatory phase. Neutrophils release chemokines that recruit circulating monocytes from the peripheral blood to the wound site. The recruited monocytes differentiate into macrophages and dendritic cells. They perform key steps in the inflammatory phase of wound healing. The proliferative stage begins with the recruitment and activation of keratinocytes and fibroblasts. At this stage, growth factors stimulate keratinocytes to re-epithelialize the wound. During this time, the temporary matrix established by platelets during hemostasis is replaced by granulated tissue. Fibroblasts secrete proteases and matrix metalloproteinases (MMPs) that degrade the temporary matrix. They also secrete collagen and other extracellular matrix (ECM) proteins into the granulation tissue. The final phase, the remodeling phase, begins as soon as granulation tissue appears. Here, fibroblasts differentiate into wound contraction myoblasts, and the collagen III that was deposited in the ECM during the proliferation stage is exchanged for collagen I, which has greater tensile strength (233, 234).

6.2 Diabetic foot ulcer healing at the molecular level

6.2.1 HIF-1α/VEGF signaling pathway

Vascular endothelial growth factor (VEGF) is a highly specific endothelial growth factor. It can promote increases in vascular permeability, extracellular matrix degeneration, vascular endothelial cell migration, proliferation and angiogenesis. Serum levels of miR-217, HIF-1α, and VEGF were measured in patients with DFU, in patients with simple diabetes mellitus (DM), and in healthy controls. Rat models of DFU were also established and treated with miR-217 inhibitors and/or with HIF-1α siRNA. It was found that inhibition of miR-217 upregulated the HIF-1α/VEGF pathway, promoted angiogenesis and decreased inflammation in DFU rats, thus effectively promoting healing of ulcer sites (235). Zhu et al. confirmed that activation of the HIF-1α/VEGF/VEGFR2 pathway promotes angiogenesis and showed that increasing angiogenesis has a therapeutic effect on wound healing in DFU (236).

6.2.2 Wnt/β-catenin signaling pathway

β-catenin is an important downstream factor in the Wnt pathway and is a multifunctional protein. It is closely related to skin damage and healing. When the Wnt/β-catenin pathway is activated, phosphorylation of β-catenin in the cytoplasm is inhibited, degradation is reduced, and β-catenin accumulates continuously. When the amount of β-catenin reaches a certain level, it enters the nucleus and interacts with T-cell transcription factors and lymphoid-enhancing transcription factors to form protein complexes. In this way, it can promote the expression of downstream target genes, facilitate the generation of epidermis and

keratinocytes, and promote wound healing (237). *Panax notoginseng* has been used to treat diabetic models. It was found that PN improves albuminuria and podocyte EMT in diabetic rats by inhibiting the Wnt/β-catenin signaling pathway, providing experimental support for novel treatment options for diabetic neuropathy (238).

6.2.3 PI3K/AKT signaling pathway

Protein kinase B, Akt, also known as PKB or Rac, plays an important role in cell survival and apoptosis. The PI3K/AKT signaling pathway regulates many critical cellular processes, including nutrient uptake, anabolic response, cell growth, differentiation and survival, proliferation, and cell motility (239). It was found that when the miR-138 inhibitors IGF-1 and LY294002 were administered to DFU rat models, the resulting downregulation of miR-138 alleviated the animals' inflammatory responses and promoted healing of DFU by stimulating the PI3K/AKT pathway and hTERT (240). Use of the plasma ED-EV method to treat diabetic mice has also been described in the literature, and it has been confirmed that this method of treatment slows the aging of mouse fibroblasts and accelerates wound healing by promoting YAP nuclear translocation and activating the PI3K/Akt/mTOR pathway (241).

6.2.4 TGF-β/Smad signaling pathway

Transforming growth factor-β (TGF-β) is considered to a polymorphic signaling pathway that is involved in many processes in both mature organisms and developing embryos, including cell growth, differentiation, apoptosis, the epithelial-mesenchymal transition, and extracellular matrix production. Smad proteins act downstream of the TGF-β family of receptors and carry signals from the cytoplasm to the nucleus resulting from the binding of TGF-β and its receptors. The TGF-β/Smad signaling pathway plays a key role in regulating extracellular matrix remodeling and wound healing (242). By observing wound healing in DFU mouse models, researchers found that the number of WDR74 and M2 macrophages in the wound tissue of DFU mice was decreased. Activation of the TGF-β/Smad pathway increased the expression of M2 macrophage markers (argininase-1 and YM1) and IL-4 while decreasing the expression of M1 macrophage markers. TGF-β/Smad pathway activation also promoted ECM production and facilitated wound closure in diabetic mice. Overexpression of WDR74 increased Smad2/3 phosphorylation, increased the number of M2 macrophages and the production of ECM, and alleviated DFU (243).

6.2.5 MAPK signaling pathway

Mitogen-activated protein kinases (MAPKs) are a group of evolutionarily conserved serine/threonine protein kinases. They are involved in various biological processes such as cell growth, apoptosis, hormone signaling, the immune response, and the inflammatory response. MAPK genes can be divided into three main subfamilies, namely, extracellular signal-regulated kinases (ERKs), Jun N-terminal kinases (JNKs) and p38 MAPKs (244). Zhu et al. used bioinformatics methods to screen for novel genes that play an active role in diabetes-related fibroblasts. The results showed that the MAPK signaling pathway plays a key role in the regulation of diabetic wound healing. MAPKAPK3, HSPA2 and TGFBR1 are potential key genes in this regulatory process. ETV4 and NPE2 play a potential role in the regulation of wound regeneration in DFU (245).

6.2.6 NF-κB signaling pathway

Nuclear factor-κB (NF-κB) is an important cellular kernel transcription factor that is involved in many physiological and pathological processes, such as inflammatory responses, immune responses, cell survival, and apoptosis. The NF-κB pathway is the most typical proinflammatory signaling pathway because it is activated to express a large number of proinflammatory factors, including cytokines, chemokines and adhesion molecules (246). Sun et al. treated a rat model of diabetic foot ulcers with paeoniflorin and found that paeoniflorin effectively inhibited NLRP3- and NF-κB-mediated inflammation in DFU by inhibiting CXCR2. Wound inflammation in DFU rats was greatly reduced, and wound healing improved (247).

6.2.7 Nrf2 signaling pathway

Nuclear transcription factor-erythroid 2-related factor 2 (Nrf2) belongs to the Cap-n-Collar family of alkaline leucine zipper proteins and is part of the most significant antioxidant stress signaling pathway. The imbalance of free radicals and antioxidants that occurs in DFU patients may lead to excessive production of ROS, resulting in tissue damage and refractory wound healing (248). Sun et al. established streptozotocin (STZ)-induced diabetic rat models and human immortalized keratinocytes treated with high glucose (HG). Both models were treated with paeoniflorin. It was found that STZ-induced diabetic rats had delayed wound healing compared with normal rats. The animals are characterized by severe oxidative DNA damage, low expression of vascular endothelial growth factor (VEGF) and transforming growth factor β1 (TGF-β1), and increased apoptosis. Treatment with PF activated the expression of Nrf2 and improved wound healing in DFU rats. *In vitro* experiments have also shown that PF accelerates wound healing, alleviates oxidative stress, increases cell proliferation and migration, reduces apoptosis, and increases the expression of VEGF and TGF-β1 through the Nrf2 pathway under hyperglycemic conditions (249).

7 Perspectives

This review summarizes the properties of different dressings to help healthcare professionals better select dressings, summarizes the healing mechanisms of diabetic foot ulcers at the cellular and molecular levels, and serves as a reference for researchers trying to develop dressings that target specific mechanisms. DFU is a devastating complication of diabetes mellitus associated with infection, amputation and death and are affecting an increasing number of diabetic patients. Dressings play a very important role in the management of DFU, and different categories of dressings each

have their own advantages and disadvantages. The correct use of dressings can improve the healing rate of DFU and lower the cost of treating DFU. However, due to the complex pathogenesis of DFU, susceptibility to infection, long duration of the disease, and the possibility of recurrence, treating DFU is a major challenge for physicians and patients. Currently, there are some challenges and limitations regarding the research and application of dressings.

At the laboratory stage, healing of rat skin wounds is very different from that of mouse wound healing models compared to human wound healing, and some of the available experimental data have been obtained from small randomized controlled trials with a high risk of bias. In addition, due to the complex pathogenesis of DFU, it is difficult to understand how certain dressings promote skin regeneration and how they interact with wound tissue cells.

At the clinical trial stage, many dressings are in dire need of well-designed randomized controlled trials to validate efficacy, and robust clinical trials are lacking. Despite the complexity and high-hazard nature of DFU, clinical trial research has accelerated the development of ideal dressings that offer hope to DFU patients. We should pay attention to promote the clinical application of emerging dressings to truly benefit patients.

At the stage of clinical application, at present, the types of clinically applied dressings are still relatively small, and they need to be changed frequently, and the replacement process consumes a lot of manpower, material and financial resources, and the effect is poor, which consumes the energy and confidence of doctors and patients. Poor patient compliance, the price of dressings is too high will also affect the clinical application of dressings.

For patients, inexpensive dressings with better efficacy, fewer potential complications, and the ability to reduce pain are more likely to be accepted.

For physicians, the quality of wound care depends largely on the correct choice of dressing. This requires medical staff to have a good understanding of the properties of different dressings to select the right dressing and change it regularly. The selection of wound dressings should be based on the specific conditions of the patient and the unique advantages of the dressing to maximize the benefits to the patient, so that the individual application of the dressing can be achieved. However, there is no standardized set of guidelines for dressing selection that can be referred to.

DFU is a prevalent and serious global health problem, suggesting future research into higher-quality clinical dressings and a more comprehensive and systematic evaluation of the effectiveness of dressings. Current dressings have their limitations, and research into the "ideal" multifunctional dressing could benefit patients with DFU. The ideal dressing should have good moisture balance, protease barrier, growth factor stimulation, antimicrobial activity, oxygen permeability, and the ability to promote autolytic debridement. Based on the recognition of the above issues, the future development of dressings should focus on intelligence, personalization, multi-target coverage, combined application of multiple dressings and accelerated clinical translation. Current research on dressings in DFU management lacks clear evidence-based guidelines and robust clinical trials on their effectiveness. There is no standardized set of guidelines for dressing selection that can be referenced. Two major strategies are key to improving overall outcomes. The first is a significant investment in conducting high-quality clinical trials, which is necessary to improve the evidence base for clinical dressing care. The second is to ensure that healthcare professionals using DFU dressings adhere to existing evidence-based guidance on the selection of appropriate dressings, and guidelines are needed to encourage clinicians to adopt those treatments that have been shown to be effective in robust studies, primarily in randomized controlled trials.

Author contributions

CY and CX conceived, supervised, writing-reviewed the manuscript, cofounded and co-administrated the project. All other authors took a part in originally draft writing. Authors approved the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Total contact casts versus removable offloading interventions for the treatment of diabetic foot ulcers: a systematic review and meta-analysis

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Objective: This study aimed to evaluate the effectiveness of total contact casts (TCCs) versus removable offloading interventions among patients with diabetic foot ulcers (DFUs).

Methods: A comprehensive search was done in databases Embase, Cochrane Library, and, PubMed. The references of retrieved articles were reviewed, up until February 2023. Controlled trials comparing the effects of TCCs with removable offloading interventions (removable walking casts and footwear) in patients with DFUs were eligible for review.

Results: Twelve studies were included in the meta-analysis, involving 591 patients with DFUs. Among them, 269 patients were in the intervention group (TCC), and 322 in the control group (removable walking casts/footwear). The analysis revealed that the TCC group had higher healing rates (Risk Ratio(RR)=1.22; 95% confidence interval(CI):1.11 to 1.34, p<0.001), shorter healing time (Standard Mean Difference(SMD)=-0.57; 95%CI: -1.01 to -0.13, P=0.010), and elevated occurrence of device-related complications (RR=1.70; 95%CI:1.01 to 2.88, P=0.047), compared with the control group. Subgroup analysis illustrated patients using TCCs had higher healing rates than those using removable walking casts (RR=1.20; 95%CI:1.08 to 1.34, p=0.001) and footwear (RR=1.25; 95%CI:1.04 to 1.51, p=0.019), but they required comparable time for ulcer healing compared with those using removable walking casts (SMD=-0.60; 95%CI: -1.22 to 0.02, P=0.058) or footwear group (SMD=-0.52; 95%CI: -1.17 to 0.12, P=0.110). Although patients using TCCs had significantly higher incidence of device-related complications than those using footwear (RR=4.81; 95%CI:1.30 to 17.74, p=0.018), they had similar one compared with those using the removable walking casts (RR=1.27; 95%CI:0.70 to 2.29, p=0.438).

Conclusion: The use of TCCs in patients with DFUs resulted in improved rates of ulcer healing and shorter healing time compared to removable walking casts and footwear. However, it is important to note that TCCs were found to be associated with increased prevalence of complications.

KEYWORDS

diabetic foot ulcers, total contact casts, removable offloading intervention, systematic review, meta - analysis

Introduction

In 2021, around 536.6 million individuals aged 20 to 79 years had diabetes worldwide, and it is projected to reach 783.2 million by 2046 (1). Additionally, there are around 541 million people with abnormal glucose tolerance (2). The International Diabetes Foundation (IDF) reports that the number of people affected by diabetic foot ulcers (DFUs) has significantly increased from an estimated 9 to 26 million in 2015 to between 40 and 60 million worldwide (3). Among people with diabetes, foot ulcers develop in approximately 19% to 34% of cases. And once they occur, there is a high recurrence rate within 3-5 years (65%). Moreover, DFUs result in a 20% incidence of lifetime lower limb amputation, with a 5-year mortality rate after amputation ranging from 50% to 70% (4).

The global costs of diabetes care, including direct and indirect expenses, have substantially risen in recent years, primarily due to foot complications. In the United States alone, the annual direct cost of diabetes care is estimated at $273 billion, with an additional $90 billion in indirect costs. Complications arising from diabetic foot conditions result in increased hospital admissions, visits to the emergency department, outpatient visits, and utilization of home health care services, leading to yearly excessive expenditure that exceeds the standard cost of diabetes-related care by 50% to 200% (5, 6).

Neuropathic foot ulcers arise due to multiple factors, such as peripheral neuropathy, peripheral arterial disease, and structural deformities in the foot. However, elevated plantar pressure plays a crucial role in initiating neuropathic foot ulcers, particularly in the absence of protective sensation (4, 7). Moreover, effective unloading of the affected area is crucial for timely wound healing, as the presence of a neuropathic ulcer can cause significant delays. Therefore, offloading therapy is considered a vital treatment approach (8, 9).

Total contact casts (TCCs) were first introduced in 1984 for the treatment of plantar ulcers (10). As the first knee-high non-removable device, it became the standard method for offloading DFUs in the early stages (11). However, emerging evidence suggests that removable devices, such as cast walkers and therapeutic shoes, are equally effective compared to TCC (12–14). Only a limited number of quantitative analyses have been performed to compare TCC with other offloading interventions (15). Despite the existence of published meta-analysis comparing TCCs and removable offloading devices (15, 16), they focused on healing time and healing rate. There is no meta-analysis examined the effectiveness of these treatment options regarding healing time, healing rate, and device-related complications in patients with DFUs so far.

Therefore, this meta-analysis was conducted to quantitatively compare TCC with other offloading measures, such as removable walking casts and footwear, with respect to healing rate, healing time, and device-related complications in patients with DFUs. This study may shed light on the selection of appropriate offloading interventions to optimize treatment outcomes and minimize complications.

Materials and methods

This study was conducted following the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3) guidelines (17). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement served as its foundation (18).

Search strategy

We searched databases including Embase, Cochrane Library, and PubMed until February 2023 to identify relevant studies that examined the outcomes associated with the use of TCCs versus removable offloading devices in patients with DFUs. Two reviewers (Bin Li and Zhengmao Zhang) conducted the literature search independently, and no restrictions were placed on language. The review team developed and piloted search strategies for databases of bibliographic records and clinical trial registries. Medical subject headings or Entree and text words like “diabetic foot” and “cast” were used. We also reviewed the reference lists of full-text articles. Detailed search strategies were seen in the Appendix.

Inclusion criteria

Participants from various countries who were over 18 years old had neuropathic DFUs. The intervention involved using TCCs on the patients. The comparators were patients with DFUs who used removable offloading devices, including removable walking casts (knee-high and ankle-high removable devices) and footwear. Outcomes were ulcer healing rates, ulcer healing time, and

device-related complications. Type of study design was randomized controlled trial or non-randomized controlled trial. Trials published in English, Dutch, Spanish, Italian, German, or Portuguese were considered for inclusion. The inclusion criteria did not impose restrictions based on the duration of reported DFUs, publication status, reported outcomes, or the outcome assessment instruments used.

The definition of Device-related Complications: Device-related Complications were defined as Complications which induced by device, including device failure, skin maceration or abrasions, infection.

Exclusion criteria

Studies were excluded if (1) data were unavailable (2); they were conference summaries, animal experiments, case reports, and systematic reviews or meta-analyses (3); they were duplicate publications (4); their full text was unavailable.

Study selection and data extraction

The review team members independently reviewed articles retrieved from databases. Firstly, the titles and abstracts of articles were reviewed to remove duplicate publications. The remaining articles then underwent full-text screening to identify studies satisfying the predefined inclusion criteria. In case of disagreements, discussions (Bin Li, Zhengmao Zhang, Jianying Xie, Quanyong LIu, and Chenxi Yang) took place, or, a third independent reviewer (Aifang Lin or Jianping Huang) was consulted, if necessary. The following information was extracted from individual studies: the first author's name, publication year, country, participant characteristics, duration, outcome measures, and details of offloading interventions. Primary outcomes were healing rates, healing time, and incidence of device-related complications.

Quality assessment

Risk of bias in individual RCTs was evaluated using the tool recommended by the Cochrane Reviews. This was conducted using the software Review Manager 5.4. Domains through which bias may be introduced into the results of RCTs included bias arising from the randomization process, bias in blinding participants and personnel, bias arising from measurement of outcomes, bias caused by missing outcome data, bias arising from selection of the reported results, and other sources of bias. In this process, any disagreements were resolve through discussion until a consensus was reached. For non-RCTs, quality assessment was done using the Newcastle–Ottawa Scale (NOS), whereas it was conducted using specific tools for cohort and case-control studies. A study can be awarded a maximum of 9 points, in which a maximum of 4, 2, and 3 can be given for the Selection, Comparability, and Outcome category, respectively. In our analysis, studies that scored above the median stars were considered to have relatively high quality, while those scoring below were deemed to have low quality.

Statistical analysis

Analysis of parallel studies was performed, where the mean change from baseline and corresponding standard deviations (SDs) were calculated. In cases where SDs change were not provided, they were estimated using the SDs at baseline and endpoint. Meta-analysis was carried out, where the Mantel-Haenszel statistical method was used to produce standard mean differences (SMD), risk ratios (RRs), and 95% confidence intervals (CIs). We compared continuous outcomes between groups using standard mean differences (SMD) and 95% CIs, while differences between dichotomous outcomes were compared using relative risks (RRs) and 95% CIs. If no events were observed in one comparison group, we added 0.5 to both groups. As recommended by the Cochrane Handbook (17), trials with no outcome events in both arms were excluded from the meta-analysis when calculating RRs. A fixed-effects model was utilized for data analysis if p-value for heterogeneity was greater than 0.1, whereas a random-effects model was employed when it was 0.1 or lower. The chi-square test was done to assess heterogeneity, where $I^2 > 50\%$ indicated significant heterogeneity. We evaluated the significance of subgroup differences to determine how categorical confounding factors affected the outcome. Sensitivity analysis was done by omitting one trial at a time to assess the stability of the results of data analysis. Additionally, Egger's test was conducted to evaluate publication bias when five or more trials of interest were analyzed. A p-value of less than 0.05 was considered the threshold of statistical significance. All the aforementioned analyses were performed using Stata/SE 15.0 software (Stata Corporation, College Station, TX).

Results

In total, 412 articles were obtained from and Cochrane Library (n=124), Embase (n=242), and PubMed (n=46). Review of these articles produced 12 studies that were finally included in the present study (12–14, 19–27). Figure 1 shows the literature selection process.

Study characteristics

In total, 591 participants were involved in the 12 studies published between 2000 to 2016. Among them, 269 participants were in the intervention group (TCC) and 322 in the control group (removable walking casts/footwear). Specifically, removable walking casts were used as offloading devices in eight studies and footwear was utilized in four studies. The length of treatments spanned from one month to six months. Study characteristics are shown in Table 1.

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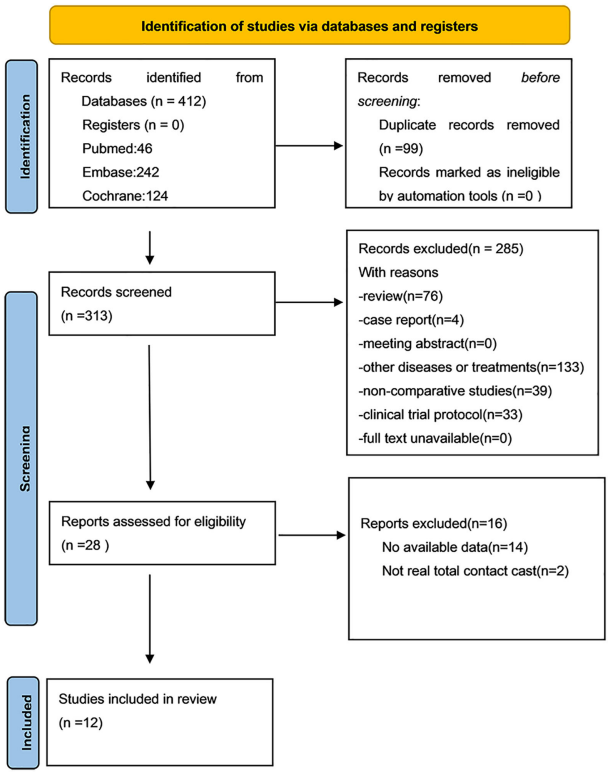

FIGURE 1
flow diagram.

Study quality

The quality of clinical trials is summarized in Figures 2, 3, and Table 2. None of the included RCTs were rated to have a high risk of bias in terms of incomplete outcome data, blinding of participants and personnel, outcome assessment, and selection of reported results. Specifically, two studies from the same pool were prone to unclear risk of bias regarding random sequence generation and received a low risk of bias score in other methodological domains. Three RCTs were rated to have an unclear risk of bias regarding allocation concealment and low risk of bias in other domains. Additionally, RCTs were pone to an unclear risk of bias in the domains of bias due to other factors. Among non-randomized controlled trials, two were rated to have a high risk of bias in the Comparability category, while they were prone to a low risk of bias in Selection and Outcome categories.

Rates of ulcer healing

Patients using TCCs had significant higher rates of ulcer healing, compared to those in the control group (RR=1.22; 95% CI: 1.11 to 1.34; p<0.001) (Figure 4), with I^2 being 35.3% (P=0.108). Subgroup analyses assessing differences in rates of ulcer healing between three types of offloading devices demonstrated very consistent results. Rates of healing were significantly higher in participants using TCCs than in those using removable walking

TABLE 1 Characteristics of the eligible studies.

Study	Year	Country	participant	Sample size		Gende (M/F)	Age (year)		Intervention			Follow-up	Outcome
				CG	EG		CG	EG	CG		EG		
Piaggesi (12)	2016	Italy	Diabetic forefoot plantar ulcer	20	20	23/17	62.3 ± 9.2	61.4 ± 9.7	removable walking boot	Removable walking cast	Total contact casting	90d or up to complete re-epithelization	Healing rates Healing time Ulcer size reduction
Lavery (19)	2014	USA	Diabetic plantar ulcers	27	23	29/21	NA	NA	a removable boot with a shear-reducing foot bed	Removable walking cast	Total contact casting	Not Mentioned	Healing rates Healing time Shear-reducing foot bed
Strakhova (21)	2014	Russia	Neuropathic Diabetic forefoot plantar ulcer	20	20	21/19	54.1 ± 9.9	49.3 ± 12.0	ankle-foot pneumoorthosis with a HAS-337 TM Orlett	Removable walking cast	Total contact casting	6 months	Healing time
Gutekunst (20)	2011	USA	Neuropathic diabetic plantar ulcers	12	11	19/4	53 ± 10	55 ± 13	removable cast walker boot	Removable walking cast	Total contact casting	Not Mentioned	Healing time Pressure reduction
Faglia (13)	2010	Italy	Neuropathic diabetic plantar ulcers	22	23	30/15	61.7 ± 10.4	59.0 ± 8.5	removable cast walker	Removable walking cast	Total contact casting	90d	Ulcer surface reduction Healing time Complications Healing rates costs

(Continued)

TABLE 1 Continued

Study	Year	Country	participant	Sample size		Gende (M/F)	Age (year)		Intervention			Follow-up	Outcome
				CG	EG		CG	EG	CG		EG		
Vandeweg (22)	2008	Netherlands	Neuropathic diabetic plantar ulcers	20	23	33/9	58.1 ± 11.1	64.8 ± 10.8	custom-made temporary footwear	Foot wear	Total contact casting	16w	Healing rates Healing time Complications Ulcer surface reduction
Caravaggi (23)	2007	Italy	Neuropathic diabetic plantar ulcers	29	29	NA	NA	NA	Aircast Pneumatic Walker	Removable walking cast	Total contact casting	90d	Healing rates Complications
Piaggesi (14)	2007	Italy	Neuropathic diabetic plantar ulcers	20	20	NA	61.1 ± 6.4	59.8 ± 8.2	Optima Diab walker	Removable walking cast	Total contact casting	12w	Complications Healing rates Healing time Time for placement Costs satisfaction
Van (24)	2003	France	diabetic plantar ulcers.	51	42	78/15	62 ± 7	58 ± 11	off-loading shoes	Foot wear	nonremovable fiberglass cast boot	Not Mentioned	Healing time complications
Birke (25)	2002	USA	neuropathic forefoot ulceration	57	13	NA	58.2 ± 11.5	47.3 ± 9.1	Healing shoe	Foot wear	Total contact casting	12w	Healing time Healing rates
Armstrong (26)	2001	USA	neuropathic foot ulcerations	20	19	32/7	NA	NA	removable cast walkers	Removable walking cast	Total contact casting	12w	Healing rates Healing time Activity of the patients
Caravaggi (27)	2000	Italy	Neuropathic diabetic plantar ulcers	24	26	34/16	59.2 ± 9.9	60.5 ± 10.7	a cloth shoe with a rigid sole with unloading alkaform insoles	Foot wear	Total contact casting	30d	Healing rates

casts (RR=1.20; 95% CI:1.08 to 1.34; p=0.001) or footwear (RR=1.25; 95% CI: 1.04 to 1.51; p=0.019) (Figure 5).

Time for healing

Patients using TCCs spent significantly shorter time healing foot ulcers than those using removable walking casts or footwear (SMD=-0.57; 95% CI: −1.01 to −0.13; p=0.010) (Figure 6), with I^2 being 78.5% (P<0.0001). However, subgroup analyses comparing TCC versus removable walking casts versus footwear showed no significant difference in the time for healing either between TCCs and removable walking casts (SMD=-0.60; 95% CI: −1.22 to 0.02; p=0.058) or between TCCs and footwear (SMD=-0.52; 95% CI: −1.17 to 0.12; p=0.110) (Figure 7).

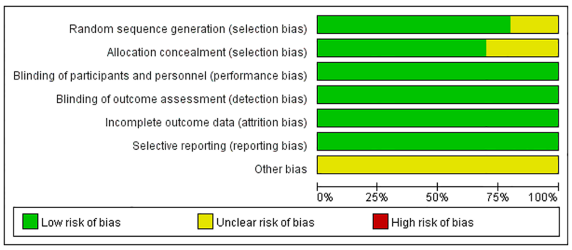

FIGURE 2
Risk of bias summary of RCTs.

Device-related complications

There were seven studies reported the device-related complications. In TCCs group, there were 30 device-related complications, of these complications, 11 were device failures, 13 were skin complications (skin abrasions or skin maceration which can heal on its own), 6 were wound infections. In control group (removable walking casts and footwear), there were 19 device-related complications, of these complications, 11 were wound infections, 6 were skin complications (skin abrasions or skin maceration which can heal on its own), 1 was transient paresthesia with no objective signs, 1 was superficial emathoma of the calf due to accidental trauma. Only 2 complications were reported in footwear subgroup, they were skin abrasions. Detailed information is shown in Table 3. Patients using TCCs reported significantly elevated occurrence of device-related complications than those in in the control group (removable walking casts and footwear) (RR=1.70; 95%CI:1.01 to 2.88, P=0.047) (Figure 8), with

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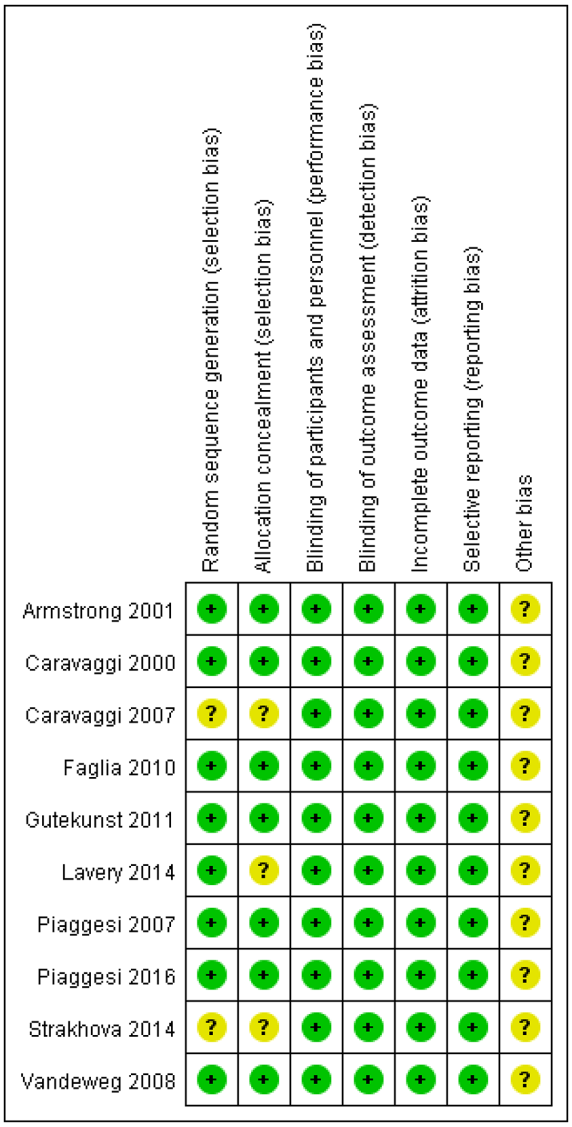

FIGURE 3
Risk of bias of each RCT.

I^2 being 37.4% (P=0.144). Subgroup analyses based on three types of devices showed that increased prevalence of device-related complications associated with TTCs was found only in the comparison of TCCs versus footwear (RR=4.81; 95% CI: 1.30 to 17.74; p=0.018), but not in that of TCCs versus removable walking casts (RR=1.27; 95CI: 0.70 to 2.29; p=0.438) (Figure 9).

Sensitivity analysis and publication bias

Sensitivity analyses demonstrated no significance change in the pooled estimates of primary outcomes. Results of Egger's test demonstrated no publication bias across included studies evaluating the effects of offloading devices regarding the time for ulcer healing (P=0.521) and occurrence of device-related complications (P=0.357). However, publication bias emerged among studies investigating rates of ulcer healing (p=0.007).

Discussion

Our meta-analysis demonstrated that TCCs significantly reduced healing time and improved healing rates compared to other removable offloading interventions (removable walking casts and footwear). However, TCCs were also associated with increased occurrence of complications. Specifically, we found that the increased prevalence of device-related complications was only observed when TCCs were compared with footwear. This finding has significant implications for the choice of treatment modality in patients with diabetic foot ulcers.

Our findings align with another recent meta-analysis, which also concluded that TCCs outperformed removable walkers because patients using the former spent shorter time on ulcer healing (15). However, that meta-analysis only focused on healing time as the primary outcome and included a limited number of studies (five in total). A systematic review suggested non-removable and knee-high offloading devices (TCCs or non-removable walkers) as the preferred treatment options for plantar neurogenic forefoot and midfoot ulcers (16). Removable offloading devices, whether knee-high or ankle-high, were considered the secondary choice among available offloading interventions. However, it did not include any meta-analyses, so its conclusions were not based on quantitative analysis, nor did it provide information on the incidence of complications associated with individual devices.

Several factors may explain these results. First, there are differences in biomechanical offloading capabilities between TCCs and removable walking casts/footwear. Compared with removable

TABLE 2 Quality evaluation of the eligible non-RCT studies with Newcastle-Ottawa scale.

Study	Selection				Comparability		Outcome		
	Representativeness	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start	Comparability on most important factors	Comparability on other risk factors	Assessment of outcome	Long enough follow-up (median≥3 months)	Adequacy (completeness) of follow-up (<10%)
Van (24)	☆	☆	☆	☆			☆	☆	☆
Birke (25)	☆	☆	☆	☆			☆	☆	☆

The meaning of the symbol ☆ is yes.

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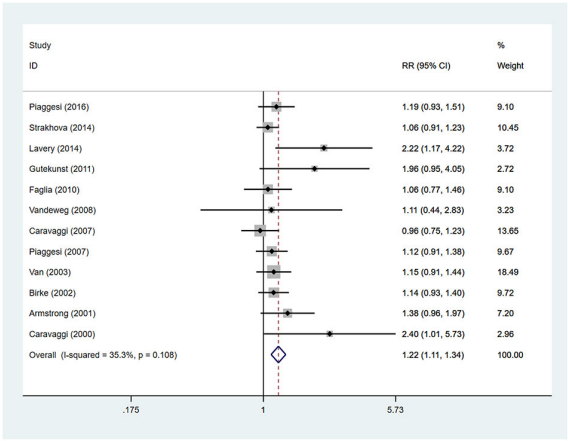

FIGURE 4
Forest plot of the comparison of the healing rate of TCC and other removable interventions. RR, relative risk.

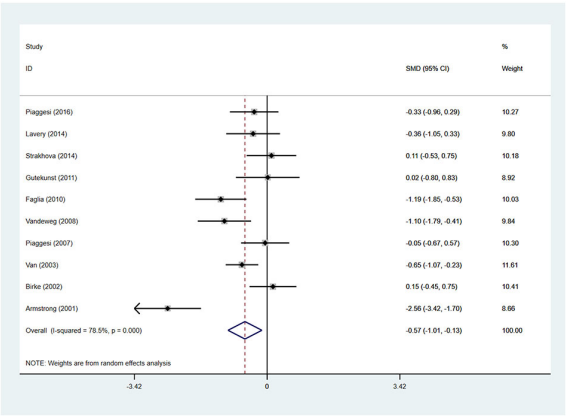

FIGURE 6
Forest plot of the comparison of the healing time of TCC and other removable interventions. SMD, standard mean difference.

interventions, TCCs can significantly reduce plantar pressure through the shaft effect and load transfer to the contralateral foot (28). Second, patient adherence varies between populations using TCCs versus removable walking casts or footwear.Studies have indicated that consistent use of foot offloading for at least 80% of daily activity is essential for its effectiveness (16, 29). Diabetic foot ulcer healing requires persistent pressure relief. The effect of offloading interventions diminishes when patients remove the device, and persistent abnormal plantar pressure may result in non-healing ulcers. Therefore, the higher adherence observed with TCCs could explain their superior effectiveness in promoting healing-related outcomes compared to removable devices. Our findings underscore the importance of patient education and adherence in managing diabetic foot ulcers. However, not all patients can adhere to these principles when using removable walking casts or footwear. A research had shown that patients, on average, used removable walking casts only for about 59% (± 22%) of their total daily activity (30), and therapeutic footwear was used for an average of 50.3% (± 32.8%) (31). The variation in comfort among different offloading devices may also influence patient compliance (32).

While patients with DFUs using TCCs demonstrated better healing time and healing rates, the use of TCCs was associated with greater frequency of complications compared to removable offloading interventions (12–14, 22, 24). This could be attributed to the fact that patients using removable offloading interventions have the option to remove the device, which allows them to identify any changes in their foot condition at an early stage.

We identified two main types of complications with TCCs: device failure and skin problems. To address device failure, we propose two strategies. First, improving the quality of the casts used can reduce the likelihood of device failure. Second, educating patients on the importance of protecting their TCCs could also

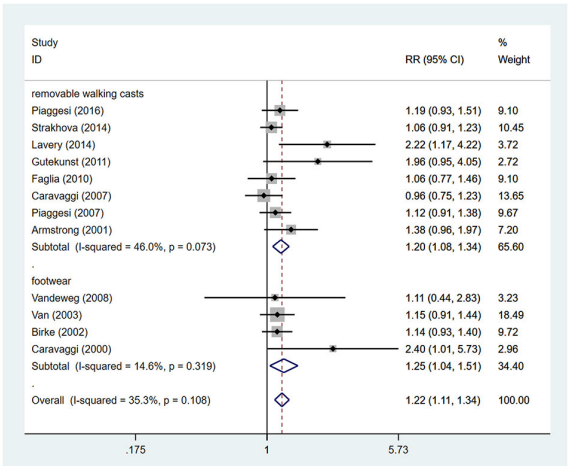

FIGURE 5
Subgroup analysis of the comparison of the healing rate of TCC and other removable interventions (removable walking casts, footwear). RR, relative risk.

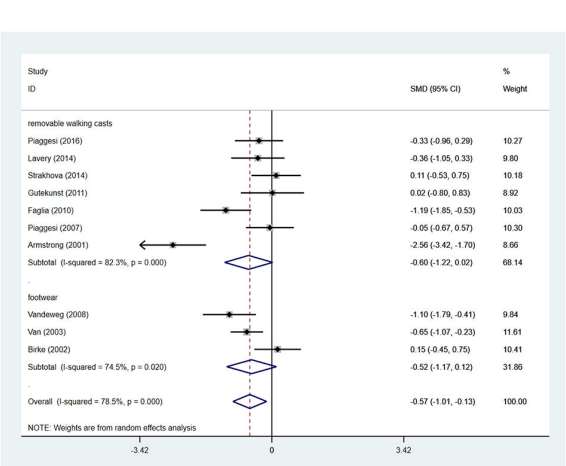

FIGURE 7
Subgroup analysis of the comparison of the healing time of TCC and other removable interventions (removable walking casts, footwear). RR, relative risk.

TABLE 3 Device-related complications in studies.

Study	TCC		Control	
	Number	complications	Number	complications
Piaggesi 2016 (12)	7	4 traumatic abrasions 3 device failure	1	1 fungal intertrigo
Lavery 2014	1	1 infection	5	4 infections 1 device-related wounds
Faglia 2010 (13)	2	2 device failure	1	1 skin maceration
Vandeweg 2008 (22)	5	5 device failure	2	2 Minor abrasions
Caravaggi 2007 (23)	5	5 serious infection req-uired antibiotic the-rapy and surgical debridment	6	6 serious infection required antibioti therapy and surgical debrid-ment
Piaggesi 2007 (14)	5	1 device failure 4 skin maceration	4	1 transient paresthesia with no objective signs 2 skin maceration 1 superficial emathoma of the calf due to accidental trauma
Van 2003 (24)	5	5 ulcer caused by the fiberglass	0	
Total	30	11 device failure 13 skin complication 6 wound infections	19	11 wound infection 6 skin complication 2 others

reduce the incidence of this complication. As for skin complications, proper molding of the cast is crucial to avoid local compression and prevent abrasions as well as other skin problems. Furthermore, keeping the patient's foot dry and clean can help prevent skin maceration and subsequent infection. These strategies, if properly implemented, could potentially enhance the effectiveness of TCCs in treating diabetic foot ulcers.

It is important to acknowledge some limitations of our study (1): Some included trials had a small sample size, with seven studies including less than 50 participants (2). Significant heterogeneity was observed in terms of healing time, prompting us to conduct subgroup analyses to identify and minimize this heterogeneity (3). Each removable walking cast differs in terms of unloading ability and wearing comfort, potentially affecting patient compliance and ulcer healing.

In conclusion, our meta-analysis indicates that TCCs resulted in a shorter time to heal foot ulcers and improved healing rates compared to removable offloading interventions in patients with DFUs. Our study also emphasizes the need for clinicians to consider the potential for increased device-related complications with TCCs, especially when compared with footwear. These findings have potential clinical implications for the selection of appropriate offloading interventions to optimize treatment outcomes and reduce complications. Future research should focus on enhancing

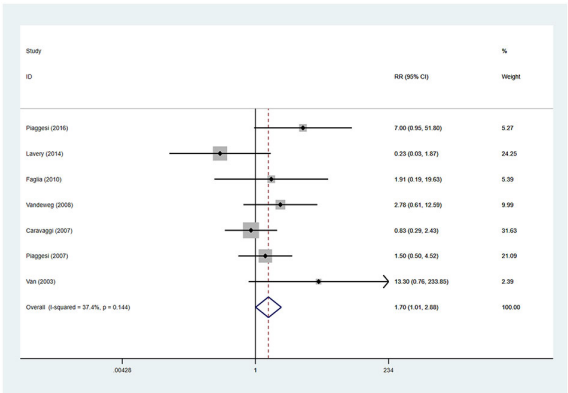

FIGURE 8
Forest plot of the comparison of the device related complications of TCC and other removable interventions. RR, relative risk.

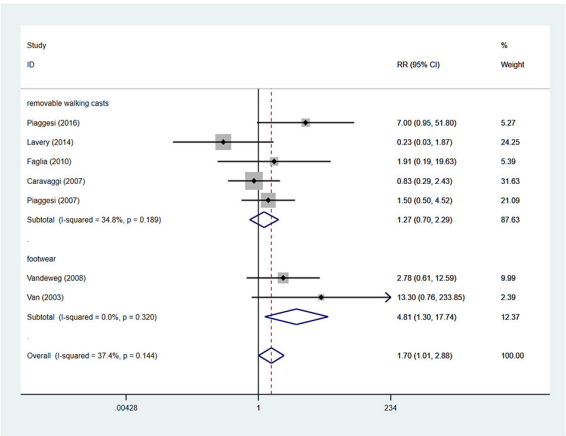

FIGURE 9
Subgroup analysis of the comparison of the device related complications of TCC and other removable interventions (removable walking casts, footwear). RR, relative risk.

the design of offloading devices to enhance patient compliance and minimize complications while maintaining effective offloading.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: BL, JH. Data curation: BL, JH. Formal analysis: BL, JH. Funding acquisition: BL, JX. Investigation: BL, JX. Methodology: BL, JX. Project administration: AL, QL. Resources: AL, QL. Software: AL, CY. Supervision: AL, CY. Validation: AL, ZZ. Visualization: JH, ZZ. Writing -original draft: BL, AL, JH, JX, QL, CY, ZZ. Writing-review & editing: BL, AL, JH, JX, QL, CY, ZZ. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix

Pubmed search strategy: Search: ((((((Diabetic foot[Title/Abstract]) OR (Foot, Diabetic[Title/Abstract])) OR (Diabetic Feet [Title/Abstract])) OR (Feet, Diabetic[Title/Abstract])) OR (Foot Ulcer, Diabetic[Title/Abstract])) OR ("Diabetic Foot"[Mesh])) AND ((((((((((((((((((((((((Casts, Surgical[Title/Abstract]) OR (Surgical Casts[Title/Abstract])) OR (Cast, Surgical[Title/Abstract])) OR (Surgical Cast[Title/Abstract])) OR (Plastic Casts[Title/Abstract])) OR (Cast, Plastic[Title/Abstract])) OR (Casts, Plastic[Title/Abstract])) OR (Plastic Cast[Title/Abstract])) OR (Plaster Casts [Title/Abstract])) OR (Cast, Plaster[Title/Abstract])) OR (Casts, Plaster[Title/Abstract])) OR (Plaster Cast[Title/Abstract])) OR (Fiberglass Casts[Title/Abstract])) OR (Cast, Fiberglass[Title/Abstract])) OR (Casts, Fiberglass[Title/Abstract])) OR (Fiberglass Cast[Title/Abstract])) OR (total contact casts[Title/Abstract])) OR (total contact casting[Title/Abstract])) OR (total contact cast[Title/Abstract])) OR (cast[Title/Abstract])) OR (casts[Title/Abstract])) OR (casting[Title/Abstract]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) OR ("Casts, Surgical"[Mesh]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))

Embase search strategy: ('diabetic foot'/exp OR 'diabetic foot':ab,ti OR 'foot, diabetic':ab,ti OR 'diabetic feet':ab,ti OR 'feet, diabetic':ab,ti OR 'foot ulcer, diabetic':ab,ti) AND ('orthopedic cast'/exp OR 'orthopedic cast':ab,ti OR 'casts, surgical':ab,ti OR 'surgical casts':ab,ti OR 'cast, surgical':ab,ti OR 'surgical cast':ab,ti OR 'plastic casts':ab,ti OR 'cast, plastic':ab,ti OR 'casts, plastic':ab,ti OR 'plastic cast':ab,ti OR 'plaster casts':ab,ti OR 'cast, plaster':ab,ti OR 'casts, plaster':ab,ti OR 'plaster cast':ab,ti OR 'fiberglass casts':ab,ti OR 'cast, fiberglass':ab,ti OR 'casts, fiberglass':ab,ti OR 'fiberglass cast':ab,ti OR 'total contact casts':ab,ti OR 'total contact casting':ab,ti OR 'total contact cast':ab,ti OR 'cast':ab,ti OR 'casts':ab,ti OR 'casting':ab,ti) AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'major clinical study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'single blind procedure'/de) AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'crossover procedure'/de OR 'double blind procedure'/de OR 'major clinical study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de OR 'single blind procedure'/de)

Cochrane Library search strategy:

#1 MeSH descriptor: [Diabetic Foot] explode all trees

#2 (Diabetic foot):ti,ab,kw OR (Foot, Diabetic):ti,ab,kw OR (Diabetic Feet):ti,ab,kw OR (Feet, Diabetic):ti,ab,kw OR (Foot Ulcer, Diabetic):ti,ab,kw (Word variations have been searched)

#3 #1 OR #2

#4 MeSH descriptor: [Casts, Surgical] explode all trees

#5 (Casts, Surgical):ti,ab,kw OR (Surgical Casts):ti,ab,kw OR (Cast, Surgical):ti,ab,kw OR (Surgical Cast):ti,ab,kw OR (Plastic Casts):ti,ab,kw (Word variations have been searched)

#6 (Cast, Plastic):ti,ab,kw OR (Casts, Plastic):ti,ab,kw OR (Plastic Cast):ti,ab,kw OR (Plaster Casts):ti,ab,kw OR (Cast, Plaster):ti,ab,kw (Word variations have been searched)

#7 (Casts, Plaster):ti,ab,kw OR (Plaster Cast):ti,ab,kw OR (Fiberglass Casts):ti,ab,kw OR (Cast, Fiberglass):ti,ab,kw OR (Casts, Fiberglass):ti,ab,kw (Word variations have been searched)

#8 (Fiberglass Cast):ti,ab,kw OR (total contact casts):ti,ab,kw OR (total contact casting):ti,ab,kw OR (total contact cast):ti,ab,kw OR (cast):ti,ab,kw (Word variations have been searched)

#9 (casts):ti,ab,kw OR (casting):ti,ab,kw (Word variations have been searched)

#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9

#11 #3 AND #10

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Diabetic foot problem in Nepal

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Introduction: Nepal is a developing country where diabetes is becoming a major health challenge due to its high prevalence of 8.5% affecting around 2 million people. Due to limited resources, there are many barriers to providing affordable and convenient diabetes care or regular screening for complications. There is no reliable data on incidence, prevalence, and complications of diabetic foot problems in Nepal.

Methods: We conducted an online survey amongst senior physicians, who were members of 'Diabetes & Endocrine Association of Nepal' to assess their perception of diabetic foot problems in Nepal.

Results: Thirty-Eight physicians responded to the survey who saw a total of 17597 patients in the preceding month. They recalled seeing 647 with 'Diabetic Foot Ulcers', giving a crude Diabetic Foot Ulcer prevalence rate of 3.7%. They recalled seeing 2522 patients with painful neuropathy that required medical treatment, giving a crude painful neuropathy prevalence rate of 14.3%. A history of foot ulcer was present in an additional 578 patients. Previous minor amputation had been performed in 215 patients (1.2%) and major amputation in 135 patients (0.8%).

Discussion: Despite having expertise in various fields there is no dedicated multi-disciplinary diabetic foot clinic in Nepal. This survey shows that diabetic foot problems are abundant in Nepal and there is a need for structured multi-disciplinary approach for screening and treatment.

KEYWORDS

diabetic foot, Nepal, ulcer, neuropathy, amputation

Introduction

Nepal is a landlocked country in South Asia, which lies along the southern slopes of the Himalayan Mountain ranges between India and the Tibet Autonomous Region of China. It has a federal system of government with seven provinces, and the capital city is Kathmandu. The health service is the responsibility of the federal government, but some tertiary care is directly funded by the central government. There is also significant private sector involvement in healthcare in urban areas. The most recent census shows the population of Nepal to be 29 million, and the urban population has reached 66.08 percent

(1). It is one of the poorest countries, with a per capita income of US $1208 (2). Although Nepal's 2015 constitution guarantees basic health care as a fundamental right, access to high-quality care remains a privilege. The central health programs supported by international donors have reduced the prevalence of some infectious diseases, improved maternal and child health, and extended life expectancy. However, the burden of poor health in Nepal has been compounded by the rising burden of non-communicable diseases (3).

Diabetes Mellitus (DM) is one of the common non-communicable diseases that Nepal is facing as a major challenge. The International Diabetes Federation reports the national prevalence of DM amongst people aged 20–79 years old in Nepal to be 4% in 2017, which is expected to rise to 6.1% by 2045 (4). A recent population-based study sampled 13 200 participants aged 20 years and above in 400 clusters of 72 districts of Nepal. They showed the prevalence of DM to be 8.5% (5)., which is consistent with recent meta-analysis of 15 papers (6).

Although the prevalence is high, there are many barriers that people with DM commonly face in Nepal. These include accessing affordable and convenient care, receiving comprehensive diabetes education, and managing their lifestyle changes. Sub-optimal knowledge and behaviors of patients often contributed to poor DM management. The scarcity of financial and human resources for healthcare in Nepal often results in the inability of the current healthcare system to provide comprehensive management of chronic diseases (7).

Diabetic foot ulcer (DFU) is one of the chronic complications of DM. This occurs due to a combination of risk factors - namely peripheral neuropathy, peripheral vascular disease, and foot deformity. The lifetime incidence of DFU amongst diabetics is between 19-34%. The risk of death at 5 years for a patient with a DFU is 2.5 times as high as the risk for a patient with diabetes who does not have a DFU (8). There is also a high risk of amputation in patients with DFU. In Nepal, there is no reliable data on incidence, prevalence, and complications of diabetic foot problems. In a community-based survey of 34 diabetic patients in an urban area of Kathmandu, 10.5% had a foot problem in the past and 56.7% had current risk factors for DFU (9). Another study was undertaken in a tertiary care center and consisted of 169 patients with peripheral artery disease and DM. It showed that DFU was present in 32.5% of these patients (10). An outpatient clinic study from Eastern Nepal showed that 1% of the patients with DM had DFU, and none of these patients suffered from a diagnosis of peripheral vascular disease (11). Another study looked at 178 patients with diabetes mellitus. These patients were either attending out-patient appointments or were in-patient at a tertiary care hospital. The prevalence of peripheral neuropathy in this population was 41% using Michigan Neuropathy Screening Instrument (12). A study consisting of 196 patients was undertaken in a tertiary care hospital in Kathmandu. About half of these patients did not have good knowledge or practices about foot care. This data, although limited, indicates higher risk of foot complications in Nepal (13). There is no reliable data on diabetic foot problems in Nepal, and there is no information about any Multi-Disciplinary Foot Clinics in Nepal.

Aim of the study

The aim of this study was to use a questionnaire directed at Diabetes Physicians in Nepal to explore the resources available for the management of diabetic foot problems, and to explore the extent of any problems regarding this management.

Methods

This was a semi-quantitative survey amongst senior physicians, who provide diabetes treatment and were members of Diabetes & Endocrine Association of Nepal (DEAN). It assessed their perception of diabetic foot problems in Nepal. All Viber group members of DEAN were invited to take part in a short online survey (Table 1) in May 2023 about their experience of treating patients with diabetes in the last one month.

TABLE 1 List of online questions sent to 'Viber group' members of Diabetes & Endocrine Association of Nepal (DEAN).

• **What is your name?**
• **Which city/village do you practice?**
• **On average how many patients with diabetes do you see every month?**
• **Of those patients with diabetes seen every month how many have 'Diabetic Foot Ulcers' (Ulcers below ankle)?**
• **Of those patients with diabetes seen every month how many have painful neuropathy that needs medical treatment?**
• **Of those patients with diabetes seen every month how many have had at least one diabetic foot ulcers in the past?**
• **Of those patients with diabetes seen every month how many have had toe amputation (minor amputation) in the past?**
• **Of those patients with diabetes seen every month how many have had amputation of leg (Major amputation) in the past?**
• **Do you have a good system of annual foot screening in your practice?**
• **Do you have good access to Podiatrists in your multi-disciplinary team?**
• **Do you have good access to radiology (For X-ray and CT/MRI) from your clinic if needed?**
• **Do you have good access to vascular surgeons from your clinic?**
• **Do you have good access to interventional radiologists (for peripheral angiogram and angioplasty) from your clinic?**
• **Do you have good access to Orthopaedic surgeons from your clinic?**
• **Do you have good access to Orthotist (custom made shoe maker) from your clinic?**
• **Do you have good access to microbiology service from your clinic?**
• **Do you have good access to off loading (eg plaster technician) from your clinic?**
• **How confident are you in managing 'Diabetic Foot Problem'**
• **Are you interested in further training to manage diabetic foot problems?**
• **Any comments?**

Inclusion criteria

- Doctors actively treating Diabetes in Nepal
- Members of DEAN
- Contributes to Viber Group of DEAN

Exclusion criteria

- Doctors not using mobile phone
- Doctors who did not respond to reminder

The questionnaire was kept short and user friendly, which could be completed on a smartphone. The questions were based on those used in data collection for National Diabetes Audit in the UK. After two weeks, reminders were sent to physicians who did not respond to the initial invitation. If the results were given in a range, the middle figure was chosen and if required was rounded to the nearest whole number. Simple descriptive analysis was done using Excel.

Results

Out of 96 eligible physicians, 38 (39.6%) completed the survey. All physicians were practicing in urban centers, with 21 (55.3%) practicing in the capital and 28 within the greater Kathmandu Valley, which consist of capital city of Kathmandu along with Patan and Bhaktapur cities. All these physicians saw a total of 17597 patients in the preceding month. They recalled seeing 647 with 'Diabetic Foot Ulcers' (Defined by ulcers below the ankle), giving a crude Diabetic Foot Ulcer prevalence rate of 3.7%. They recalled seeing 2522 patients with painful neuropathy that required medical treatment, giving a crude painful neuropathy prevalence rate of 14.3%. A history of foot ulcer was present in an additional 578 (3.3%) patients. Previous minor amputation had been performed in 215 patients (1.2%) and major amputation in 135 patients (0.8%) (Table 2).

Regarding the presence of a multi-disciplinary team, Diabetes Physicians had access to podiatrists in only 5 (13.2%) centers; with the 33 centers (86.8%) not having access to foot care practitioners. In contrast, all physicians had good access to orthopedic surgeons and microbiology services. All modalities of investigations including MRI were available to 35 (92.1%) physicians, with one having access to X-Ray only and two having access to none. 30 (78.9%) physicians had access to vascular surgeons within their center, and 23 (60.5%) had good access to interventional radiologists (for peripheral angiogram and angioplasty). Plaster technicians were available in 18 (47.4%) centers, but we did not collect data on whether they were actively used in clinics to manage diabetic foot ulcers. Only nine clinics (23.7%) had good access to orthotists, with the majority (76.3%) not having any facilities for custom made shoes (Table 3).

Of all practicing physicians, 25 (65.8%) had a good system of annual foot screening. When broken down to the number of patients these physicians see, 12090 (68.7%) patients had annual diabetic foot screening. The exact details of such screening program were not collected. When asked to score numerically their confidence in managing 'Diabetic Foot Problems' in with 10 being most confident, physicians gave an average score of 6.7. Thirty-five (92.1%) physicians were interested in receiving further training to manage diabetic foot problems.

TABLE 2 Presence of diabetic foot pathology amongst 17597 patients.

Condition	Number	Percentage
Active Diabetic foot Ulcer	647	3.7%
Active Painful Neuropathy	2522	14.3%
Previous foot Ulcer (Now healed)	578	3.3%
Previous Minor Amputations	215	1.2%
Previous Major Amputations	135	0.8%

Discussion

This is the first study that has collected data from physicians treating diabetes on their experience of the management of foot problems in Nepal. There is no clear distinction between primary care, secondary care, and tertiary care in Nepal, so the sample collected was across all these levels. All physicians were practicing in urban areas, so there is no data on rural populations. However, according to the most recent census, 66% of the Nepalese population live in urban area (1). Urban residents had almost double the risk of developing diabetes when compared with rural residents (5), so our data is likely to be representative of the national problem. The prevalence of ulcers in this study (3.7%) is lower than the reported global prevalence of 6.3% (14). In a similar study from India, Diabetic foot ulcers were found in 4.54% of newly diagnosed type 2 diabetes mellitus patients (15), which is similar to our findings. Our sample did not collect data on new or follow up patients and whether they were attending primary or secondary care settings.

There is no dedicated Multidisciplinary Diabetic Foot Clinic in Nepal. The earliest Multidisciplinary Diabetic Foot Clinic was

TABLE 3 Available facilities for multi-disciplinary management of diabetic foot ulcer in 38 centres.

Facility	Number	Percentage
Podiatrist on site	5	13.2%
Orthopaedic surgeons	38	100%
Vascular surgeons	30	78.9%
MRI	35	92.1%
No radiology facility	2	5.3%
Interventional Radiologist	23	60.5%
Plaster Technician	18	47.4%
Orthotist	9	23.7%

established in 1981 at King's College Hospital in London, UK (16). After that, many Multidisciplinary Diabetic Foot Clinics were established all over the world, which has led to a reduction in amputations. One study in New Zealand showed that after the conception of a multidisciplinary diabetic foot clinic, there was a reduction in hospital admissions, a seven-fold reduction in major amputations, a reduction in mortality rate by 50%, and an overall reduction in total costs (17). Therefore, it is important that steps are taken to set up such clinics in Nepal, providing there is a suitable workforce and suitable facilities available. There is a distinct lack of podiatrists and orthotists in Nepal. As there is no podiatry training scheme in Nepal, interested nurses can be trained to specialize in foot care. Similarly, local people can be trained to manufacture suitable footwear for diabetes patients. These have been practiced in local leprosy hospitals with remarkable success (18). The initiation of a Multidisciplinary Diabetic Foot Clinic is of great importance. As the majority of diabetes physicians are interested in learning about diabetic foot problems, appropriate training programs should contain information about how to set up and refer to new Multidisciplinary Diabetic Foot Clinics (19).

Of all reported patients on our study, only 68.7% had annual foot screening. This number is expected to be much lower in rural area, where even implementing access to basic health care is difficult. In 1988, the government of Nepal introduced the Female Community Health Volunteers. They are frontline workers in the Nepalese healthcare system and are trusted by community members. There are over 51,000 members in Nepal as of the end of 2020 (20). They can be trained in annual diabetic foot screening and foot education.

The current Nepalese healthcare system, consisting of mixed public and private funding, is not equipped to manage the growing number of people with diabetes; and is unable to provide adequate prevention, diagnosis, and management services for diabetes (7). A multilevel, coordinated approach is necessary to bridge the current gap between the community and the health system to ensure equal access to diabetes services for all Nepalese people. In Nepal, the national health insurance program was first introduced in 2015. This now covers the whole country. It gives special financial relief to patients who suffer from conditions such as heart disease and chronic kidney disease requiring dialysis. It does not include financial aid diabetics, which is a key risk factor for these conditions (21). There is also a problem in the uptake and retention of patients in this scheme. There is an imbalance between the population's expectations of health insurance and the institutions who deliver the insurance (22). Therefore, it is essential that policy makers in Nepal highlight the importance of managing chronic conditions like diabetes in their national health insurance program. There should be regulatory structures to define and ensure that a minimum quality of care is delivered; at all levels within both public and private health-care institutions.

Strengths and limitations of this study

This was a small survey, and data was based on recollection of cases rather than independent review of case notes. In Nepal, most diabetes service in urban areas are provided within the private sector, and the record keeping is not always adequate. In general, patients tend to visit various institutions for their numerous health conditions; rather than stick to a single one provided by either the public sector or by an insurance scheme. Therefore, reviewing of records from a single institution is unlikely to be reliable. As this was a study based on physician's perception of the problem in an average month, there could be a recall bias. A key limitation in this study was that we did not get any responses from physicians practicing in rural areas. This is mainly because private diabetes physicians practice in urban areas, and secondary care hospitals are also based in urban areas.

Conclusions

Our survey captured approximately 40% of all physicians practicing diabetes management in Nepal. DEAN is the only organization where all such physicians become a member. The DEAN Viber group is very active in promoting communication between professionals. Therefore, we believe that we were able to capture recall data on a large number of patients. The preliminary findings from this physician survey show a lack of community foot protection with very few podiatrists, and a need for development of Multidisciplinary Diabetic Foot Clinics. In addition, the work should be followed up with a prospective audit of outcomes for persons living with diabetes who suffer diabetic foot ulceration.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

SR: Conceptualization, Writing – review and editing. SB: Conceptualization, Data curation, Formal Analysis, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Increase in antibiotic resistance in diabetic foot infections among peruvian patients: a single-center cross-sectional study

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Background: Diabetic foot is one of the most significant complications in individuals with diabetes and is closely associated with lower limb amputation. The antibiotic susceptibility patterns of these bacterial isolates play a critical role in guiding effective treatment strategies We aimed to determine the most common bacterial agents causing diabetic foot infections in a tertiary-care hospital in Peru.

Methods: Clinical and microbiological data were collected from 181 patients diagnosed with diabetic foot infections and positive microbiological culture results. All the samples were analyzed with the Vitek 2 compact system and the cut-off points were defined with the CLSI M100 guide. The data were segregated based on mono-microbial or poly-microbial cultures, bacterial types, and antibiotic susceptibility profiles.

Results: A total of 32 bacterial species were identified, predominantly Gram-negative (63%). The most frequent bacterial agents isolated were *Staphylococcus aureus* (19.9%), *Escherichia coli* (12.2%), *Pseudomonas aeruginosa* (8.3%), and *Proteus vulgaris* (6.6%). These bacteria commonly exhibited resistance to Ampicillin, Ciprofloxacin, Levofloxacin, Trimethoprim-sulfamethoxazole, and Cefuroxime. *E. coli* showed the highest antibiotic resistance (19 antibiotics), while Gentamicin, Tobramycin, and Levofloxacin demonstrated the highest sensitivity against the most prevalent bacteria. Gram-negative bacteria also exhibited notable antibiotic-susceptibility to Meropenem, Piperacillin/tazobactam, and Amikacin. Regarding the presence of Extended-Spectrum Beta-Lactamase, 54 isolates tested positive, with 35 (64.8%) and 14 (42.4%) of these being *S. aureus and E. coli*.

Conclusions: Bacterial agents causing diabetic foot infections pose a constant concern, particularly due to the increasing antibiotic resistance observed. This

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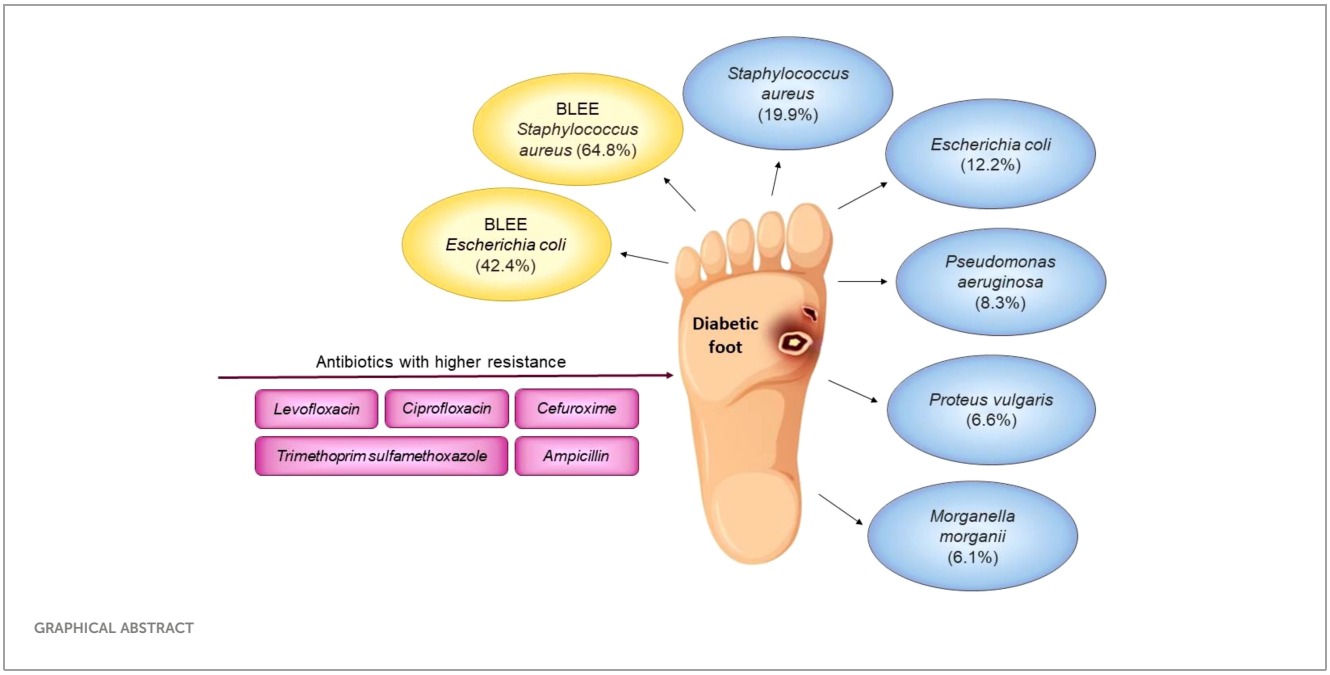
difficulty in treating the condition contributes to a higher risk of amputation and mortality. Further research on bacterial susceptibility is necessary to determine appropriate dosages for pharmacological treatment and to prevent the overuse of antibiotics.

KEYWORDS

diabetic foot, infections, staphylococcus aureus, antibiotic resistance, *Escherichia coli*, diabetes mellitus



GRAPHICAL ABSTRACT

1 Introduction

Globally, diabetes mellitus is a widespread health concern, affecting more than 529 million individuals, with prevalence spanning across all age groups, from 65 to 95 years (1). This surge in the number of diabetes cases can be attributed to the escalating risk factors, including excess body weight, obesity, sedentary lifestyles, and imbalanced diets (2). Diabetes has a significant impact on the quality of life and reduces life expectancy of affected individuals. Moreover, it gives rise to various morbidity issues, encompassing both microvascular and macrovascular complications. These complications manifest as visual impairments, ranging from partial loss of vision to complete blindness, as well as serious health conditions such as acute myocardial infarction, renal failure, stroke, and peripheral neuropathy and peripheral arterial diseases that may necessitate amputations (1).

Diabetic foot is a significant complication of Diabetes Mellitus, often associated with diabetic sensory-motor polyneuropathy (in fact, diabetic polyneuropathy alone accounts for 50% of diabetic foot cases), occlusive peripheral arterial disease, or a combination of both (3). These patients have an increased risk of infection, affecting approximately 50% of them, and infection is the leading factor associated with lower limb amputations (4). Infections in these patients usually result from skin discontinuity caused by trauma (mechanical/thermal) or ulceration. Diabetic foot infection is defined as an infection in soft tissue or bone anywhere below the malleolus in a diabetic individual (5).

The main microorganisms isolated in diabetic foot infections are Staphylococcus aureus, Proteus spp, Escherichia coli, *Peptostreptococcus, Veillonella*, and *Bacteroides* (3). However, microbiology of the lesions can vary based on different patient factors, including the characteristics and duration of the lesion, prior use of antibiotics, and local microbiology (6). Generally, most infections are polymicrobial, hence the use of empiric broad-spectrum antibiotics are necessary initially and then tailoring treatment based on antibiotic susceptibility results. In severe infections, surgical debridement may also be required (7).

In Peru, the two main complications of diabetes are diabetic foot and peripheral diabetic neuropathy, with a prevalence of 30% and 7%, respectively (8). Regarding the local microbiology of diabetic foot infections, it varies among different populations,

ranging from gram-positive isolates such as Staphylococcus aureus (9), to bacteria like Escherichia coli and Enterococcus faecalis (10), which show high resistance to at least five commonly used antibiotics, such as ciprofloxacin, levofloxacin, nitrofurantoin, trimethoprim/sulfamethoxazole, and ampicillin/sulbactam (9). Despite these previous reports, not all hospitals have characterized bacterial infections in diabetic foot patients, making it important to understand changes in pathogen frequency and potential resistance patterns to avoid complications and ensure proper microbiological surveillance.

The objective of this study was to determine the most frequent bacterial agents causing diabetic foot infections in a tertiary hospital in Peru. This study also aimed to characterize the antibiotic resistance profile of the infectious isolates from diabetic foot infections, highlighting differences between nosocomial and community-acquired pathogens.

2 Methods

2.1 Study design and setting

This retrospective study was conducted at the María Auxiliadora Hospital, a tertiary hospital located in the district of San Juan de Miraflores, Lima (Peru). Managed by the Ministry of Health, this hospital facility in the southern region proudly offers an extensive capacity of around 472 beds and accommodates approximately two thousand daily consultations. Around a thousand consultations per month are about type 1 and 2 diabetes in all care departments. It serves as an essential healthcare institution for the local community, playing a crucial role in meeting their medical needs.

2.2 Population and inclusion criteria

The study population consisted of 181 patients with type two diabetes mellitus and diagnosed with diabetic foot (11). The clinical and microbiological data of these patients were considered as the unit of analysis based on the following inclusion criteria:

- Tissue samples from diabetic foot, whether from the hospitalization area, emergency department, or the diabetic foot unit in the outpatient consultation.
- Samples with microbiological cultures containing Gram-positive and Gram-negative bacterial isolates.
- Samples with complete information on susceptibility profiles.

Patients with incomplete data records, cultures with non-bacterial isolates, samples from other areas different from the foot of a diabetes patient, patients with type 1 diabetes and gestational diabetes, and samples from patients with foot or lower limb amputations not related to diabetes were excluded.

2.3 Microbiological and clinical data gathering

All samples were analyzed using the Vitek 2 compact system (bioMérieux, LePort, France) following standardized operational procedures of the hospital. Data were directly collected from the system (clinical isolation data and antibiotic susceptibility profile) into a data collection form for the study, which also included clinical information (demographic and symptoms data) obtained from the SIGHOS system (12). SIGHOS, the System for Integrated Health Information Management, is a robust clinical data system within the Comprehensive Health Insurance (SIS) framework under the Ministries of Health. Its primary function is to seamlessly connect and integrate health care network data, facilitating both epidemiological analysis and clinical monitoring. The data were categorized according to mono-microbial or poly-microbial cultures, bacterial types, susceptibility profiles, patient age, and gender.

2.4 Statistical analysis and ethical considerations

Data analysis was performed using SPSS v24.0 (IBM, Armonk, US) for Windows. Descriptive analysis was used to estimate the frequency of each bacterial isolation. The clinical data obtained from SIGHOS were analyzed descriptively. Antimicrobial resistance categories (sensitive, intermediate, and resistant) were defined based on the Vitek 2 compact cut-off and CLSI M100 guidelines (13). Additionally, the frequency of mono or poly-microbial cultures and extended-spectrum beta-lactamase (ESBL) presence were identified.

This study has adhered to the guidelines of the Declaration of Helsinki (14). It has also received approval from the Ethics Committee of the Hospital María Auxiliadora (HMA/CIEI/008/2021, May 26, 2021) and the Universidad Norbert Wiener (Exp.528-2021, April 26, 2021).

3 Results

Out of a total of 181 positive cultures obtained from diabetic foot samples collected between January and December 2019, 128 were from male patients (70.7%), and an equal number were from the outpatient clinic area (128, 70.7%). Most patients belonged to the age group of 61 to 70 years, accounting for 35.9% (65/181), followed by 51 to 60 with 30.9% (56/181) and 71 to 80 years with 14.3% (26/181). In smaller proportions, there were groups aged 41 to 50 years with 8.8% (16/181) and >40 years with 1.7% (3/181).

A total of 32 bacterial species were identified, with 21 being Gram-negative (63%) and 11 Gram-positive (37%). The most frequently isolated Gram-positive species was Staphylococcus aureus with 36 isolations (19.9%), followed by Enterococcus faecalis with 9 isolations (5.0%). Among the Gram-negative

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bacteria, Escherichia coli had the highest frequency with 22 isolations (12.2%), followed by Pseudomonas aeruginosa with 15 isolations (8.3%) and Proteus vulgaris with 12 isolations (6.6%) (Table 1).

Regarding the susceptibility pattern, among the 114 isolates of Gram-negative bacteria, the antibiotics with the highest antimicrobial resistance were Ampicillin (89.7%), Cefuroxime (75.9%), followed by Trimethoprim-sulfamethoxazole (64.6%), and Ciprofloxacin (61.5%); the lowest resistance was observed for Ertapenem with 3.4%. On the other hand, the highest antimicrobial sensitivity was observed for Carbapenems (> 85.4%), Amikacin (85.3%), followed by Piperacillin/tazobactam (82.5%), while the lowest sensitivity was observed for Ampicillin (6.9%) and Fosfomycin (1.5%). Among the 67 Gram-positive bacteria, the antibiotics with the highest antimicrobial resistance were Penicillin (95.4%), Ampicillin (87.7%), Clindamycin (80.7%), and Oxacillin (76.4%). Daptomycin, Vancomycin, and Teicoplanin were resistant in all isolates, while Penicillin (4.6%) showed the lowest resistance (Figure 1).

In terms of frequencies, the order of bacteria with the highest isolation rates was *Staphylococcus aureus* (19.9%), *Escherichia coli* (12.2%), *Pseudomonas aeruginosa* (8.3%), *Proteus vulgaris* (6.6%), and *Morganella morganii* (6.1%). While Gram-negative bacteria had the highest number of isolations, *Staphylococcus* aureus was the most frequently isolated species.

Considering the bacteria with the highest incidence (*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Morganella morganii*), it was observed that they share a higher percentage of resistance to Ampicillin, Ciprofloxacin, Levofloxacin, Trimethoprim-sulfamethoxazole, and Cefuroxime. *Escherichia coli* showed the highest number of antibiotic resistance (19 antibiotics), followed by *Proteus vulgaris* (17 antibiotics) (Table 2).

The antibiotics that showed the highest sensitivity against the most incident bacteria were Gentamicin (46.9%, 45/96), Tobramycin (46.9%, 45/96), and Levofloxacin (34.4%, 33/96). Notably, Meropenem (86.6%, 52/60), Piperacillin/tazobactam (81.6%, 49/60), and Amikacin (83.3%, 50/60) showed significant sensitivity against Gram-negative bacteria.

Regarding the presence of Extended-Spectrum Beta-Lactamase (ESBL), 54 isolates tested positive, with 35 (64.8%) of these being *Staphylococcus aureus*. *Staphylococcus haemolyticus* followed with 8 positive cases (7.4%). Additionally, a total of 33 isolates were related to Extended-Spectrum Beta-Lactamase, with *Escherichia coli* showing the highest positivity at 14 (42.4%), followed by *Klebsiella pneumoniae* with 7 (21.1%) (Figure 2).

TABLE 1 Frequency of bacterial isolations in diabetic foot.

Isolated bacteria	n	%
Gram negative bacteria	114	63.0%
Acinetobacter baumannii complex/haemolyticus	6	3.3%
Burkholderia cepacia complex	1	0.6%
Citrobacter sp	4	2.2%
Citrobacter freundii	2	1.1%
Citrobacter murliniae	1	0.55%
Citrobacter youngae	1	0.55%
Enterobacter sp	13	7.2%
Enterobacter cloacae	9	5.0%
Enterobacter aerogenes	2	1.1%
Enterobacter cancerogenus	1	0.55%
Enterobacter hormaechei	1	0.55%
Escherichia coli	22	12.2%
Klebsiella sp	11	6.1%
Klebsiella oxytoca	1	0.6%
Klebsiella pneumoniae	10	5.5%
Morganella morganii	11	6.1%
Proteus sp	19	10.5%
Proteus mirabilis	7	3.9%
Proteus vulgaris	12	6.6%
Providencia rettgeri	4	2.2%
Pseudomona sp	16	8.8%
Pseudomonas aeruginosa	15	8.3%
Pseudomonas stutzeri	1	0.5%
Serratia sp	3	1.7%
Serratia fonticola	1	0.6%
Serratia marcescens	2	1.1%
Stenotrophomonas maltophilia	4	2.2%
Gram-positive bacteria	67	37.0%
Enterococcus sp	10	5.5%
Enterococcus faecalis I'll	9	5.0%
Enterococcus faecium	1	0.5%
Staphylococcus sp	55	30.4%
Staphylococcus aureus	36	19.9%
Staphylococcus cohnii subsp. Cohnii	1	0.55%
Staphylococcus epidermidis	3	1.7%
Staphylococcus haemolyticus	8	4.4%
Staphylococcus hominis subesp. Hominis	1	0.55%
Staphylococcus schleiferi subespecie coagulans	1	0.55%

(Continued)

4 Discussion

We found that the most frequent isolates were *S. aureus, E. coli, P. aeruginosa, P. vulgaris, and M. morganii.* These bacteria showed a higher common resistance to Ampicillin, Ciprofloxacin, Levofloxacin, Trimethoprim-sulfamethoxazole, and Cefuroxime. It is noteworthy that E. coli had the highest resistance to antibiotics, while Gentamicin, Tobramycin, and Levofloxacin were the most effective

TABLE 1 Continued

Isolated bacteria	n	%
Staphylococcus sciuri	3	1.7%
Staphylococcus xylosus	2	1.1%
Streptococcus dysgalactiae subspecies dysgalacti	2	1.1%
TOTAL	181	100%

antibiotics against the most prevalent bacteria. Notably, there was a significant sensitivity to Meropenem, Piperacillin/tazobactam, and Amikacin among Gram-negative bacteria.

The study's strengths include the use of an updated database compared to other national studies between 2010 and 2016 (9, 15) and the use of automated methods for analyzing antibiotic resistance. Additionally, the findings contribute scientifically to Spanish-speaking countries, as often the results align with foreign studies but are not mentioned or included in them (16–21).

Our results indicate that although Gram-negative bacteria were the most common (63%), Staphylococcus aureus was the most frequently isolated species. Similar results were found in China (17.7%) (17), Nigeria (15.6%) (18), and Sudan (18.2%) (19). Together, these results agree with an international microbiological review, where *S. aureus* remains one of the most important pathogens in diabetic foot infections, with a frequency of approximately 50% in monomicrobial infections. Additionally, the incidence of *P. aeruginosa* is increasing, ranging from 10% to 26.6% (15). Although this pathogen was not the most frequent in this study, studies conducted in Nicaragua found a prevalence of 24.4% and 38.8% (22, 23).

At the Hospital Nacional Edgardo Rebagliati Martins of EsSalud, Gram-negative bacteria predominated (69.5%). However, regarding the frequency of bacteria, the results were opposite to ours, with E. coli being the most common bacteria (23.4%), followed by *E. faecalis* (14.1%) and S. aureus (13.3%) (9). Similar findings were seen in a provincial hospital, where 64.29% of the bacteria were Gram-negative, with E. coli being the most frequent (16.07%), followed by S. aureus (14.29%) (15). Foreign countries also showed similar results, with *E. coli* being the most frequent bacteria in Iran with 20.5% (20), and Lebanon with 15% (21). Considering these reports, *S. aureus, E. coli, and P. aeruginosa* appear to be the most prevalent bacteria in diabetic foot infections worldwide.

Regarding the antibiotic susceptibility pattern of the bacteria, it was observed that Gram-negative bacteria showed high levels of

FIGURE 1
Antibiotic susceptibility of Gram positive and negative bacterial isolates in diabetic foot.

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TABLE 2 Antibiotic resistance of the major bacterial isolates in diabetic foot.

	Staphylococcus aureus (n=36)	*Escherichia coli (n=22)*	*Pseudomonas aeruginosa (n=15)*	*Proteus vulgaris (n=12)*	*Morganella morganii (n=11)*
Antibiotic	R (%)	R (%)	R (%)	R (%)	R (%)
Imipenem	_	-	47	-	9
Meropenem	_	-	47	-	-
Ertapenem	_	5	_	-	-
Colistin	_	5	20	92	100
Amikacin	_	-	27	-	-
Cefoxitin	_	14	_	8	18
Pip/Tazo	_	14	20	-	-
Tigecycline	_	15	_	33	-
Amox/A Clav	69	36	_	25	100
Gentamicin	61	68	53	17	9
Tobramycin	61	55	40	17	18
Cefepime	_	68	47	25	9
Cefotaxime	_	73	_	42	_
Ceftazidime	_	73	33	33	18
Cefuroxime	_	77	_	92	100
Trimet/Sulfa	31	77	_	75	82
Aztreonam	_	77	73	50	18
Amp/ Sulbactam	_	68	_	25	100
Levofloxacin	67	82	47	8	36
Ampicillin	97	90	_	92	100
Ciprofloxacin	67	90	60	50	73
Fosfomycin	17	18	_	25	91
Ceftaroline	44	_	_	_	_
Clindamycin	78	_	_	_	_
Daptomycin	-	_	_	_	_
Erythromycin	75	_	_	_	_
Linezolid	-	_	_	_	_
Mupirocin	19	_	_	_	_
Oxacillin	67	_	_	_	_
Penicillin	97	_	_	_	_
Synercid	14	_	_	_	_
Teicoplanin	-	_	_	_	_
Tetracycline	22	_	_	_	_
Vancomycin	-	_	_	_	_

- means that no isolates with resistance to that antibiotic were found.

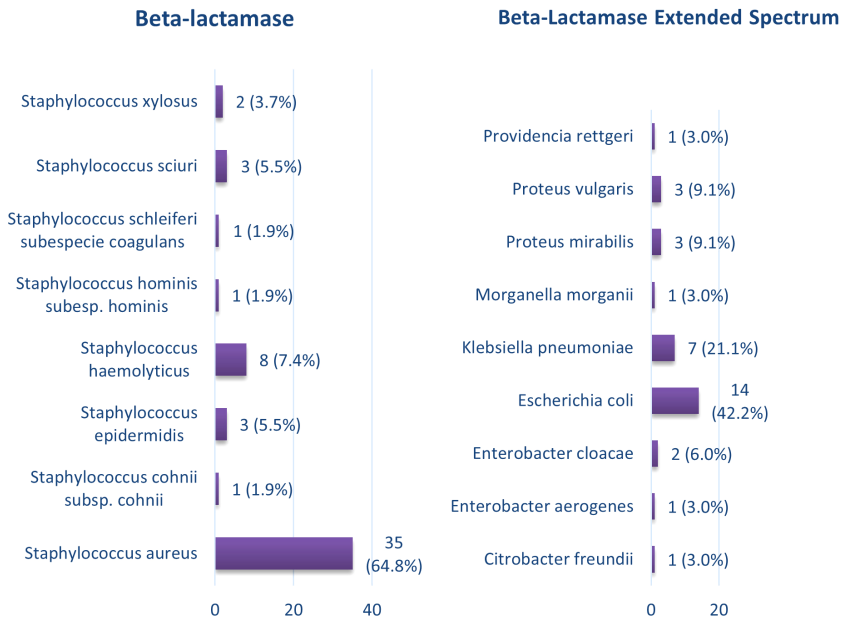

FIGURE 2
Bacterial isolates in diabetic foot with the presence of extended-spectrum beta-lactamases.

antimicrobial resistance to Ampicillin (89.7%), Cefuroxime (75.9%), Trimethoprim-sulfamethoxazole (64.6%), and Ciprofloxacin (61.5%). On the other hand, they displayed higher sensitivity to Carbapenems (>85.4%), Amikacin (85.3%), and Piperacillin/tazobactam (82.5%), while Ampicillin (6.9%) and Fosfomycin (1.5%) had lower sensitivity. These findings differ from another Peruvian study, where P. aeruginosa and A. baumannii showed a high resistance to carbapenems of 83% and 100%, respectively (9). However, both studies agree that Gram-negative bacteria showed low sensitivity to Ampicillin and high sensitivity to Carbapenems and Amikacin (15). Additionally, Enterobacteria (*E. coli, K. pneumoniae, P. mirabilis, and P. vulgaris*) showed a resistance rate of 89.4% to ciprofloxacin, which is a first-line drug in treatment (9). In Nigeria, Gram-negative bacteria also displayed high resistance to Trimethoprim-sulfamethoxazole (89%) and ciprofloxacin (54.3%) (18).

In Gram-positive bacteria, a higher antimicrobial resistance was observed to Penicillin (95.4%), Ampicillin (87.7%), Clindamycin (80.7%), and Oxacillin (76.4%). However, a 100% antimicrobial sensitivity was found for Daptomycin, Vancomycin, and Teicoplanin. These results align with other Peruvian studies where a 71% resistance to Oxacillin in these bacteria was found (9, 15). In Nigeria, resistance to Penicillin G was also observed (66.1%), along with low resistance to Piperacillin/tazobactam (6.8%) and Amikacin (10.2%) (18).

Focusing on bacteria with the highest incidence, especially S. aureus, internationally, high levels of antibiotic resistance have been observed, representing a significant risk and limiting future treatment options. Specifically, Methicillin resistance rates range from 16% to 44%, even reaching 50% in Lebanon (16, 21). In this study, bacteria with the highest incidence, such as *S. aureus, E. coli, P. aeruginosa, Proteus vulgaris, and Morganella morganii*, showed a high percentage of common resistance to Ampicillin, Ciprofloxacin, Levofloxacin, Trimethoprim-sulfamethoxazole, and Cefuroxime. Additionally, other studies have found that Pseudomonas aeruginosa is resistant to any carbapenem, with a prevalence ranging from 5.4% (16).

As previously mentioned, Gentamicin, Tobramycin, and Levofloxacin showed the highest sensitivity to the most incident bacteria. In China, Gram-positive bacteria showed low resistance to Gentamicin (17), whereas in Nigeria, both Gram-positive (40.1%) and Gram-negative (54.3%) bacteria displayed high resistance to this antibiotic (18). Sudan recorded a resistance rate of 65.2% for *S. aureus*, while Nicaragua observed complete resistance to this bacterium (23).

The results obtained reveal variability in bacterial susceptibility to antibiotics, but most of them show concerning resistance to these medications. A recent systematic review demonstrated that infections caused by multidrug-resistant bacteria have increased in recent years, associated with a higher prevalence of diabetic foot ulcers (24). This phenomenon is linked to the prolonged use of broad-spectrum antibiotics, necessary to penetrate the bacterial biofilm but also triggering survival mechanisms and increased resistance. This has a negative impact on amputation and mortality rates in diabetic patients (24). It is crucial to address this problem and seek effective therapeutic alternatives to fight infections in diabetic foot, avoiding the indiscriminate use of antibiotics and promoting strategies that limit the development of bacterial resistance.

On the other hand, sodium-glucose cotransporter-2 (SGLT-2) inhibitors have emerged as a valuable addition to the therapeutic arsenal for managing diabetes mellitus. These medications function

by promoting glycosuria, leading to reduced blood glucose levels. While this effect can be beneficial for glycemic control, it may inadvertently contribute to impaired tissue perfusion in the lower extremities, which is a well-established risk factor for diabetic foot complications (25). As such, there is a growing need for comprehensive research to elucidate the precise relationship between SGLT-2 inhibitors and diabetic foot infections, shedding light on the clinical implications and guiding the development of preventive strategies in diabetic patient populations.

Another contemporary aspect is the role of SARS-CoV-2 infections on diabetic foot. The COVID-19 pandemic has had far-reaching effects on global healthcare systems and has also influenced the management and severity of diabetic foot syndrome (26). Individuals with diabetes are already predisposed to various complications, including this syndrome, due to factors such as neuropathy and impaired vascular function. However, the pandemic has introduced several additional challenges that have the potential to exacerbate the severity of diabetic foot (27). Firstly, disruptions in healthcare access and routine check-ups during lockdowns or overwhelmed healthcare systems have made it difficult for diabetic patients to receive timely foot care and monitor their condition (28). Secondly, some studies have shown that individuals with poorly controlled diabetes are at higher risk of severe COVID-19 outcomes, which may indirectly worsen diabetic foot severity by affecting overall health and immune responses (29, 30). Furthermore, the stress and anxiety associated with the pandemic have led to lifestyle changes, including altered dietary habits and reduced physical activity, which can further contribute to poor glycemic control and increased diabetic food syndrome risk (31).

5 Limitation

This study has certain limitations that need to be considered when interpreting the results. Firstly, the sample was limited to diabetic foot patients from a single tertiary hospital, which implies that the frequency of bacteria, as well as their resistance and sensitivity to antibiotics, may vary in other health centers located in urban, rural, or mountainous areas (15). Therefore, caution is necessary when generalizing the findings to other populations and clinical settings. Another important limitation is that the study did not consider the presence of fungi, such as *Candida albicans and/or Candida tropicalis*, which often coexist and have fungal growth alongside the studied bacteria (32). The omission of these microorganisms could have affected the complete understanding of infections associated with diabetic foot and their treatment. Despite these limitations, this study has successfully identified the most common bacteria in diabetic foot infections and their resistance and sensitivity profiles to different antibiotics used in clinical practice. These findings provide valuable information for the management and treatment of infections in patients with diabetic foot, although a broader and more comprehensive evaluation in future studies is required to address the mentioned limitations and obtain a more accurate view of the situation.

6 Conclusion and future direction

In this study, S. aureus, E. coli, P. aeruginosa, P. vulgaris, and M. morganii were identified as the most common bacteria in diabetic foot infections. These bacteria showed resistance to various antibiotics, such as Ampicillin, Ciprofloxacin, Levofloxacin, Trimethoprim-sulfamethoxazole, and Cefuroxime, and Escherichia coli was the most resistant. However, Levofloxacin was found to be one of the most effective antibiotics against these prevalent bacteria. Additionally, Gram-negative bacteria showed notable sensitivity to Meropenem, Piperacillin/tazobactam, and Amikacin.

Bacterial resistance in diabetic foot infections is a growing global concern as it hinders treatment and increases the risk of serious complications such as the need for amputation and mortality. Therefore, it is crucial to focus on studying the susceptibility of bacteria to antibiotics to ensure appropriate prescription dosages in pharmacological treatment and to avoid overuse of these medications. Understanding the resistance and sensitivity of bacteria causing diabetic foot infections is essential to guide the choice of antibiotics and ensure effective treatment. Furthermore, it would be pertinent to consider the assessment of fungal infections in future research endeavors. This inclusion would contribute to a more comprehensive understanding of the microbiota implicated in these infections, further enriching the scope of the study. This will help optimize clinical outcomes and reduce complications associated with these infections. Continued research and data updates on bacterial resistance are necessary to adapt therapeutic strategies and effectively address this public health challenge.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Hospital María Auxiliadora (HMA/CIEI/008/2021, May 26, 2021) and the Universidad Norbert Wiener (Exp.528-2021, April 26, 2021). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JM-S: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft,

Writing – review & editing, Investigation, Visualization. JC: Conceptualization, Data curation, Investigation, Writing – original draft. DP-R: Conceptualization, Data curation, Investigation, Writing – original draft, Visualization. EG-P: Data curation, Formal analysis, Writing – review & editing, Visualization. CS: Investigation, Methodology, Writing – review & editing, Conceptualization, Validation. HC-P: Methodology, Writing – review & editing, Project administration, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparison of healing effectiveness of different debridement approaches for diabetic foot ulcers: a network meta-analysis of randomized controlled trials

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Objectives: The choice of the debridement method is very important for the healing of diabetic foot ulcers (DFUs), but the relative effectiveness of different debridement methods in the healing of DFUs remains unclear. This study conducted a network meta-analysis of the relative healing effectiveness of different debridement methods in patients with DFUs.

Methods: We performed a literature search in PubMed, Embase, and Cochrane Library from database inception up to 30 June 2023 for screening randomized controlled trials on the healing effectiveness of debridement in DFUs. Outcome measures included ulcer healing rate and ulcer area reduction rate. The Cochrane Risk Bias Tool, version 2.0, was used to assess the risk of bias in the included trials. R software was used for performing statistical analysis and GraphPad Prism was used for image plotting.

Results: A total of 19 randomized controlled trials were included, and 900 patients with DFUs were assessed in this analysis. The proteolytic fraction from the latex of *Vasconcellea cundinamarcensis* (P1G10) in enzymatic debridement showed the best ulcer healing rate (SURCA = 0.919) when compared with the standard of care (SOC) group, with a mean difference (MD) and 95% confidence interval (CI) of 1.40 (0.57, 2.36). Kiwifruit extract demonstrated the best effect on the ulcer area reduction rate (SURCA = 0.931), when compared with that in the SOC group, with an MD and 95% CI of 0.47 (0.27, 0.66).

Conclusion: Enzymatic debridement was superior to other debridement methods in terms of ulcer healing rate and ulcer area reduction rate in patients with DFUs. However, as the quality of the included trials is low, enzymatic debridement can be used as a candidate debridement method in addition to sharp-based debridement in clinical practice.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023441715.

KEYWORDS

debridement, diabetic foot ulcers, healing rate, area reduction, network meta-analysis, randomized controlled trial

1 Introduction

The prevalence of diabetic foot ulcers (DFUs) has steadily increased. The International Diabetes Foundation estimated that 40–60 million people worldwide have DFUs (1). If left untreated, DFUs can progress to soft tissue infections and gangrene, resulting in limb loss (2). The latest meta-analysis revealed that DFUs are associated with a high overall mortality rate of nearly 50% within 5 years (3), posing a grave threat to patients' wellbeing. DFUs typically arise from a combination of factors, including prolonged hyperglycemia, neuropathy, and vascular disease (4). DFU management involves various aspects, such as wound debridement, infection control, and ulcer healing. Wound debridement is considered a crucial intervention in DFU management, as it accelerates ulcer healing and reduces the risk of severe complications. The process involves eliminating non-viable wound bed and wound edge tissue, including excess callus, non-viable dermal tissue, foreign substances, and bacterial components, to promote wound healing (5). Currently, several approaches for debridement are available, such as mechanical debridement, including sharp debridement, surgery, wet-to-dry (6), ultrasound (7), hydrosurgery (8), or biological debridement (maggot debridement therapy) (9), and non-mechanical debridement, including autolytic (hydrogel (10) or alginate (11)) or biochemistry debridement (enzymatic) (12). While experts universally recognize the significance of regular wound debridement for enhancing DFU healing, available evidence supporting the most effective debridement method remains limited.

In May 2023, the International Working Group on the Diabetic Foot (IWGDF) (13) significantly updated the guidelines for DFU diagnosis and treatment. The guidelines emphasize that no debridement method can fully replace sharp instrument debridement, which remains the gold standard approach. Early aggressive initial and sequential debridement is essential for ulcer care. However, the specific approach to debridement may vary based on individual patient and ulcer characteristics, as well as cost and convenience considerations (14). While sharp debridement is highly recommended, the guidelines do not clearly recommend the relative effectiveness of other debridement methods for patients with DFUs. Therefore, to address this knowledge gap, a network meta-analysis (NMA) that integrates and assesses existing research data from randomized controlled trials (RCTs) was conducted to evaluate the relative healing effectiveness of different debridement methods in patients with DFUs. This NMA aimed to provide more specific guidance for clinical practice, offering a more reliable foundation for future research and treatment strategies. Thus, the objective of this study was to improve the treatment outcomes for patients with DFUs, reduce their suffering, and minimize the risk of complications.

2 Methods

2.1 Registration

This NMA adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) statement for systematic evaluation and meta-analysis (15). The study protocol was registered with the International Prospective Systems Evaluation Register (PROSPERO; registration no. CRD42023441715).

2.2 Search strategies

A comprehensive search was performed in three electronic databases (PubMed, EMBASE, and Cochrane Library) using a search strategy centered around the PICOS tool: Population (patients with DFU), Intervention (mechanical or non-mechanical debridement), and type of study (RCT). Supplementary Table S1 in the Additional Materials section presents the full list of search terms. Additionally, the reference lists of previous systematic reviews and meta-analyzes in this field were checked to identify any missing articles. All retrieved documents were stored in the EndNote version X9 database (Thomson ResearchSoft, Stanford, CA, United States).

2.3 Research selection

Studies that met the following inclusion criteria were selected (1): Subjects: adult patients with a confirmed diagnosis of type 1 or type 2 diabetes, wherein the diagnosis was made based on the World Health Organization 1999 and American Diabetes Association standards (16), meeting the IWGDF 2023 standard diagnosis for patients with DFU (17). No restrictions were imposed on nationality or race, and patients with gestational diabetes mellitus were not included in the test process. (2) Intervention measures: The experimental group underwent debridement using mechanical or non-mechanical debridement methods with no limitation on the treatment course and debridement frequency; (3) Control measures: standard of care (SOC); (4) Research type: RCT.

Studies that met the following exclusion criteria were not selected: (1) review articles, systematic evaluation, abstracts, conference papers, retrospective studies, cross-sectional studies, and cross-RCTs; (2) studies lacking relevant outcome indicators or extractable data; (3) animal and cell studies; (4) studies on patients with gestational diabetes; and (5) non-English literature.

Two researchers (PN and YL) independently screened the titles and abstracts to identify potentially eligible articles. Subsequently, a full-text search was performed to include eligible articles. In case of conflicting opinions, a third researcher (HC) made the final decision on selecting conflicting articles.

2.4 Data extraction

Data were extracted using a predesigned spreadsheet. Two researchers (PN and YL) independently extracted data from the included studies, including information on author, year, country, sample size, comparison, treatment details (various types of debridement and SOC), and outcome indicators (ulcer healing rate and ulcer area reduction rate). When outcome indicators were presented only in images, GetData Graph Digitizer 2.25 (GetData Software Development Company, Sydney, Australia) was used to collect the data of outcome indicators. Any discrepancies in the extracted data were resolved by a third researcher (JZ).

2.5 Risk-of-bias assessment

The Cochrane Risk Bias Tool, version 2.0, was used to assess the risk of bias in the included studies. This involved evaluating random

sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Study quality was categorized as low, unclear, or high risk of bias. Two researchers (YL and JK) independently evaluated all studies, and disagreements between the two researchers were resolved by a third researcher (JZ).

2.6 Data analysis

Statistical analysis was conducted using R software, version 4.3.1 (R Core Team, Vienna, Austria) and the packages "netmeta," "gemtc," and "rjags" (18) were used; the image plotting was performed using GraphPad Prism, version 9.4.1 (GraphPad Software, San Diego, CA, United States). First, we constructed a network plot as a simple overview to display all available evidence for each intervention. Second, we performed Bayesian network analysis based on Markov Chain Monte Carlo (18) to analyze the ulcer healing rate and ulcer area reduction rate in patients with DFUs for different debridement approaches. The number of tuning and simulation iterations was set at 5,000 and 20,000, respectively. An I^2 value of ≤50% indicated minimal or no heterogeneity between studies, leading to the adoption of the fixed-effects model. Otherwise, the random-effects model was used (19). The results of the generated League Table were expressed using mean difference (MD) and 95% confidence interval (CI), and the data were not statistically significant when the 95% CI value contain 0. Then, to assess the probability of each intervention being the most effective, the surface under the cumulative ranking curve (SUCRA) was calculated (with a value ranging from 0 to 1). A higher SUCRA value indicated a greater likelihood of a treatment being highly effective or having the highest level of effectiveness, thereby maximizing the potential for achieving optimal outcome indicators (20). Finally, heterogeneity analysis was conducted for all included studies, wherein heterogeneity was considered to exist when $I^2 > 50\%$. A value of $\alpha = 0$. 05 was considered to indicate statistical significance.

3 Results

3.1 Research selection and characteristics

A total of 2,481 studies were identified in our initial database search, covering the period from the inception of the databases to 30 June 2023. Additionally, when manually searching the reference lists of previous systematic reviews and meta-analyzes, two additional studies that met the inclusion criteria were identified. A total of 1,548 studies were excluded after eliminating duplicate articles. Fifty studies were excluded because they were non-human or non-English studies, 856 were excluded because they were non-RCTs or cross-RCTs, and 623 were excluded because they did not conform to the PICO principles of the study. Finally, 19 RCTs (Figure 1) involving 900 patients with DFUs were included in the analysis. The baseline characteristics of the population are listed in Table 1. The advantages and disadvantages of different debridement methods are shown in Table 2. The debridement methods reported in the selected studies mainly include sharp debridement, surgical debridement, ultrasonic debridement, enzymatic debridement, and autolytic debridement.

3.2 Risk of bias in studies

The risk of bias was assessed for all the included RCTs. Among the 19 studies, 10 did not specifically describe the generation of random sequences, 10 did not specifically describe the concealment scheme of RCTs, 11 did not specifically describe the method of blinding participants and implementers, and 13 did not specifically describe the blinding scheme of the outcome measure. The data reported in 12 studies were incomplete, those in 3 studies might have been selectively reported, and those in 15 studies may have had reporting bias. The risk-of-bias plots showed individual and overall document-level quality separately (Figure 2).

3.3 Healing rate

A total of 14 RCTs investigated the effect of different debridement procedures on the ulcer healing rate in patients with DFU. A network diagram of the ulcer healing rate is shown in Figure 3A. The heterogeneity test indicated an I^2 value of 23%; hence, the fixed-effects model was used. According to SUCRA analysis and the League Table (Table 3A), the proteolytic fraction from the latex of *Vasconcellea cundinamarcensis* (P1G10) in enzymatic debridement showed the best effect on the ulcer healing rate in patients with DFUs (SUCRA = 0.919). The cumulative probability ranking graph is shown in Figure 4A, with an MD and 95% CI of 1.40 (0.57, 2.36) when compared with the SOC group.

3.4 Area reduction rate

A total of 14 RCTs evaluated the effect of different debridement procedures on the ulcer area reduction rate in patients with DFU, and a network diagram of the ulcer area reduction rate is shown in Figure 3B. The heterogeneity test indicated an I^2 value of 9%; hence, the fixed-effects model was used. According to SUCRA analysis and the League Table (Table 3B), kiwifruit extract in enzymatic debridement had the best effect on the reduction rate of the DFU area (SUCRA = 0.931). The cumulative probability ranking graph is shown in Figure 4B, with an MD and 95% CI of 0.47 (0.27, 0.66) when compared with the SOC group.

3.5 Heterogeneity assessment

The heterogeneity test was performed separately for the two outcome indicators. For the ulcer healing rate, the heterogeneity of the network comparison of sharp + SOC vs. hydrogel + sharp was 73.1%, and the heterogeneity of the network comparison of ultrasonic + SOC vs. SOC was 64.2% (Figure 5A). Regarding the ulcer area reduction rate, the heterogeneity of the network comparison of SOC vs. alginate was 65.1% (Figure 5B). The network comparison heterogeneity of the other studies was less than 50%.

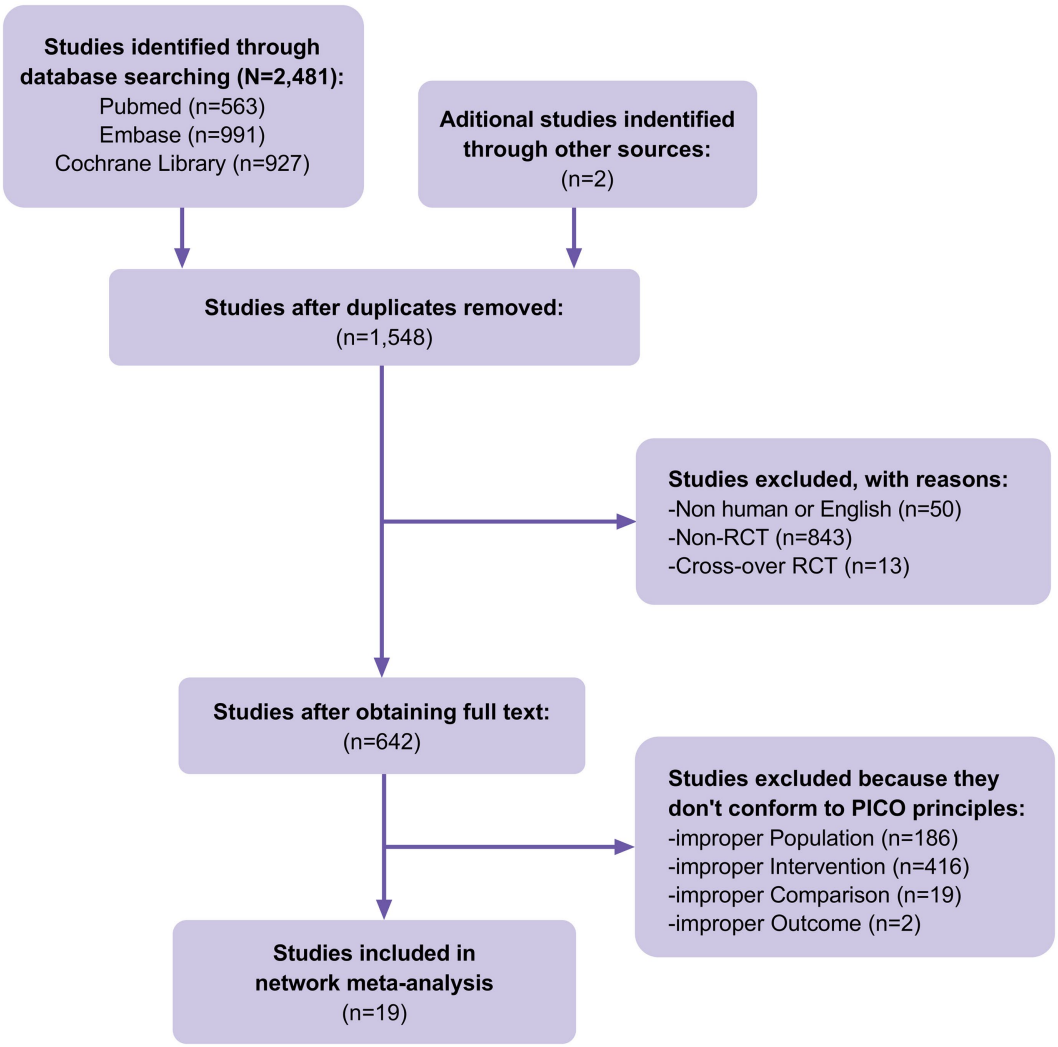

FIGURE 1
Flow of trials through the review.

4 Discussion

DFU is a common complication among patients with diabetes, and its treatment options are diverse and complex. Debridement, as an essential treatment method, has garnered significant attention. To the best of our knowledge, this NMA represents the first report on an NMA comparing the healing effectiveness of various debridement methods for DFU. The debridement methods included in the final studies were mechanical debridement (sharp, surgery, or ultrasound), enzymatic debridement (clostridial collagenase ointment [COO], P1G10, or kiwifruit extract), and autolytic debridement (hydrogel or alginate). In this NMA, P1G10 debridement demonstrated the best wound healing rate among the enzymatic debridements (SUCRA = 0.919). Kiwifruit extract debridement exhibited the highest ulcer area reduction rate (SUCRA = 0.931), and COO, another enzymatic debridement, also demonstrated high effectiveness.

Enzymatic debridement, which has a long history and wide application in wound debridement for patients with burns (40–42), was found to be an excellent debridement method for DFUs in our NMA. Enzymatic debridement involves applying proteases from various sources (e.g., bacteria, plants, or animals, as seen in COO, P1G10, and kiwifruit extract) to promote the degradation of the necrotic tissue at the bottom of the wound and remove foreign bodies and secretions, thereby accelerating the wound healing process (12). Although the results of this study show that enzymatic debridement is advantageous in DFU treatment, the latest IWGDF 2023 guidelines still recommend sharp debridement as the preferred debridement method for diabetic ulcers because, although experts generally agree on the need for regular wound debridement to promote wound healing, studies presenting high-quality evidence on debridement and confirmation of the best debridement methods are still relatively limited (13). Nonetheless, the advantages of enzymatic debridement cannot be disregarded, particularly in the management of DFUs in some low-income areas that may lack skilled personnel, training programs, sterile instruments, and standard sharp debridement. Thus, in healthcare systems with such limitations, enzymatic debridement can be considered as an alternative (13). When enzyme debridement is performed for DFUs, the patient's wound is first thoroughly evaluated, including the location, size, depth, and degree of infection of the wound. According to the nature and condition of the wound,

TABLE 1 Characteristics of RCTs on the effectiveness of debridement in patients with diabetic foot ulcers.

Study	Region	Criteria	Type	Intervention			Comparison			Follow-up	Outcome
				N	Ulcer area(cm^2)	Method	*N*	Ulcer area(cm^2)	Method		
Piaggesi et al. (21)	Italy	Wagner	Neuropathic	21	NA	Surgical + SOC	20	NA	Sharp + SOC	6 months	H
Ennis et al. (22)	USA	Wagner	NA	27	NA	Ultrasonic + SOC	28	NA	SOC	3 months	H
Amini et al. (23)	Iran	Wagner	Neuropathic or Neuroischemic	20	6.8 ± 3.5	Ultrasonic + SOC	20	9.9 ± 7.6	SOC	6 months	H, A
Yao et al. (24)	USA	Wagner	Neuropathic	8	2.2 ± 1.7	Ultrasonic + SOC	4	2.1 ± 0.9	SOC	5 weeks	A
Michailidis et al. (25)	Australia	UTWCS	NA	5	NA	Ultrasonic + SOC	5	NA	Sharp + SOC	6 months	H
Bajpai et al. (26)	USA	NA	NA	4	NA	Ultrasonic + SOC	4	NA	SOC	3 months	H, A
Lázaro-Martínez et al. (27)	Spain	UTWCS	Neuropathic	27	7.5 ± 7.6	Ultrasonic + SOC	24	4.2 ± 3.3	Surgical + SOC	6 months	H, A
Tallis et al. (28)	USA	BWAT	Neuropathic	24	3.0 ± 2.1	COO + Sharp	24	2.4 ± 2.1	Sharp	3 months	H, A
Galperin et al. (29)	USA	Wagner	NA	9	8.1 ± 8.1	CCO	8	7.8 ± 6.9	Hydrogel	1 month	A
Motley et al. (30)	USA	UTWCS	Neuropathic	28	2.0 ± 1.1	COO + Sharp	27	1.8 ± 1.6	Hydrogel + Sharp	3 months	H, A
Lantis et al. (31)	USA	Wagner	Neuropathic	88	3.0 ± 3.6	Trial 1: COO	86	2.5 ± 3.2	Trial 1: SOC	3 months	A
						Trial 2: COO			Trial 2: Hydrogel		
						Trial 3: COO			Trial 3: Sharp		
						Trial 4: COO + Sharp			Trial 4: Sharp		
Tonaco et al. (32)	Brazil	NA	Neuropathic	27	NA	P1G10	23	NA	Hydrogel	4 months	H
Mohajeri et al. (33)	Iran	NA	Neuropathic	17	4.2 ± 0.9	Kiwifruit extract + Sharp	20	4.0 ± 0.7	SOC + Sharp	3 weeks	A
Kardoust et al. (34)	Iran	Wagner	Neuropathic	9	2.2 ± 0.7	Kiwifruit extract	9	2.0 ± 0.6	SOC	1 month	A
Jensen et al. (35)	USA	Wagner	NA	14	NA	Hydrogel + Sharp	17	NA	SOC + Sharp	5 months	H
Djavid et al. (36)	Iran	Wagner	Neuropathic	30	3.1 ± 2.5	Hydrogel	31	3.5 ± 4.2	SOC	6 months	H, A
Della Pepa et al. (37)	Italy	UTWCS	Neuropathic, Ischemic, or Neuroischemic	20	2.1 ± 1.8	Hydrogel + Sharp	20	2.3 ± 2.7	SOC + Sharp	3 months	H, A
Donaghue et al. (38)	USA	Wagner	NA	50	2.6 ± 0.5	Alginate	25	3.0 ± 0.6	SOC	2 months	H, A
Lalau et al. (39)	France	NA	Neuropathic	39	8.0 ± 10.5	Alginate	38	8.8 ± 16.0	SOC	6 weeks	H, A

UTWCS, University of Texas Wound Classification System; BWAT, Bates-Jensen Wound Assessment Tool; COO, Clostridial collagenase ointment; SOC, Standard of care; P1G10, Proteolytic Fraction from Latex of *Vasconcellea cundinamarcensis*; H, healing rate; A, area reduction rate.

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TABLE 2 Advantages and disadvantages of different debridement methods.

Method	Explanation	Advantages	Disadvantages
Mechanical debridement			
Sharp debridement	Use a sharp tool, such as a scalpel or scissors, to remove dead tissue in the dressing room	- Guideline recommendation - Quick - Specific - Less costly	- Painful - Large injury
Surgical debridement	Use surgical techniques to remove necrotic tissue in the operating room	- Clear thoroughly - Deep-tissue samples were collected for pathological examination. - Provide a clean bed for future operations such as transplants or flaps	- High technical requirements - Painful - Larger injury - Expensive
Wet-to-dry debridement (6)	Gauze moistened with salt water is allowed to dry and removed with dead tissue	- Quick	- Non-specific - Easily damages healthy tissue - Painful
Ultrasound debridement (7)	Use the sound energy generated by ultrasound to remove dead tissue	- Quick - Specific	- May cause pain - Expensive
Hydrosurgery (8)	The wound is irrigated with high-pressure water, either manually or with a mechanical spray device	- Quick - Suited for larger wounds	- Non-specific - Cross-infection - May cause pain - Expensive
Biological debridement (maggot debridement therapy) (9)	The sterile maggots were placed directly on the infected area and wrapped with close net dressing while actively avoiding healthy tissue	- Relatively quick - Ultraspecific	- Difficulty accessing maggots - May cause minor pain - Patients may resist for psychological reasons
Non-mechanical			
Autolytic debridement (hydrogel (10) or alginate (11))	Relies on a dressing type that permits the wound to remain moist and facilitates autolysis of the devitalized tissue	- Convenient and simple - Selective for non-viable tissue - Minimal or no discomfort - Less costly	- Slow process - May lead to softening of the surrounding tissue and infection - Not ideal for heavily infected wounds
Biochemistry (enzymatic debridement) (12)	Uses the application of enzymes such as collagenase to help lyse non-viable tissue	- Convenient and simple - Selective and specific for non-viable tissue - Minimal or no discomfort	- Slow process - May cause allergic reactions or other discomfort - Not ideal for heavily infected wounds

the appropriate enzyme drugs should be selected and applied. Before enzyme debridement, the wound should be well prepared, including cleaning the wound and removing dirt. Enzymes are usually applied onto the wound surface in the form of ointments or liquids, and it is important to ensure even application onto the wound. Then, cover the wound to prevent the enzyme drug from spilling over while keeping the wound moist. The treatment process requires regular monitoring to observe changes in dead tissue and wound healing. Treatment usually needs to be performed every day or every few days, depending on the wound condition. In addition, enzyme debridement therapy is often used in combination with other treatment strategies, such as antibiotic therapy, foot pressure relief, and blood glucose management. It is essential to continuously monitor the patient's response, including the rate of wound healing, infection, and comfort, and to adjust treatment strategies, if necessary.

In addition to sharp debridement, mechanical debridement in this NMA includes surgery and ultrasound. However, these debridement modalities have demonstrated poor effectiveness on both DFU healing and ulcer area reduction, while they are expensive; require a sterile environment, well-trained practitioners, and specific devices; and are contraindicated in patients with coagulation disorders (43). However, it cannot be denied that surgical debridement is more thorough, especially suitable for wounds with severe infections, and this approach also has the advantage of obtaining deep-tissue specimens for pathological

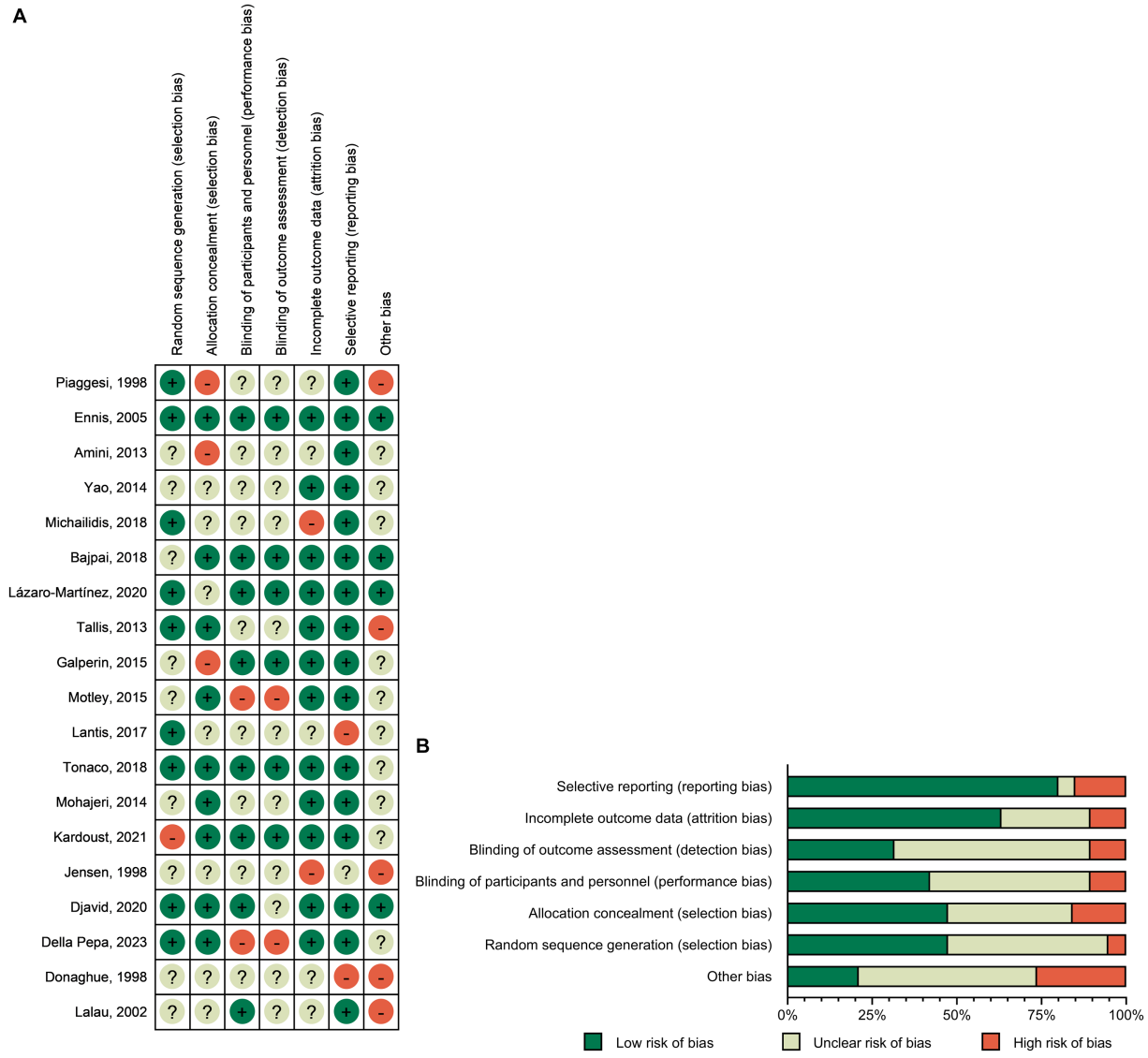

FIGURE 2
Risk-of-bias graph: **(A)** Risk-of-bias summary: review authors' judgments about each risk-of-bias item for each included study. **(B)** Risk-of-bias graph: judgments about each risk-of-bias item presented as percentages across all included studies.

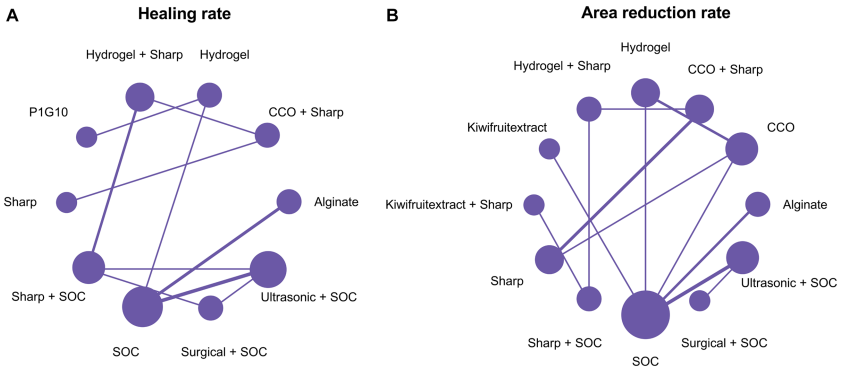

FIGURE 3
Network plots. **(A)** Healing rate; **(B)** Area reduction rate. COO, Clostridial collagenase ointment; SOC, Standard of care; P1G10, Proteolytic Fraction from Latex of *Vasconcellea cundinamarcensis*.

TABLE 3 Mean difference (MD) and 95% confidence interval (CI) for outcome measures.

A. Healing rate

Alginate									
−0.59 (−1.46, 0.25)	CCO + Sharp								
−0.17 (−0.92, 0.53)	0.41 (−0.51, 1.34)	Hydrogel							
−0.50 (−1.33, 0.30)	0.09 (−0.15, 0.36)	−0.32 (−1.21, 0.57)	Hydrogel + Sharp						
−1.05 (−2.09, −0.10)	−0.45 (−1.64, 0.66)	−0.86 (−1.64, −0.25)	−0.55 (−1.71, 0.54)	P1G10					
−0.39 (−1.30, 0.51)	0.20 (−0.07, 0.53)	−0.21 (−1.18, 0.76)	0.11 (−0.27, 0.51)	0.66 (−0.49, 1.89)	Sharp				
−0.37 (−1.12, 0.34)	0.22 (−0.23, 0.68)	−0.19 (−1.01, 0.62)	0.12 (−0.25, 0.51)	0.67 (−0.36, 1.78)	0.01 (−0.53, 0.55)	Sharp + SOC			
0.35 (−0.06, 0.82)	0.95 (0.24, 1.70)	0.53 (−0.01, 1.15)	0.85 (0.20, 1.57)	1.40 (0.57, 2.36)	0.75 (−0.03, 1.55)	0.73 (0.18, 1.34)	SOC		
−0.17 (−0.89, 0.52)	0.42 (−0.08, 0.94)	0.00 (−0.78, 0.81)	0.32 (−0.11, 0.78)	0.87 (−0.13, 1.97)	0.22 (−0.37, 0.81)	0.19 (−0.01, 0.46)	−0.53 (−1.10, −0.01)	Surgical + SOC	
−0.18 (−0.86, 0.47)	0.41 (−0.12, 0.96)	0.00 (−0.75, 0.77)	0.31 (−0.15, 0.80)	0.86 (−0.11, 1.93)	0.21 (−0.41, 0.82)	0.19 (−0.10, 0.50)	−0.54 (−1.07, −0.08)	−0.01 (−0.25, 0.23)	Ultrasonic + SOC

B. Area reduction rate

Alginate											
−0.08 (−0.21, 0.04)	CCO										
−0.06 (−0.47, 0.35)	0.02 (−0.37, 0.41)	CCO + Sharp									
0.01 (−0.13, 0.16)	0.10 (0.01, 0.19)	0.08 (−0.33, 0.48)	Hydrogel								
0.18 (−0.66, 1.03)	0.27 (−0.57, 1.10)	0.25 (−0.50, 0.99)	0.17 (−0.68, 1.01)	Hydrogel + Sharp							
−0.33 (−0.55, −0.11)	−0.25 (−0.45, −0.04)	−0.27 (−0.71, 0.18)	−0.35 (−0.56, −0.13)	−0.52 (−1.38, 0.35)	Kiwifruit extract						
0.15 (−1.08, 1.36)	0.23 (−0.99, 1.44)	0.21 (−0.94, 1.36)	0.13 (−1.09, 1.35)	−0.04 (−0.91, 0.83)	0.48 (−0.76, 1.71)	Kiwifruit extract + Sharp					
0.17 (−0.23, 0.57)	0.25 (−0.13, 0.64)	0.23 (0.14, 0.33)	0.15 (−0.23, 0.55)	−0.02 (−0.76, 0.73)	0.50 (0.07, 0.94)	0.02 (−1.13, 1.18)	Sharp				
0.32 (−0.90, 1.53)	0.40 (−0.81, 1.61)	0.38 (−0.76, 1.52)	0.30 (−0.91, 1.51)	0.14 (−0.73, 1.00)	0.65 (−0.58, 1.88)	0.17 (0.03, 0.31)	0.15 (−0.99, 1.29)	Sharp + SOC			
0.13 (0.03, 0.24)	0.22 (0.15, 0.28)	0.20 (−0.20, 0.60)	0.12 (0.02, 0.22)	−0.05 (−0.89, 0.79)	0.47 (0.27, 0.66)	−0.01 (−1.23, 1.21)	−0.04 (−0.42, 0.35)	−0.18 (−1.39, 1.02)	SOC		
0.01 (−0.51, 0.53)	0.09 (−0.42, 0.61)	0.07 (−0.57, 0.72)	0.00 (−0.52, 0.52)	−0.17 (−1.15, 0.81)	0.34 (−0.20, 0.89)	−0.14 (−1.45, 1.18)	−0.16 (−0.80, 0.48)	−0.31 (−1.61, 1.00)	−0.12 (−0.63, 0.39)	Surgical + SOC	
−0.07 (−0.21, 0.08)	0.02 (−0.11, 0.14)	0.00 (−0.42, 0.41)	−0.08 (−0.22, 0.06)	−0.25 (−1.10, 0.60)	0.27 (0.04, 0.48)	−0.21 (−1.43, 1.01)	−0.24 (−0.64, 0.16)	−0.38 (−1.60, 0.83)	−0.20 (−0.30, −0.10)	−0.08 (−0.58, 0.42)	Ultrasonic + SOC

Clinically important difference favoring row treatment	No difference	Clinically important difference favoring column treatment

COO, Clostridial collagenase ointment; SOC, Standard of care; P1G10, Proteolytic Fraction from Latex of *Vasconcellea cundinamarcensis*.

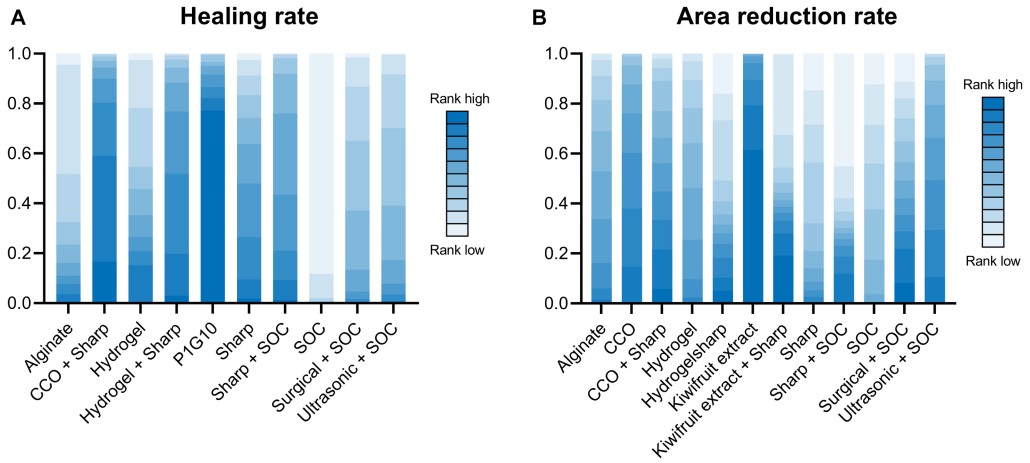

FIGURE 4
Cumulative probability ranking graph. **(A)** Healing rate; **(B)** Area reduction rate. COO, Clostridial collagenase ointment; SOC, Standard of care. P1G10, Proteolytic Fraction from Latex of *Vasconcellea cundinamarcensis*.

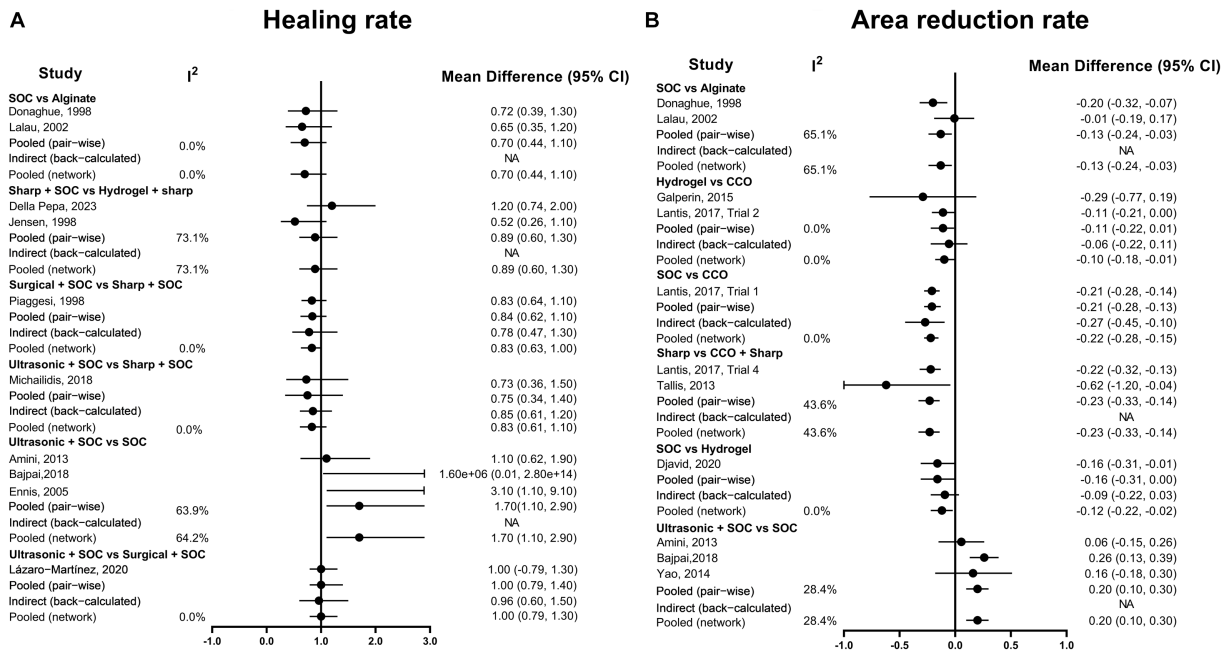

FIGURE 5
Heterogeneity assessment graph. **(A)** Healing rate; **(B)** Area reduction rate. COO, Clostridial collagenase ointment; SOC, Standard of care.

examination. Ultrasound debridement causes less trauma than sharp debridement, thereby reducing patient discomfort. Clinicians should also be aware that, during ultrasound debridement, there is a potential risk of exposure to aerosolized microorganisms and fragments from the wound (5). In this NMA, two autolytic debridements, namely, hydrogel and alginate, were mainly included. Although autolytic debridement is a conservative treatment strategy, it did not demonstrate high effectiveness in the included studies. Chronic wounds heal slowly, depending on appropriate response conditions and the patient's physiological response, thus increasing the risk of skin degeneration due to prolonged exposure of the surrounding skin to a moist environment (43). Unfortunately, this study did not identify any RCTs that met our inclusion criteria for wet-to-dry, hydrosurgery, and biological debridement. Wet-to-dry debridement, owing to its non-selective removal of granulation tissue, is prone to damaging healthy tissue and causing increased patient discomfort (5). Although hydrosurgery offers the advantage of shorter processing time and suitability for larger wounds, it may pose a risk of cross-contamination, and research on hydrosurgery is very limited (8). Regarding biological debridement, one RCT on maggot debridement was published as a meeting abstract without peer review (44). In 2019, an RCT (45) reported on maggot debridement, but the study mainly aimed to determine the outcome of inflammatory indicators, which did

not align with the outcome of the present study; hence, it was also excluded. However, biological debridement, which involves the digestive action of sterile maggots from *Lucilia sericata* to remove devitalized epithelial cells (46), has shown effectiveness in some chronic ulcers (47). Nevertheless, societal negative perceptions of maggots have hindered the acceptance of this option among patients and practitioners. At the same time, it is essential to recognize that different debridement methods may yield different results in various patients and different conditions. Therefore, clinicians should assess the advantages and complementarity of different debridement approaches and apply them reasonably in clinical practice. When formulating a treatment plan, clinicians should perform a comprehensive assessment based on the patient's specific conditions, ulcer characteristics, and feasibility to ensure the most suitable treatment for each individual.

It is essential to acknowledge that all the studies included in this NMA had important methodological limitations, primarily stemming from the lack of blinding in most studies, resulting in a high risk of bias that substantially reduces the reliability of the results. When assessing heterogeneity, our NMA revealed notable mesh comparison heterogeneity in certain cases. For instance, the comparison of SOC + sharp vs. hydrogel + sharp in terms of ulcer healing rate exhibited 73.1% heterogeneity. In this context, Della Pepa's study relied on patients' daily home dressing changes without blinded treatment, while Jensen's study was relatively old, not strictly randomized, and carried a high risk of bias. Similarly, the heterogeneity of ultrasonic + SOC vs. SOC in terms of ulcer healing rate was 64.2%. Both Bajpai and Ennis studies showed significantly higher healing rates in the ultrasonic + SOC group, with both studies having the same follow-up duration (3 months) and relatively high quality. By contrast, Amini's study found similar healing rates between ultrasonic + SOC and SOC groups, which may be attributed to the relatively long follow-up time (6 months) and the fact that the ulcers were mostly healed. Furthermore, Amini's study lacked strict randomization and blinding, and its quality was low. In the network comparison of ulcer area reduction rate, the heterogeneity of alginate vs. SOC was 65.1%. Studies conducted by Donaghue and Lalau were relatively outdated and had a high risk of bias. Donaghue's study might have had selective reporting, leading to publication bias, while Lalau's study had a significantly shorter follow-up duration than Donaghue's study. Therefore, to validate these findings, future research should focus on conducting more rigorous, high-quality, large-sample RCTs.

This NMA has several limitations. The varied length of the study, follow-up time, debridement frequency, and definitions of healing affected the outcome indicators of healing rate and ulcer area reduction rate. Additionally, more than half of the included studies had a high risk of bias, suggesting caution when applying the results to clinical practice. Moreover, because of the limitations in data extraction from the included literature, this study discussed only the comparison of different debridement methods for DFUs in terms of the ulcer healing rate and ulcer area reduction rate and did not address the safety and cost-effectiveness of these methods.

5 Conclusion

Although sharp debridement remains the preferred debridement method for most DFUs globally, there is mounting evidence supporting the advantages of enzymatic debridement in ulcer healing rate and ulcer area reduction rate. However, given the current low research quality, enzymatic debridement should be considered as a candidate debridement method alongside sharp debridement in clinical practice. To confirm these results, future research should focus on more rigorous, high-quality, large-sample RCTs. Clinicians should conduct a comprehensive assessment based on each patient's specific conditions, ulcer characteristics, and feasibility to provide the most appropriate treatment.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

PN: Data curation, Funding acquisition, Methodology, Writing – original draft. YL: Writing – review & editing. JK: Writing – review & editing. HC: Funding acquisition, Resources, Supervision, Writing – review & editing. JZ: Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1271706/full#supplementary-material

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Case report: The use of PRP in the treatment of diabetic foot: case series and a review of the literature

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Background: Diabetes mellitus is a prevalent chronic condition that significantly impacts global health. Diabetic foot complications, such as foot ulcers, pose a substantial burden on individuals with diabetes and can lead to serious consequences, including amputation. Platelet-rich plasma (PRP) has emerged as a promising therapeutic approach for enhancing the healing of diabetic foot ulcers.

Methods: In our study, we treated 12 patients with chronic diabetic ulcers using PRP injections administered at three-week intervals. Our objective was to assess the reduction in wound size and the rate of complete healing at 6 months after the start of the treatment. Additionally, we conducted a comprehensive literature review to contextualize our findings.

Results: Out of the 12 patients, 8 achieved complete healing of their diabetic foot ulcers, while the remaining four showed significant improvement with more than 50% reduction in the initial lesion size. 3 patients developed mild irritation at the inoculation site. These outcomes, combined with the evidence from published studies, highlight the effectiveness of PRP in promoting the healing of diabetic foot ulcers.

Conclusion: In conclusion, our study demonstrates the potential of platelet-rich plasma (PRP) as a successful therapeutic option for enhancing the healing process of chronic diabetic foot ulcers. The favorable outcomes observed, including a high rate of complete healing and significant wound size reduction, underscore the value of PRP treatment in managing this challenging complication. Further research and larger studies may provide additional insights into the mechanisms and long-term benefits of PRP in diabetic wound healing.

KEYWORDS

PRP, diabetic foot, wound care, ulcer, case series, literature review

Introduction

Diabetes mellitus is a prevalent chronic condition that poses significant health challenges worldwide (1). Its complications can affect multiple organ systems (causing retinopathy, renal failure and other conditions (2)), with diabetic foot complications being among the most consequential and debilitating. During the lifetime of a diabetic patient, there is approximately a 19% to 34% risk of developing a foot ulcer, with an increasing incidence in recent years due to the growing life expectancy (3). The comorbidities associated with diabetic ulcers are significant, including peripheral neuropathy, peripheral arterial disease, foot ulcers, and infections, which can lead to amputation in up to 20% of cases (4). In recent years, the use of Platelet-Rich Plasma (PRP) has increasingly gained prominence in the treatment of skin lesions and defects, finding applications not only in alopecia and skin rejuvenation but also in surgical wounds (5), scar treatment (6), and ulcers (7). PRP has become an effective tool in the treatment of these conditions, occupying a significant role in the field of dermatology, plastic surgery and wound healing. In this study, we present a series of cases involving the treatment of diabetic foot lesions using platelet-rich plasma (PRP).

Materials and methods

We selected 12 patients between 2022 and 2023 (after obtaining informed consent) with diabetic foot ulcers that had not shown signs of healing for at least three months with conventional treatments. In addition to standard wound care (disinfection, debridement, and moist dressings), we administered perilesional platelet-rich plasma (PRP) injections during the initial outpatient visit and at a three-week interval. Patients with unstable hemodynamics due to ischemic heart disease or coagulation disorders, as well as those on anticoagulant and/or non-steroidal anti-inflammatory drug (NSAID) therapy, were excluded. Patients with the following characteristics were also excluded: platelet count below 150,000/mm^3, uncontrolled diabetes mellitus (glycated hemoglobin level ≥ 75 mmol/l based on the latest laboratory data obtained within 28 days of enrollment), requirement of ongoing oral corticosteroid therapy (> 20 mg/day of prednisolone or equivalent), a history of malignant tumors with disease-free interval of three years or less and patients who are pregnant or planning to become pregnant, in order to optimize the outcome of the treatment (8). We did not make patient selections based on gender, and we did not recruit patients under the age of 18.

The product used in the study was obtained using the classical Tube Method (9). Once the blood sample (approximately 30 ml) is collected, it is gently mixed to ensure proper mixing with the anticoagulant (sodium citrate 3.8%) present in the tubes. Subsequently, two cycles of centrifugation are performed. In the first phase, the product is centrifuged at 1500 rpm for 10 minutes, resulting in the separation of the cellular components from the plasma. Using a 10 ml L/L syringe with a 22G needle, all the plasma is aspirated from the six tubes and transferred to the remaining three tubes, which are then subjected to further centrifugation at 5000 rpm for 10 minutes. The final yield of the process is approximately 3 mL of product with a volume ratio of 10:1 and a platelet concentration around ¾ times higher than whole blood (ranging from 1.1×10^6 to 1.7×10^6 platelets/µl).

The treatment of the wound is divided into several phases. Before proceeding with wound disinfection using iodopovidone, it is crucial to assess the presence of bacteria in the wound through a qualitative swab. The presence of an infection represents a negative prognostic factor and can compromise the response to treatment. In case the culture examination is positive, targeted antibiotic therapy will be administered based on the antibiogram. In the second phase, after thorough disinfection, surgical debridement (Wound Bed Preparation) is performed, involving the removal of non-vital tissues until a clean and bleeding wound bed is achieved. Subsequently, a second disinfection is carried out. The actual treatment involves the infiltration of 3 ml of PRP onto the wound bed and along the wound's edge, using a 1 ml syringe and a 30G needle. At the end of the procedure, the ulcer is covered with a non-adherent dressing, using non-adherent gauzes.

This procedure is repeated once three week when changing the dressing until the healing of the wound or for a maximum of 12 weeks.

The dimensions (based on the greatest diameter) of the lesions were evaluated upon entry into the study and at a three-month interval after the last injection. Additionally, the rate of complete wound healing (defined as the absence of any breaks in the epidermis) was quantified (10). The ulcers were assessed using the PUSH scale (11) at the beginning of the treatment (T0)and at the 6-month follow-up(T6).

We then conducted a literature search on PubMed and Scopus using the following search terms: "PRP AND diabetic foot", "PRP AND diabetic ulcer", "Platelet rich plasma AND diabetic foot", "Platelet rich plasma AND diabetic ulcer".

Results

Out of the 12 treated patients, 4 were male and 12 were female. The age ranged from 65 to 81 years, with a mean of 76 years and a median of 78 years. The average size (based on the greatest diameter of the lesion) at the beginning of the treatment was 2.17 cm (with a median of 2 cm and a range between 1 cm and 4.4 cm). None of the ulcers treated was gangrenous according to the Wagner Score (see Table 1) (12). Six patients had high blood pressure, and five met the criteria for metabolic syndrome (defined as having three or more of the following five criteria: waist circumference over 40 inches (men) or 35 inches (women), blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 40 mg/dl (men) or 50 mg/dl (women), and fasting blood sugar over 100 mg/dl) (13).

At the end of the treatment, 8 patients achieved complete healing with restitution ad integrum of the skin (with a complete healing rate of 66.67%), while the remaining four subjects experienced partial healing (>50% reduction in size of the lesion), with an average size of 1.1 cm (median 1.1 cm, range 1-1.2 cm)

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TABLE 1 Cumulative data of the patients treated.

	Patients treated (n=12)
Sex	
- Male	4
- Female	8
Age (years)	
- Mean	76
- Median	78
- Range	65-85
BMI	
- Mean	-26.4
- Median	-27
- Range	-23-28.5
HbA1c (mmol/l)	
- Mean	67 mmol/l
- Median	65 mmol/l
- Range	57-73 mmol/l
ABI (Ankle/Brachial Index)	
- Mean	0.94
- Median	0.8
- Range	0.6-1.2
Comorbidities	6 patients with clinical hypertension
	5 with metabolic syndrome
Wagner Score	- 8 (grade 2)
	- 4 (grade 3)
Distribution of the ulcers	- 2 hindfoot
	- 6 midfoot
	- 4 forefoot
Push score T0	
-Mean	6
-Median	6
-Range	3-10
Push Score T6	
-Mean	1.23
-Median	0
-Range	0-4
Dimension of the lesion before the treatment (Cm)	
-Mean	2.17
-Median	2
-Range	1-4.4

(Continued)

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TABLE 1 Continued

	Patients treated (n=12)
Dimension of the lesion after the treatment (Cm) (counting complete healing as 0 cm)	
-Mean	0,4
-Median	0
-Range	0-1,2
Rate of complete healing	66,67% (8/12)
Adverse effects	3 mild irritations at the inoculation site

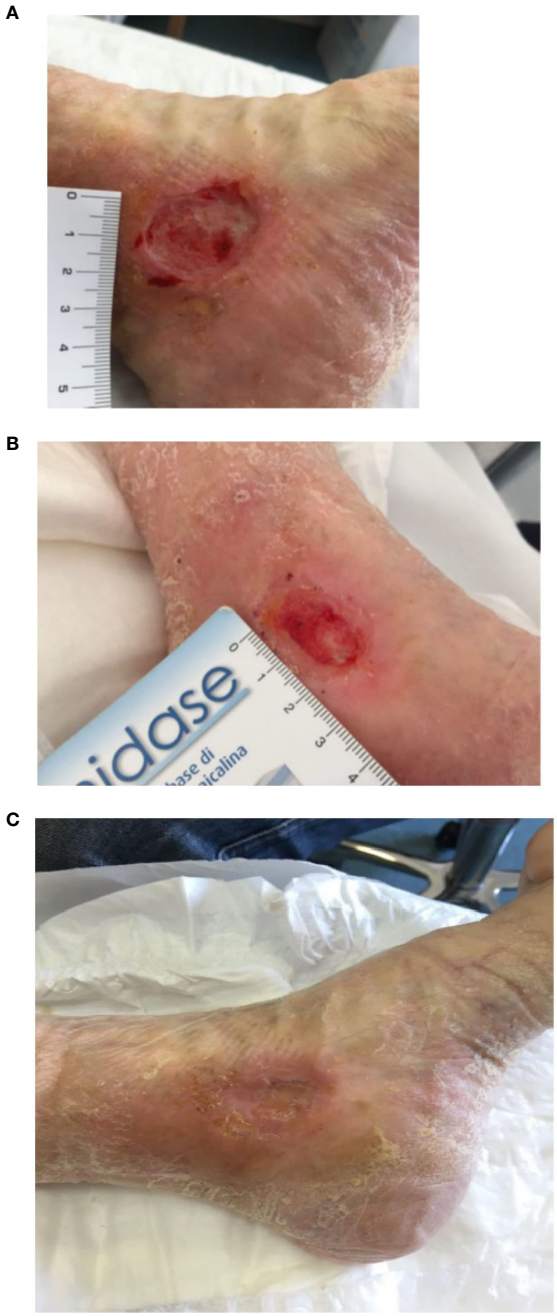

FIGURE 1
Patient with peri malleolar ulcer before the treatment **(A)**, after the first PRP injection **(B)** and at the end of the treatment **(C)**.

(Table 1) (Figures 1A–C). No major adverse effect or infections of the lesions were observed during the treatment, 3 patients developed mild irritation at the inoculation site.

Discussion

The use of PRP has been introduced in clinical practice for approximately 20 years (14–19), although the first studies analyzing this technique date back to the 1990s (20–23).

From the early studies, the efficacy of using plasma derivatives has demonstrated significant effectiveness in accelerating recovery time and wound healing speed. Patients treated with plasma derivatives showed a weekly healing rate of 0.4 cm2 compared to 0.13 cm2 in non-treated patients (22). In 2009, a systematic review conducted in Brazil (24) analyzed 18 studies, including 7 randomized clinical trials. The review highlighted a significant effect on the healing process (95% CI odds ratio 2.94-20.31). However, it also noted a lack of consistency in the type of treatment and protocol used, as well as variability in the type of dressings and study design (25). This variability among the studies has made it difficult to establish a unified standard in this field of research and reflects the considerable challenges in implementing standardized protocols for the treatment of difficult wounds. During the same period, a prospective randomized trial conducted in Greece (26) compared the healing of large difficult wounds (>2.5 cm in any one dimension) using a protease-modulating matrix with or without the addition of platelet-derived growth factors. The study did not find statistically significant differences in accelerating the healing process between the two groups. Another interesting application of PRP was tested in an Italian study in 2009 (27), where PRP was used as an adjuvant to autologous adipose tissue grafting in the treatment of lower limb ulcers and cervical facial defects. This combined treatment demonstrated efficacy both *in vitro*, where it increased the survival of adipose cells, and *in vivo*, with complete healing of all lower limb lesions achieved in an average of 9.7 weeks. A study conducted in 2015 (28) evaluated the use of PRP in the treatment of diabetic foot ulcers in patients with lower limb vascular diseases. The study included 72 patients, 30 of whom had Critical Limb Ischemia (CLI). The patients were treated for a period of 24 months, and the results showed a reduction in ulcer area of >90% in 52 patients and a limb salvage rate of 89% (100% in patients without CLI, 73% in patients with CLI). These findings demonstrated the effectiveness of PRP even in challenging patients with multiple comorbidities. Results similar to those have been obtained from a Japanese study (29). During the same period, other studies have demonstrated an improvement in the healing process through the use of PRP in diabetic foot ulcers (30–35). Other studies, on the other hand, have considered the antibacterial effect of PRP (30) to reduce the incidence of superinfections in the lesions (36, 37). Recently, new methods have been devised to deliver the growth factors in PRP, such as in a 2020 Chinese study where an injectable hydrogel with Platelet-Rich Plasma release was developed (38). Other studies have evaluated the efficacy of PRP treatment based on the administration vehicle, and they have found that the most effective mode of administration remains perilesional injection. Indeed, in a study from 2023, patients treated with topical PRP gel showed slower healing rates compared to those treated with perilesional injections (39).

The action of PRP in wound healing appears to be caused by the presence of numerous growth factors (such as TGF-B, PDGF, FGF, and ECGF), chemical mediators like histamine and serotonin, and proteins such as CTAP-3 and PF4, with effects on angiogenesis and the activation of extracellular matrix (ECM) cells. The existence of these growth factors, particularly when VEGF and FGF-2 are concurrently present (40), triggers the development of new blood vessels at the injection site, as observed in both animal models (41) and *in vivo* studies (42). Additionally, the presence of VEGF seems to enhance blood flow (42). Additionally, PRP has antibacterial properties. These combined mechanisms are the basis for PRP's action in wound healing (43–45).

Conclusion

Platelet-rich plasma (PRP) has been widely used in the treatment of diabetic foot and associated wounds, demonstrating effectiveness and utility over time, along with a reduced rate of complications. Recent biotechnological advancements are opening new avenues in its delivery and the development of combined therapies, thus leading to increasingly exciting prospects in regenerative medicine.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

PI: Writing – original draft, Writing – review & editing. CD: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. AP: Data curation,

Writing – original draft. SS: Data curation, Writing – original draft. MC: Data curation, Writing – review & editing. DB: Methodology, Writing – review & editing. PD: Data curation, Writing – original draft. DS: Conceptualization, Writing – review & editing. LI: Methodology, Writing – review & editing. SI: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Evaluation of the healing potential of short-term ozone therapy for the treatment of diabetic foot ulcers

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Background: The availability of research on short-term ozone therapy for diabetic foot ulcers (DFUs) is limited, and even when it is accessible, it mainly comprises of basic analysis conducted during long-term ozone therapy. This study was to evaluate the efficacy of short-term ozone therapy in promoting wound healing in DFUs.

Methods: A retrospective analysis was conducted on 89 patients with type 2 diabetes complicated by DFUs. The patients were divided into two groups: ozone therapy group (n=41) and control group (n=48). Wound condition, change of bacterial types, changes in inflammatory indicators (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], and procalcitonin [PCT]), vascular endothelial growth factor (VEGF), cytokines [Interleukin 6 (IL-6) and tumor necrosis factor-α(TNF-α)], and oxidative stress levels (superoxide dismutase [SOD], malondialdehyde [MDA], and total antioxidant capacity [T-AOC]) were observed pre-treatment and after 1 week. After a 12-week of follow-up, wound healing rate, amputation rate, inpatient day, duration of antibiotics, reinfection rate, incidence of new ulcers, readmission rate, and reoperation rate, and cumulative wound healing rate using Kaplan-Meier curves were assessed.

Results: After 1 week of treatment, the ozone therapy group showed higher VEGF, SOD, and T-AOC levels compared to the control group (P<0.05), while CRP, PCT, ESR, IL-6, TNF-α, MDA levels and bacterial types were lower (P<0.05). The ozone therapy group had a higher wound healing rate after a 12-week follow-up (P<0.05). Kaplan-Meier curves indicated a higher cumulative wound healing rate in the ozone therapy group (P<0.05). Additionally, the ozone therapy group had lower inpatient day, duration of antibiotics, reinfection rate, and readmission rate compared to the control group (P<0.05).

Conclusion: Short-term ozone therapy is effective in promoting wound healing in DFUs by reducing inflammation, increasing growth factor levels, improving oxidative stress status, shortening healing time, and improving long-term prognosis. These findings suggest the potential of short-term ozone therapy as a valuable treatment modality for DFUs.

KEYWORDS

diabetic foot ulcers, ozone therapy, short-term, wound, healing

Introduction

Diabetic foot ulcers (DFUs) is a severe complication of diabetes that can result in ulcers, infections, or tissue damage in the feet. By 2025, it is estimated that over 125 million out of 500 million people with diabetes globally will develop foot ulcers (1). The prevalence of DFUs in the global population is 6.3% (2). Shockingly, every 20 seconds, one patient loses a leg due to diabetes (3). The annual mortality rate among DFUs patients is as high as 11%, while amputees face a staggering 22% rate (4). DFUs treatment is challenging and expensive, burdening patients and their families both psychologically and economically, and posing significant challenges for healthcare systems worldwide.

DFUs is complex and often accompanied by an imbalance in oxidative stress. Hyperglycemic DFUs patients experience an accumulation of excessive peroxides in their bodies. This oxidative stress accelerates cell apoptosis, damages the microvasculature, and hinders DFUs wound healing. Thus, oxidative stress plays a crucial role in the development and control of DFUs (5).

Traditional wound dressing methods frequently result in chronic non-healing wounds, adding to the difficulty and cost of clinical treatment. Ozone, composed of three oxygen atoms, rapidly breaks down into oxygen, with one oxygen atom serving as a potent oxidant that can eliminate microorganisms and activate antioxidant enzymes (6). Studies have demonstrated the application of ozone therapy in various conditions, including periodontitis, pain management, tumors, and diabetic wounds (7–10). As an adjunct therapy for DFUs, the effectiveness of ozone therapy varies. Some research suggests that ozone therapy is more effective than standard treatment for DFUs management (11). However, there is also a study indicating that ozone therapy has no significant impact on DFUs healing (12). The duration of ozone therapy for DFUs varies among studies, with treatments ranging from a 12-14 day therapy performed by Rosul et al. to a continuous 20-day therapy conducted by Zhang et al. (13, 14). The frequency of ozone therapy is generally once daily, twice weekly, or once every three days. (12, 14, 15). Hospitalized patients can typically adhere to this therapy frequency, but for discharged patients living far from medical facilities, maintaining the prescribed ozone therapy frequency can present challenges, leading to potential treatment interruptions. Research on short-term ozone therapy for DFUs is scarce, and even if available, it primarily consists of basic analysis conducted during long-term ozone therapy. Given these considerations, we propose investigating the effectiveness of short-term ozone therapy for DFUs. Thus, this study aims to evaluate the short and long period efficacy of short-term ozone therapy in hospitalized DFUs patients and provide valuable clinical guidance for the management of DFUs using ozone therapy.

Materials and methods

Study subjects

A retrospective analysis was conducted on 89 hospitalized patients with type 2 diabetes complicated by DFUs between July 2022 and April 2023. Of the participants, 55 were males and 34 were females, with ages ranging from 40 to 74 years (62.89± 7.64). The duration of diabetes ranged from 1 to 23 years (10.46 ± 5.52), while the duration of DFUs ranged from 1 week to 48 weeks (6.31 ± 6.93). DFUs diagnosis followed the diagnostic criteria set by the International Diabetic Foot Working Group Guidelines (16). Participants were divided into two groups based on treatment method: the ozone therapy group (n=41) and the control group (n=48). The ozone group received ozone therapy in addition to the treatment provided to the control group.

Inclusion criteria were as follows: (1) age between 18 and 80 years; (2) ankle-brachial index between 0.7 and 1.2; (3) wound area >4cm^2; (4) Wagner grade 2, 3, or 4.

Exclusion criteria included: (1) patients with malignant transformation of diabetic ulcers; (2) patients with severe primary diseases affecting the heart, brain, liver, kidney, hematopoietic system, or mental health; (3) patients who did not adhere to prescribed treatment or had incomplete clinical data that could affect evaluation of treatment efficacy; (4) patients intolerant to treatment and experienced adverse reactions; (5) patients with connective tissue diseases; (6) active Charcot foot syndrome; (7) other infectious or contagious diseases.

Contraindications: (1) Glucose-6-phosphate dehydrogenase deficiency; (2) Toxic thyroid hyperfunction; (3) Platelet count below 50,000 and severe coagulation disorders; (4) Acute alcohol poisoning; (5) Excessive and acute bleeding; (6) Seizure condition; (7) Hemochromatosis; (8)Patients undergoing copper or iron therapy.

The study protocol was explained to participants, and written informed consent was obtained. The study was approved by the Ethics Committee of Xuzhou Central Hospital (XZXY-LK-20220629-055) and conducted in accordance with the Helsinki Declaration.

Data collection

Clinical data collection included demographic information, diabetes complications and comorbidities, duration of diabetes, wound location, and wound severity.

Basic treatment

Individualized treatment approaches were provided based on patients' conditions, including glycemic control, improved circulation, infection control, nutritional support, blood pressure management, lipid control, and offloading strategies. Antibiotics were empirically administered in the early stages based on clinical judgment. Then, based on the culture of wound necrotic tissue microorganisms, susceptibility testing, and clinical response, antibiotics were adjusted. Toe amputation and debridement were performed based on foot conditions, targeting osteomyelitis and necrotic bones.

Ozone therapy

Ozone therapy was administered using the Kastner Ozomed Smart Devices made in Germany. Patients were comfortably positioned, and wound dressings were opened. Necrotic tissue was debrided. Wound exudate was gently removed using sterile gauze, and the wound was rinsed with 0.9% saline. A disposable plastic tube was placed approximately 2cm away from the wound and secured with adhesive tape. The other end of the tube was connected to the vacuum hole of the ozone therapy instrument. A sterile ozone bag was applied to cover and seal the limb (The sealing ring is pulled apart, slowly sliding the affected foot into the ozone to avoid touching the wound. Once the wound is fully covered, the sealing ring is adjusted for a tight fit.). The air in the bag was evacuated, and medical ozone gas (ozone concentration of 35 μg/ml) was introduced into the bag for 30 minutes. (Figure 1) Therapy was administered once a day, with close monitoring of patient condition. The plastic bag should be securely sealed to prevent any air leakage. Additionally, it is crucial to maintain a steady room temperature and ensure good indoor ventilation. Ozone therapy was immediately stopped in case of adverse reactions. At the end of treatment, ozone was withdrawn and decomposed from the bag through the Kastner Ozomed Smart Devices. The bag was then separated from the patient, and the wound was covered and dressed with sterile dressings. (Figure 2) All patients underwent conventional dressing changes using sterile Vaseline gauze.

The Bates-Jensen wound assessment tool

The Bates-Jensen wound assessment tool, consisting of 13 wound characteristics, was used to assess the wounds (17). Each characteristic had five levels of description. Scores were assigned to each level, and the total score was obtained by summing all individual item scores. A higher total score indicated a more severe wound condition. After 1week of treatment, wound scores were evaluated.

Blood specimen collection

Peripheral venous blood samples were collected from patients in both groups in the morning, after overnight fasting, at the baseline and after 1 week of treatment.

Endpoint

The primary outcome was the rate of complete wound closure at 12 weeks. Complete wound closure was defined as full epithelialization without any breakdown or exudate. Secondary outcomes included index hospitalization outcomes (surgeries during admission and inpatient day), outcomes after hospital discharge (duration of antibiotics, healed at end of study, new ulcer formation rate, reinfection rate, readmission rate, surgery after discharge), change of bacterial types, and wound scores, changes in inflammatory markers (ESR, CRP, and PCT), VEGF, IL-6, TNF-α, and oxidative stress levels (SOD, MDA, and T-AOC) in serum before and after 1 week of treatment.

Statistical methods

Data analysis and graph plotting were performed using SPSS version 21.0 and GraphPad Prism version 9. Differences in normally distributed variables were analyzed Student's t-test. Non-normally distributed variables were analyzed using non-parametric tests. Count data is typically presented as frequencies (in percentages) and analyzed using the chi-square test. Numeric variables were tested using the Kaplan-Meier (K-M) test to assess the distribution. All tests were two-sided, and a significance level of 0.05 was set.

Results

Comparison of baseline characteristics

There were no significant differences in baseline characteristics between the ozone therapy group and the control group (all $P>0.05$), as shown in Table 1.

Comparison of Bates-Jensen wound assessment tool scores

After 1 week of treatment, the ozone therapy group showed significantly lower wound scores compared to the control group ($P<0.001$) (Table 2).

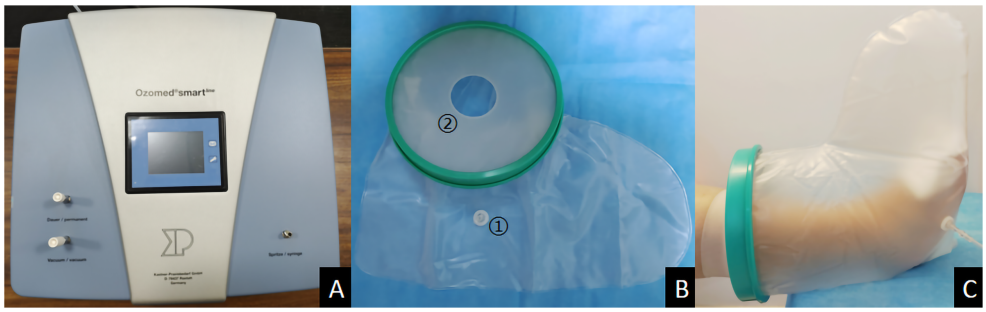

FIGURE 1
Photo illustrations ozone therapy for diabetic foot ulcer. **(A)** Kastner Ozomed Smart Devices; **(B)** Ozone bag:①Ozone ventilation port ②Sealing ring (high elasticity and good sealing performance); **(C)** Ozone therapy for diabetic foot ulcer.

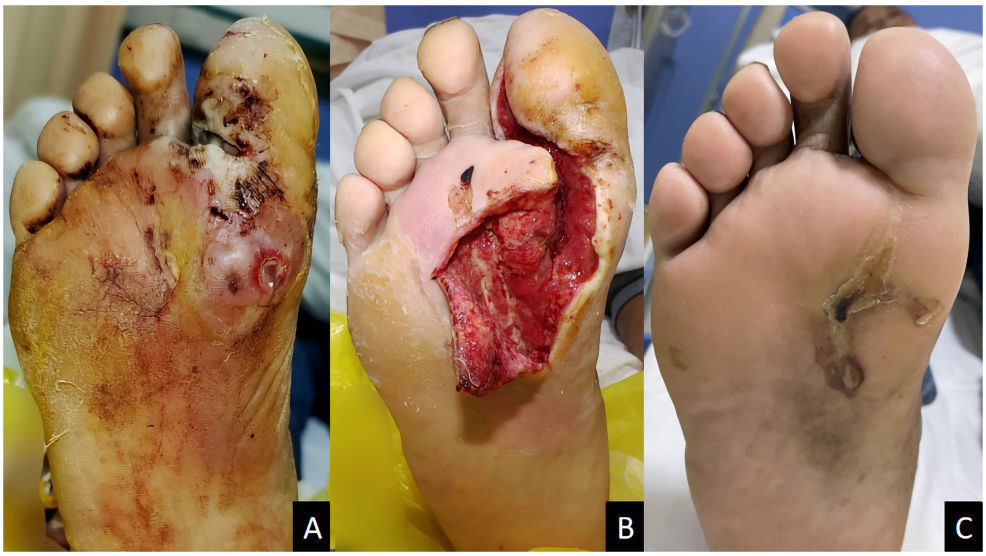

FIGURE 2
A male diabetic foot ulcer patient aged 64 years with deep abscess on the right foot for 2 weeks. **(A)** Before treatment; **(B)** 1 week after ozone therapy; **(C)** 58 days after treatment.

Comparison of inflammatory markers

There were no differences in ESR (83.58 ± 9.05 vs 85.41 ± 12.53 mm/h, *P*=0.427), CRP (85.32 ± 12.35 vs 87.13 ± 11.51mg/L, *P*=0.476), and PCT (0.61 ± 0.38 vs 0.62 ± 0.30ng/ml, *P*=0.860) levels between the control group and the ozone therapy group before treatment. However, after 1 week of treatment, there were significant differences in ESR (61.04 ± 9.56 vs 44.59 ± 12.47 mm/h, *P*<0.001), CRP (48.17 ± 4.65 vs 33.54 ± 4.58mg/L, *P*<0.001), and PCT (0.22 ± 0.22 vs 0.09 ± 0.09ng/m, *P*<0.05) levels (Figure 3).

Comparison of cytokine levels

Before treatment, there were no differences in IL-6 (18.54 ± 2.36 vs 19.18 ± 3.52 ng/L, *P*=0.607) and TNF-α (32.38 ± 4.27 vs 33.21 ± 4.42 ng/L, *P*=0.494) levels between the control group and the ozone therapy group. However, after 1 week of treatment, there were significant differences in IL-6 (12.10 ± 2.39 vs 8.96 ± 1.37 ng/L, *P*<0.001) and TNF-α (23.42 ± 4.42 vs 20.57 ± 4.04 ng/L, *P*<0.01) levels (Figure 4).

Comparison of growth factors

Before treatment, there were no differences in average serum VEGF (70.94 ± 4.49 vs 69.93 ± 4.23 ng/L, *P*=0.281) levels between the control group and the ozone therapy group. However, after 1 week of treatment, there were significant differences in VEGF (89.98 ± 6.26 vs 99.50 ± 5.81 ng/L, *P*<0.001) levels (Figure 5).

Comparison of oxidative stress

Before treatment, there were no differences in SOD (33.18 ± 3.52 vs 32.01 ± 3.91 IU/ml, *P*=0.138), T-AOC (1.75 ± 0.13 vs 1.71 ± 0.19 IU/ml, *P*=0.484), and MDA (5.05 ± 0.41 vs 5.12 ± 0.49μmol/L, *P*=0.376) between the control group and the ozone therapy group. After 1 week of treatment, both groups showed increased SOD (50.06 ± 3.51 vs 60.13 ± 3.42 IU/ml, *P*<0.001) and T-AOC (2.04 ± 0.12 vs 2.14 ± 0.16 IU/ml, *P*<0.01), and decreased MDA (3.23 ± 0.34 vs 3.02 ± 0.33μmol/L, *P*<0.01). The differences were more significant in the ozone therapy group, and all differences were statistically significant (Figure 6).

Change of bacterial types between the two groups

A total of 63 bacterial strains were isolated in the control group, while 55 bacterial strains were isolated in the ozone therapy group. Following 1 week of treatment, the ozone therapy group exhibited a reduced bacterial strains on the wound compared to the control group (2/55[3.6%] vs 9/63 [14.3%], *P*=0.047) (Supplementary Table 1).

Comparison of wound healing rate

After a 12-week follow-up, the ozone therapy group had a higher wound healing rate compared to the control group (32/41 [78.0%] vs 28/48[58.3%], *P*=0.048), and the cumulative wound healing rate was higher in the ozone therapy group (Log Rank=6.740, *P*=0.009, Figure 7). Additionally, the ozone therapy group had shorter inpatient day and duration of antibiotics, and

TABLE 1 Comparison of clinical characteristics between the two groups.

Variables	Group		P-value
	Control	Ozone	
N	48	41	
Gender (male/female)	30/18	25/16	0.883
Age (years)	62.73 ± 6.78	63.07 ± 8.63	0.609
Smoking (%)	19 (39.6)	14 (34.1)	0.597
Drinking (%)	16 (33.3)	17 (41.5)	0.429
Duration of Diabetes (year)	10.54 ± 5.70	10.37 ± 5.38	0.755
Duration of Diabetic Foot Ulcers (weeks)	6.54 ± 7.77	6.05 ± 5.87	0.967
FPG (mmol/L)	8.97 ± 2.82	10.40 ± 4.03	0.124
HbA1c (%)	9.95 ± 2.08	10.60 ± 2.92	0.241
Albumin (g/dL)	35.37 ± 4.98	34.46 ± 4.94	0.378
eGFR (mL/min/1.73m2)	95.72 ± 16.07	94.86 ± 15.41	0.798
Wound Area (cm^2)	11.93 ± 3.59	12.82 ± 3.93	0.251
ABI	0.84 ± 0.11	0.82 ± 0.12	0.248
Hypertension (%)	16 (33.3)	15 (36.6)	0.748
Coronary Artery Disease (%)	14 (29.2)	12 (29.3)	0.992
Cerebral Infarction (%)	11 (20.8)	9 (22.0)	0.913
Diabetic Retinopathy (%)	27 (56.3)	21 (51.2)	0.635
Diabetic Peripheral Neuropathy (%)	30 (62.5)	27 (65.9)	0.742
Wagner Grade (%)			0.971
2	10 (20.8)	8 (19.5)	
3	25 (52.1)	21 (51.2)	
4	13 (27.1)	12 (29.3)	
Wound Location			0.937
Forefoot	36 (75.0)	32 (78.0)	
Midfoot	7 (14.6)	5 (12.2)	
Heel	5 (10.4)	4 (9.8)	

Continuous variables are expressed as Mean ± SD.
FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; ABI, ankle-brachial index.

TABLE 2 Comparison of Bates-Jensen wound assessment tool score between the two groups.

	Control	Ozone	p
Before-treatment	47.42 ± 3.55	48.07 ± 3.35	0.374
After-treatment	44.15 ± 3.94	40.37 ± 3.69	<0.001

lower rates of reinfection and readmission compared to the control group (P<0.05) (Table 3).

Adverse events

There were no potential human and environmental hazards associated with ozone therapy. Additionally, DFUs patients had no complications or side effects due to ozone therapy.

Discussion

In this study, the ozone therapy group exhibited a higher healing rate compared to the control group. This finding aligns with a study conducted by Izadi et al., where the ozone therapy group had a greater healing rate than the control group after a follow-up period of 180 days (100% vs 75%) (15). Additionally, Wainstein observed that at week 24, specifically in the per protocol cohort (PP), the proportion of completely closed wounds was notably higher in the ozone therapy group compared to the control group (81% vs 44%) (18). The possible reasons for this could be the impact of ozone on bacterial cell membranes and the activation of the non-specific immune system. Ozone has oxidative properties that can disrupt the bacterial cell membrane by oxidizing phospholipids and lipoproteins, effectively killing bacteria in a short period of time (19). Additionally, ozone indirectly activates the non-specific immune system, leading to processes such as phagocytosis activation and interferon production (6). This immune activation contributes to the elimination of multiple bacteria, reducing the duration of antibiotic treatment and accelerating the healing process of DFUs. In this study, ozone therapy has shown promising results in reducing the bacterial diversity on the surface of DFUs. The finding aligns with previous research on the subject (12). It's worth mentioning that in this study, the ozone therapy group showed a shorter duration of antibiotics compared to the control group. Ozone also enhances the activity of enzymes such as superoxide dismutase, hydrogen peroxide, and oxidized glutathione reductase. By doing so, it effectively clears free radicals, promotes local tissue metabolism, stimulates fibroblast proliferation, facilitates collagen fiber formation, and supports angiogenesis. Furthermore, ozone encourages the growth of granulation tissue and epithelial cells (20), thereby aiding tissue repair and positively influencing the healing of DFUs. Ultimately, these beneficial effects of ozone therapy may lead to a shorter inpatient day for patients. In this study, the ozone therapy group also had a shorter inpatient day (18.65 ± 4.93 days) compared to the control group (15.66 ± 4.01 days). In contrast, other studies, such as the one conducted by Rosul et al., reported an inpatient day of 23.42 ± 0.45 days in the control group and 17.09 ± 0.27 days in the ozone therapy group (13). Likewise, Dhamnaskar et al. reported a median average hospitalization time of 13 days versus 9 days (11). These variations in hospitalization time may stem from factors such as the severity of the foot wounds in the selected patients, the concentration of ozone used in treatment, the duration of treatment, and the frequency of treatment.

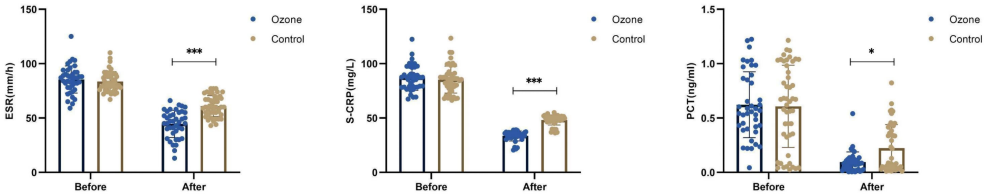

FIGURE 3
Comparison of the inflammatory markers between the two groups. "*" <0.05; "***" <0.001.

According to the Bates-Jensen Wound Assessment tool, this study demonstrated a significant improvement in DFUs with ozone therapy, which is consistent with findings reported by Zhang et al. (14), and the study by Kasmawati et al. suggested no significant effect of ozone on wound healing (12), despite the usage of different wound assessment tools. In our study, the ozone therapy group exhibited lower levels of ESR, CRP, and PCT compared to the control group, indicating a potential role of ozone in reducing wound inflammation. These inflammatory markers, ESR, CRP, and PCT, have been previously associated with DFUs prognosis (21–23), aligning with other reports suggesting that ozone therapy can effectively reduce inflammation in DFUs (15, 24, 25).The underlying mechanism for these observations may involve the bactericidal effects of ozone. Ozone has the ability to eliminate bacteria within the wound, consequently reducing damage caused by bacterial colonization to the epithelial cells. This process

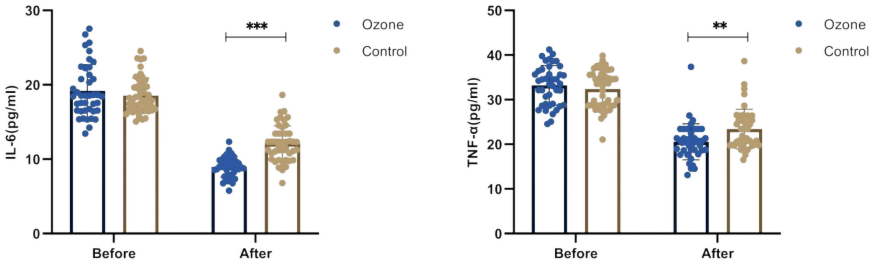

FIGURE 4
Comparison of the serum cytokine between the two groups. "**" <0.01; "***" <0.001.

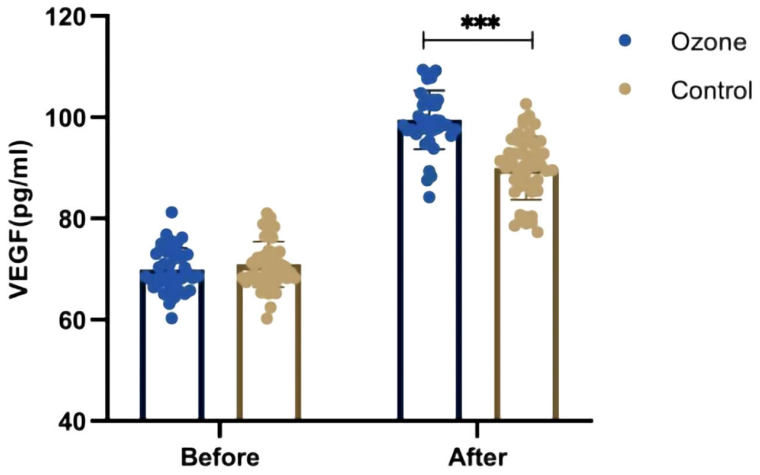

FIGURE 5
Comparison of the serum VEGF between the two groups. "***" <0.001.

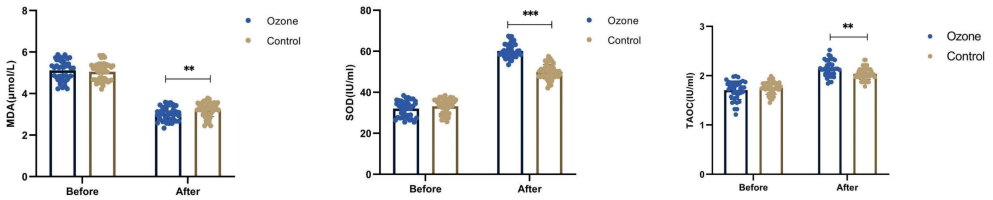

FIGURE 6
Comparison of the oxidative stress between the two groups. "**" <0.01; "***" <0.001.

alleviates wound inflammation and decreases the presence of inflammatory cells and factors in the bloodstream. Ozone therapy has also demonstrated the ability to inhibit the production of cytokines such as IL-6 and TNF-α. Lower levels of these cytokines are beneficial for promoting the healing and repair of wounds (26, 27). Supporting our findings, our study also demonstrated lower levels of IL-6 and TNF-α in the ozone therapy group.

Ozone has the capability to eliminate free radicals, enhance local tissue metabolism, stimulate the division of fibroblast cells, and promote the formation of collagen fibers. It facilitates the secretion of growth factors by macrophages and fibroblast cells, leading to angiogenesis and the growth of granulation tissue, resulting in an accelerated wound healing process. The therapeutic mechanism of ozone in skin wound healing can be attributed to the upregulation of growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and platelet-derived growth factor (PDGF) (28, 29). These growth factors play a crucial role in regulating cellular proliferation during tissue repair. By stimulating these growth factors, the regenerative capacity of cells increases, thereby expediting the wound healing process. In our study, the average level of VEGF in the ozone therapy group was found to be higher than that in the control group, indicating its involvement in the formation of granulation tissue (30).

DFUs are characterized by uncontrolled oxidative stress and reduced antioxidant capacity, leading to an imbalance in oxidation-

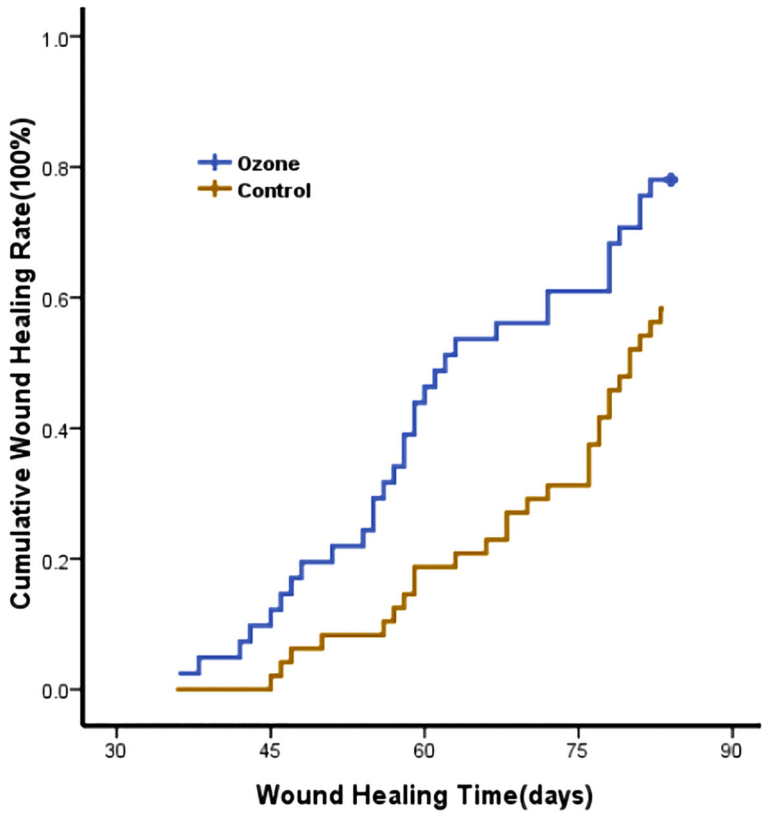

FIGURE 7
Kaplan-Meier healing curve analysis-days to heal(p=0.009).

TABLE 3 Wound Outcomes between the two groups.

Characteristic	Group		P-value
	Control N=48 (%)	Ozone N=41 (%)	
Index Hospitalization Outcomes			
Surgeries during admission			0.980
Debridement	10 (20.8)	8 (19.5)	
Incision, drainage and debridement	19 (39.6)	17 (41.5)	
Amputation foot toe and debridement	19 (39.6)	16 (39.0)	
Amputation leg and debridement	0 (0.00)	0 (0.00)	
Inpatient Day	18.65 ± 4.93	15.66 ± 4.01	0.003
Outcomes After Hospital Discharge			
Duration of Antibiotics (days)	31.42 ± 6.00	27.51 ± 6.03	0.003
Healed at End of Study	28 (58.3)	32 (78.0)	0.048
New Ulcer Formation	8 (16.7)	5 (12.2)	0.552
Reinfection	11 (22.9)	3 (7.3)	0.044
Hospital Readmission Foot	13 (27.1)	4 (9.6)	0.038
Surgery after Discharge	12 (25.0)	4 (9.6)	0.062
Incision, drainage and debridement	6 (50.0)	3 (75.0)	
Amputation foot toe and debridement	6 (50.0)	1 (25.0)	
Amputation leg and debridement	0 (0.00)	0 (0.00)	

reduction. Excessive oxidative stress can impair all stages of DFUs repair. SOD plays a critical role in the antioxidant process by effectively scavenging harmful reactive ozone species and reducing oxidative stress-induced tissue damage. A study conducted by Gregorio et al. showed that after ozone therapy in DFUs patients, SOD activity increased, potentially due to improved ozone supply, enhanced tissue blood circulation, and activation of the body's antioxidant defense system (31). T-AOC reflects the overall antioxidant capacity of the body. Following ozone therapy, T-AOC activity significantly increases, thus reducing oxidative stress. MDA is an indicator of oxidative stress levels. Ozone therapy can lower MDA levels, reducing lipid peroxidation reactions, mitigating tissue damage, and promoting DFUs healing. Previous research has also demonstrated ozone's ability to decrease oxidative stress in conditions such as COVID-19 and lumbar disc-related radicular pain (32, 33).

In our 12-week follow-up, the reinfection rate in the ozone therapy group was 7.3%, compared to 22.9% in the control group, demonstrating the effectiveness of ozone therapy. The control group exhibited a higher readmission rate, likely attributed to the development of new ulcers and reinfections. As the wound healing time extends, the likelihood of new ulcers and reinfections increases. Although our study did not show a reduction in amputation rate with ozone treatment, Dhamnaskar et al. and Izadi et al. reported a decrease in the likelihood of wound reamputation in the ozone therapy group (11, 15), which contrasts with our findings.

This study has several limitations. Firstly, it is a retrospective study, while prospective randomized controlled studies provide stronger evidence. Secondly, the study was conducted at a single center. Lastly, our follow-up period was limited to 12 weeks, and longer-term follow-up would yield greater significance.

In conclusion, this study investigates the short-term effects and long-term prognosis of ozone therapy in DFUs. Ozone therapy reduces inflammation, enhances the expression of growth factors, promotes wound healing, shortens healing time, and improves long-term prognosis. Therefore, advocating for the clinical application of ozone therapy in DFUs management is well-founded.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by ethics committee of Xuzhou Central Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

HS: Conceptualization, Writing – original draft. HH: Investigation, Writing – review & editing. XL: Formal Analysis, Writing – review & editing. HG: Conceptualization, Writing – review & editing. JL: Conceptualization, Methodology, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1304034/full#supplementary-material

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Validity and reliability of the English version of the Diabetic Foot Self-Care Questionnaire: a cross-cultural adaptation

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Introduction: The objective of this study was to carry out the cross-cultural adaptation and validation of the Diabetic Foot Self-Care Questionnaire into the English language, broadening the applicability of this patient-reported outcome measure and improving the monitoring of patients with diabetic foot disease.

Methods: The validation study into English was conducted in two phases: cross-cultural adaptation and psychometric validation study. Short Form-12 Version 2, EuroQoL-5D and Foot Function Index were used to analyze the criterion validity. Item response, internal consistency, standard error of measurement, minimal detectable change and construct validity were calculated in the validation phase.

Results: An English version of the questionnaire (DFSQ-UMA-En) was successfully obtained. A total of $n = 193$ participants were tested to confirm the validity and reliability of the questionnaire. Internal consistency values ranged from very good to excellent (Cronbach's α =0.889–0.981), and reliability was excellent (ICC = 0.854–0.959). Standard error measurement value was =2.543. Criterion validity ranged from $r = 0.429$ to $r = 0.844$. For construct validity, Kaiser-Meyer-Olkin test was =0.752.

Conclusion: DFSQ-UMA-En is a valid and reliable tool with good readability and comprehension features. This questionnaire addresses foot self-care behaviors in patients with diabetic foot disease, standing out as essential for early diagnosis and prevention strategies in clinical and research settings.

KEYWORDS

diabetic foot, chronic complications, patient-reported outcome, questionnaire, self-care, assessment

1 Introduction

According to the International Working Group on the Diabetic Foot, diabetic foot disease (DFD) is defined as the infection, ulceration, or destruction of tissues of the foot of an individual diagnosed with diabetes mellitus (DM), coexisting with neuropathy and/or peripheral arterial disease in the lower limbs (1). It is the chronic complication of DM with the highest mortality rate, most frequently caused by amputation of the lower limbs (2).

Epidemiology data and costs due to hospitalization are worsening over the years, with incidence and prevalence being higher in low-income areas (3, 4). In this context of resource scarcity, the best prevention strategies arise from the early diagnosis of DFD based on the implementation of assessment tools with high accuracy, availability, and applicability.

Assessment tools aimed at diagnosis can be classified according to the source of the given outcome: biomarkers, objective clinical outcome measures, and clinician-reported or patient-reported outcome measures (CROMs and PROMs, respectively) (5). The latter are capable of tracking changes in clinical symptoms over time, improving the quality of care, and enhancing disease control, in addition to their easy distribution and low cost (6).

Recent systematic reviews have concluded that PROMs lack availability and psychometric quality for patients with DFD. The Diabetic Foot Self-Care Questionnaire (DFSQ-UMA) was identified as the best option for assessing foot self-care (7–9). The evaluation of self-care is essential in chronic diseases, since higher levels of self-care have been associated with better health outcomes, including decreased hospitalization, costs, and mortality (10). DFSQ-UMA is currently available in the Spanish, French and Arabic languages (11–13).

Global data from 2022 confirms that the English language is the largest according to the number of speakers, and the third largest language according to the number of native speakers (about 373 million native speakers) (14). Highly populated countries with high income inequality and low gross domestic product *per capita*, such as India, Nigeria and South Africa, are examples of English-speaking countries (15).

The objective of this study is to make the cross-cultural adaptation and validation of the DFSQ-UMA into the English language, broadening the applicability of this PROM and allowing for the improvement of the monitoring of DFD patients.

2 Materials and methods

2.1 Study design

The validation study of DFSQ-UMA into English was conducted in two different phases. The first phase consisted in the translation and cross-cultural adaptation of the DSFQ-UMA from its original version into English (DFSQ-UMA-En). The second stage consisted in a validation study and analysis of the psychometric properties of the DFSQ-UMA-En.

The participants of this study were recruited from the Diabetic Foot Unit of the Birkirkara Health Center (Birkirkara, Malta), from 1st October 2022 to 30th January 2023, and based on the following inclusion criteria: aged 18 or older, diagnosed with diabetic foot disease, and no history of major surgery on the lower limbs. On the other hand, the study excluded those participants who did not autonomously understand the questions due to cognitive impairment, as well as those who were not native English speakers or sufficiently proficient in English. Participants who left any of the questions unanswered were also excluded.

2.2 Ethical considerations

This study was conducted in accordance with the recommendations of the Declaration of Helsinki, following the ethical principles for research involving human subjects, and the data were handled in accordance with Organic Law 3/2018 of December 5th, regarding the Protection of Personal Data and the Guarantee of Digital Rights. All participants provided their informed consent to participate in the study. Additionally, the Ethics Committee of the University of Malta approved the execution of this study with protocol number 4113_26032020.

2.3 Diabetic Foot Self-care Questionnaire of the University of Malaga

The DFSQ-UMA is a 16-item questionnaire that was designed to analyze self-care practices in patients with DFD. The DFSQ-UMA consists of three specific subcategories of foot self-care: self-care (assessed by questions 1–7), self-management and self-examination (assessed by questions 8–11), and footwear and socks (assessed by questions 12–16). Each question is scored on a Likert scale from 0 to 4, for a maximum total score of 64. The obtained score is then weighted on a 0-to-100 scale for better result comprehension, where higher values indicate poorer self-care (11, 12).

2.4 Translation and cross-cultural adaptation

Guidelines from the International Test Commission along with recommendations from the current scientific literature were followed to ensure that the conceptual and terminological adaptation of the questions in the DFSQ-UMA was carried out correctly (16).

The process of translating and cross-culturally adapting the DFSQ-UMA into the English version was carried out in four steps:

- Translation of the DFSQ-UMA from the original Spanish version into English: this translation was performed by two native and independent translators who were blinded to each other. The translations were compared to create the preliminary version of the DFSQ-UMA-En.
- A back-translation into the original language was performed by two independent translators, who were native Spanish speakers.
- The preliminary version was reviewed by an expert committee consisting of $n = 7$ researchers, who discussed any discrepancies between versions.
- A pilot test was conducted with $n = 25$ subjects using the obtained version before reaching the final version.

Figure 1 presents a schematic summary of the entire process undertaken in the translation and cross-cultural adaptation of the DFSQ-UMA-En.

2.5 Criterion validity

To perform criterion validity tests, the following questionnaires were used:

Short Form-12 Version 2 (SF-12-v2): This questionnaire consists of 12 items designed to assess well-being and functional capacity. In addition to the results obtained from version 1 (Physical and Mental

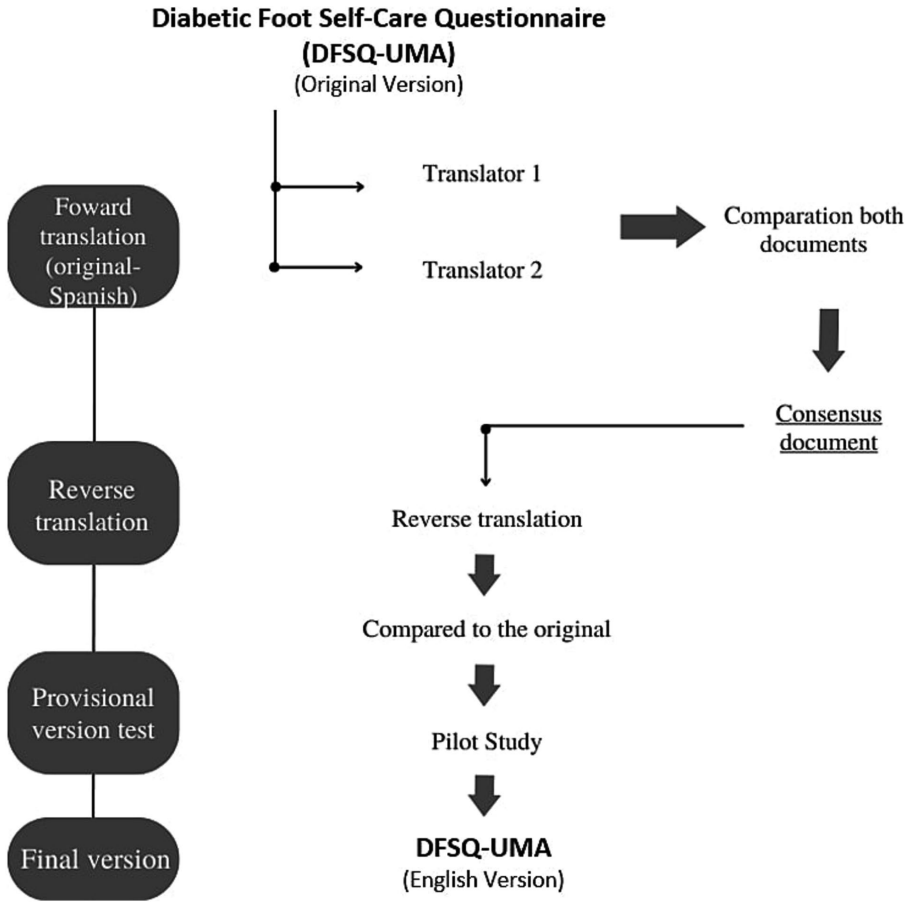

FIGURE 1
Flowchart of the cross-cultural adaptation of the DFSQ-UMA—English version.

Health Status), it yields 8 new dimensions (in alphabetical order): bodily pain, physical functioning, social functioning, emotional role, physical role, mental health, general health, and vitality. The score for each component ranges from 0 to 100, where a higher score indicates better health status. This questionnaire has shown reliability values ranging from 0.60 to 0.78, with internal consistency >0.8 (17).

EuroQoL-5D: this questionnaire is composed of 5 questions that assess the quality of life of individuals through 5 different dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is assessed using three different levels: 1 - no problems; 2 - slight or moderate problems; 3 - severe problems or incapacity. The combination of all questions with possible responses allows describing 243 potential health states, which are weighted based on the responses provided to derive a score on health status and quality of life. Additionally, EuroQol-5D is complemented by a visual analogue scale (VAS) that assesses the patient's perceived quality of life, where higher values indicate better quality of life. The reliability of EuroQol is indicated by an ICC = 0.7 (18).

Foot Function Index (FFI): this self-administered questionnaire consists of 23 questions aimed at evaluating functional capacity in the foot by assessing stiffness, social functioning, difficulty in movement, activity level, and pain. The reliability for this questionnaire ranges from 0.69 to 0.87, while internal consistency ranges from 0.73 to 0.96 (19).

2.6 Data collection

Following the recommendations of the COSMIN guidelines, all participants initially completed the English version of the DFSQ-UMA-En, EuroQoL-5D, SF-12, and FFI. Subsequently, to perform the analysis of internal validity, reliability, and the calculation of consistency levels, the participants filled out the DSFQ-UMA-En again 5 days after the first completion. Two blinded researchers were responsible for data collection and analysis.

2.7 Data analysis

A descriptive analysis of the sample was conducted in two different approaches, depending on the variable under consideration. Firstly, the frequency of questions regarding participants' educational level, gender, and pharmacological treatment was described. Then, a descriptive analysis of the sample was performed by calculating the mean and standard deviation for age and duration of DM diagnosis, as well as for the chosen measurement instruments: DFSQ-UMA-En, SF-12-v2, EuroQoL-5D, and FFI. Subsequently, a distribution analysis of the sample was conducted using the Kolmogorov–Smirnov test. The ceiling/floor effects were analyzed, which were considered to

be present when at least 15% of participants achieved the maximum or minimum value on the DFSQ-UMA-En in their responses.

To calculate item response, the intraclass correlation coefficient (ICC) was used, while the internal consistency of the measures was calculated using Cronbach's α. Both measures were classified using the following scale: excellent: ≥0.80; good: 0.60–0.80; moderate: 0.40–0.60; and poor: ≤0.40 (20).

The standard error of measurement (SEM) and the minimal detectable change at 90% confidence level (MDC90) were calculated. To calculate SEM, the formula $SEM = s\sqrt{1 - r}$ was used, where "s" represents the test score's standard deviation, and "r" was Pearson's correlation coefficient. For MDC90, the formula $MDC90 = SEM \times \sqrt{2} \times 1.65$ was utilized.

For the analysis of the structure and construct validity, the maximum likelihood extraction method was performed. Since this is a cross-cultural adaptation of the DFSQ-UMA into the English version, the authors decided to maintain the original questionnaire's structure. For this reason, factor extraction was forced into three factors.

For criterion validity, the SF-12-v2, EuroQoL-5D, and FFI questionnaires were used. A correlation analysis was conducted between the DFSQ-UMA-En and these questionnaires through the calculation of Pearson's coefficient. The results were structured according to the following scale: $r \geq 0.75$ (strong); $0.50 \leq r \leq 0.74$ (moderate); and $r \leq 0.49$ (poor) (21). The structure and validity of the construct was analyzed from the extraction by maximum likelihood (EML). To maintain the original structure of the DFSQ-UMA, a 3-factor forced model was performed. In addition, to perform the EMV, the requirement of a minimum of 10 subjects per item was satisfied (minimum number = 90 – subjects measured = 243).

Criterion validity was calculated by analyzing the degree of correlation between the DFSQ-UMA and the Spanish versions of the questionnaires: EuroQoL-5D (22), FFI (23), SF-12-v2 (24). Pearson's correlation coefficient was structured according to the following scale: $r \leq 0.49$ (poor), $0.50 \leq r \leq 0.74$ (moderate), $r \geq 0.75$ (strong). To perform the statistical analysis of this study, the SPSS software V.23.0 (Armonk, NY, United States) was used.

In order to conduct the statistical analysis, the literature recommends having a final sample size equal to or greater than 10 subjects for each item included in the questionnaire. Therefore, to carry out the cross-cultural adaptation and validation study of the DFSQ-UMA-En, 160 subjects would be required. This study was conducted with $n = 193$ subjects (25). To perform the Exploratory Factor Analysis (EFA), the requirement of a minimum of 10 subjects per item was met (minimum number = 90 – items measured = 243). The statistical software IBM SPSS Statistics V.23 (Armonk, NY, United States) was utilized for the statistical analyzes in this study.

3 Results

The translated and adapted English version of the DFSQ-UMA (DFSQ-UMA-En) is provided in Supplementary material. Table 1 presents the descriptive characteristics of the sample, showing the results as a function of participant gender, education level, and pharmacological treatment. The description is based on the frequency of the responses obtained. It is observed that 51.8% of the surveyed participants were males, with the predominant education level being primary education, followed by higher education, accounting for 45.8 and 35.9% of participants, respectively. The most frequently used pharmacological treatment was oral medication, with a total of 136 patients (70.5%).

Table 2 presents the descriptive characteristics of the sample for those variables where the mean and standard deviation of the results were calculated. These variables include the age of the participants and the number of years since they were diagnosed with diabetes. Furthermore, the results of all outcome variables, namely DFSQ-UMA-En, SF12-v2, EuroQoL-5D, and FFI, both the total values and those obtained in all the subscales composing these tools, are included. In the analysis of the floor/ceiling effect, it was observed that 7 participants achieved the minimum score, while 9 reached the maximum score, accounting for 3.6 and 4.7% of the participants, respectively. Based on the observed results, it is considered that the floor/ceiling effect is not relevant in DFSQ-UMA-En. The average time to complete DFSQ-UMA-En was 4.21 min.

The internal consistency analysis of the DFSQ-UMA-En yielded Cronbach's α values ranging from 0.889 (self-exploration) to 0.981 (self-care). In addition, item response results showed ICC values ranging from 0.854 (Item 9) to 0.959 (Item 14). For further details, please refer to Table 3. Furthermore, the observed SEM values were 2.543, while the MDC90 was 5.933.

Regarding construct validity assessment, the Kaiser-Meyer-Olkin (KMO) test yielded a value of 0.752, indicating statistically significant Bartlett's sphericity test results ($p < 0.001$), with 120 degrees of freedom and a Chi-square value of 1070.326. When forcing the extraction to three factors, they collectively explained 49.035% of the variance (see Table 4). Table 5 displays the loadings of each item on the three extracted factors, while Figure 2 illustrates the screen plot of all the items that comprised the DFSQ-UMA-En.

For criterion validity assessment, the SF12-V2, EuroQoL-5D, and FFI questionnaires, as well as various subcategories of different questionnaires, were utilized. Table 6 displays the correlation values of the DFSQ-UMA-En, along with its different subcategories. Both the overall score of the DFSQ-UMA-En and the self-care subcategory exhibited higher correlation levels with all reference instruments for criterion validity compared to those observed in the self-exploration and socks/shoes subcategories. For a more in-depth analysis of the correlation results, please refer to Table 6.

4 Discussion

The main objective of this study was to perform the translation and the cross-cultural adaptation of DFSQ-UMA into the English language, as this is a specific questionnaire for the assessment of foot self-care in patients with DFD. The readability and comprehension features regarding the items of the new English version were satisfactory, as well as in terms of psychometric properties.

4.1 Translation and cross-cultural adaptation of DFSQ-UMA into DFSQ-UMA-En

In addition to the original version of the DFSQ-UMA in the Spanish language, this questionnaire has been previously translated

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TABLE 1 Descriptive characteristics of the sample and frequencies.

		Frequency	Percentage	Cumulative percentage
Sex	Male	100	51.8	51.8
	Female	93	48.2	100
Education level	Primary education	90	45.8	45.8
	Secondary education	67	35.9	81.7
	Higher education	30	15.4	97.1
	Other	1	0.7	97.8
	None	5	2.2	100.0
Pharmacological treatment	Oral	136	70.5	70.5
	Insulin	20	10.4	80.8
	Both	29	15.0	95.9
	None	8	4.1	100.0
N	193			

into other languages, such as Arabic (12), Persian (26), Turkish (27), and French (13). The process of translation and validation of this questionnaire in English followed the current recommendations in the scientific literature (28). This included the use of native translators who were external to the field of study to facilitate the comprehension of the translated version while ensuring that the terminology used remained consistent to maintain the sense and meaning of the questions as in the original version. This translation and cultural adaptation will, therefore, provide all clinical professionals and researchers in English-speaking regions with a tool for assessing the self-management of patients with DFD.

Furthermore, the potential results obtained using this questionnaire in English can be compared with results measured in other versions of the same questionnaire, allowing for cross-cultural and cross-linguistic research in the field of diabetic foot care and management.

4.2 Construct validity

During the construct validity analysis, the researchers decided to maintain the structure of the original questionnaire, as it is a translated version (11). The analysis proved that the DFSQ-UMA had a three-factor structure. The three factors extracted frm the DFSQ-UMA-En explained a total variance of 49.035%. Other versions have also performed exploratory factor analyzes, extracting three factors. However, the explained variance value varies between 48.1% in the Arabic version (slightly higher than that in the French version) and 60.88% in the original version. Therefore, the explained variance falls within the range of values observed in the other versions that have been analyzed (12, 13, 26, 27).

Kaiser-Meyer-Olkin test showed a value of 0.752 in the English version, which is lower than the values of 0.866 and 0.872 observed in the Turkish and Persian versions, respectively, as well as the 0.89 observed in the original and French versions. However, if the usual criteria for factor extraction had been strictly followed, i.e., >10% variance, eigenvalue >1.0, and the inflection point of the screen plot, it seems that the DFSQ-UMA-En would have a two-factor structure.

4.3 Internal consistency and test–retest validity

The DFSQ-UMA-En questionnaire demonstrated internal consistency, as indicated by Cronbach's $\alpha = 0.928$. The sub-scales showed values ranging from 0.889 (self-exploration) to 0.981 (self-care) (Table 3). These results agree with those observed in the Arabic version, where internal consistency ranged from 0.887 to 0.983, as well as the French version (Cronbach's α: 0.911–0.925). However, they appear to be higher than those observed in the original version (Cronbach's α: 0.89), calculated only for the total score of the questionnaire, and in the Persian and Turkish versions, where Cronbach's α values ranged from 0.750 to 0.884 and 0.771 to 0.880, respectively.

Furthermore, item response results showed ICC values ranging from 0.854 (Item 9) to 0.959 (Item 14) (Table 3). The observed results are consistent with those of the original version (ICC: 0.89–0.92) and the Arabic version (ICC: 0.841–0.956). However, the observed values were higher than those reported in the Turkish version (ICC: 0.32–0.69) and the French version (ICC: 0.48).

4.4 Criterion validity

The FFI, SF12-V2, and EuroQoL-5D questionnaires, along with their subdimensions, were used for criterion validity. Correlation levels of the total score of the DFSQ-UMA-En with each category of the SF12-v2 are generally good or excellent, except for "Body pain" and "General health" subcategories. On the other hand, the strongest correlation observed with the EuroQoL-5D questionnaire was not achieved with the total score of the DFSQ-UMA-En (ranging from 0.744 to 0.844), but rather with the "Self-care" subcategory, which showed correlation values of 0.858 and 0.924.

This might indicate that, while the DFSQ-UMA-En reliably and validly assesses the quality of life of patients, the scores of the other subcategories also allow for the evaluation of complementary aspects of the subject. Similarly, the correlation observed with the FFI questionnaire, where correlation values are good or excellent, can be interpreted in a similar manner.

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TABLE 2 Descriptive characteristics of the sample based on mean and SD.

		Min	Max	Mean	SD
Age (years)		42	90	65.29	10.56
DM duration (years)		0	53	15.83	11.62
DFSQ-UMA-En	Total	0	100	65.99	12.70
	Self-care	15	35	28.15	5.46
	Self-assessment	7	20	16.28	2.41
	Footwear and socks	12	24	19.91	2.76
FFI	Pain	5	22	9.65	4.42
	Stiffness	6	18	9.95	2.48
	Difficulty	11	39	20.18	6.37
	Activity	2	12	3.90	1.64
	Social	6	18	7.96	2.22
	TOTAL	33	91	51.64	13.23
SF-12	Physical Function	22.11	51.81	32.39	9.72
	Role Physical	20.32	30.98	23.72	4.25
	Bodily Pain	16.68	26.87	17.92	3.31
	General Health	18.87	44.74	29.90	3.36
	Vitality	27.62	40.87	36.67	2.75
	Social Functioning	16.18	36.37	20.83	7.76
	Role Emotional	11.35	22.53	20.73	2.86
	Mental Health	21.87	34.06	32.04	3.45
	Physical Component State	17.43	31.20	20.99	3.72
	Mental Component State	29.21	53.51	39.02	7.72
EuroQol_VAS		0.230	1.000	0.73	0.20
EuroQol_5D		19.00	100.00	76.34	16.49
N		193			

TABLE 3 Internal consistency and reliability.

Cronbach's Alpha	Total	0.928
	Self-care	0.981
	Self-assessment	0.889
	Footwear and socks	0.897
ICC (Item responses)	0.854 (Item 9)–0.959 (Item 14)	

In summary, the DFSQ-UMA-En appears to be a valuable tool for assessing the quality of life of patients with DFD, and its subcategories provide insights into various aspects of their well-being and self-care. The correlations with other established questionnaires indicate the questionnaire's validity and its ability to complement existing assessment tools. When comparing the DFSQ-UMA-En with other versions of the DFSQ-UMA, it becomes apparent that only two of the published versions (the original version and the French version) conducted criterion validity analyzes. However, it is important to note that the reference instruments used for this analysis in those versions differ from those used in the DFSQ-UMA-En. In the original version (11), criterion validity was assessed by correlating the questionnaire with HbA1c levels and blood sugar levels, while the French version used HbA1c levels (13), resulting in correlation values of $r=0.15$ (HbA1c) and $r=0.226$ (glucose) in the original version and $r=0.17$ (HbA1c) in the French version. Consequently, the results observed in these different versions cannot be directly compared with those used in the validation of the DFSQ-UMA-En.

Comparing criterion validity across different versions of a questionnaire can be challenging when reference instruments and validation methodologies differ. Researchers should carefully consider the specific context and goals of their research when selecting a version of the questionnaire, in order to ensure that it aligns with their objectives and the characteristics of their study population.

For the assessment of criterion validity, the FFI, EuroQol, and SF12-v2 questionnaires were chosen, not matching the questionnaires selected for the original validation study in the Spanish language (11). This choice was due to a broader availability of valid and reliable questionnaires in the English language that fulfill more accurately the purposes of DFSQ-UMA.

Other questionnaires with good psychometric properties such as the Diabetes Self-Management Questionnaire (29) and Summary of Diabetes Self-Care Activities (30) do not address foot care. The exclusion of foot self-care in DM patients ignores the high mortality rate of DFD and the costs it generates on public healthcare systems (2, 4), thus the presence of items regarding foot health should be considered in the development of future PROMs.

4.5 Future research implications

The adaptation of questionnaires into other languages allows comparing the results obtained in different settings that may use the same instrument. Therefore, this facilitates the development of common intervention, assessment, and monitoring strategies. However, the adaptation process must adhere to recommendations found in the literature, which implies questionnaire translation, cross-cultural adaptation, and the evaluation of psychometric characteristics. These steps ensure that the developed versions maintain content equivalence and serve as clear, reliable, and assessable tools (31).

From this approach, the DFSQ-UMA is a specially designed tool for assessing self-care practices among patients with DFD. The accurate evaluation of this aspect is crucial, since numerous interventions proposed in the literature to improve cost-effectiveness rely on patient education. Specific aspects reflected in the DFSQ-UMA, such as self-care, self-assessment, and footwear/sock management, are essential. Having a tool explicitly designed to assess this therapeutic aspect is pivotal for effective patient monitoring.

This study demonstrates that the DFSQ-UMA-En is an optimal tool for assessing and monitoring self-care practices among English-speaking population with DFD. This will enable clinical professionals and researchers to conduct future investigations. There is one questionnaire similar enough to DFSQ-UMA in the scientific

TABLE 4 Eigenvalues and variance explained by items from the DFSQ-UMA En.

Component	Eigenvalues			Squared charge extraction sums		
	Total	Variance (%)	Cumulative %	Total	Variance (%)	Cumulative %
1	4.787	29.919	29.919	4.787	29.919	29.919
2	1.736	10.853	40.772	1.736	10.853	40.772
3	1.322	8.264	49.035	1.322	8.264	49.035
4	1.207	7.544	56.580			
5	1.051	6.571	63.151			
6	1.002	6.261	69.412			
7	0.958	5.988	75.400			
8	0.845	5.282	80.682			
9	0.630	3.937	84.620			
10	0.545	3.409	88.029			
11	0.446	2.788	90.816			
12	0.384	2.403	93.219			
13	0.338	2.113	95.332			
14	0.327	2.042	97.374			
15	0.246	1.541	98.914			
16	0.174	1.086	100.000			

TABLE 5 Matrix of components from DFSQ-UMA-En.

	Factor 1	Factor 2	Factor 3
DFSQ-UMA-En_1	0.731	−0.221	−0.440
DFSQ-UMA-En _2	0.744	−0.142	−0.286
DFSQ-UMA-En _3	0.746	−0.145	−0.219
DFSQ-UMA-En_4	0.732	0.082	−0.111
DFSQ-UMA-En_5	0.646	0.248	−0.170
DFSQ-UMA-En_6	0.507	0.229	0.015
DFSQ-UMA-En_7	0.718	0.021	0.224
DFSQ-UMA-En_8	0.491	−0.425	0.346
DFSQ-UMA-En_9	0.236	−0.469	−0.221
DFSQ-UMA-En_10	0.450	−0.491	0.348
DFSQ-UMA-En_11	0.287	0.262	0.469
DFSQ-UMA-En_12	0.493	0.182	0.175
DFSQ-UMA-En_13	0.440	0.494	0.399
DFSQ-UMA-En_14	0.384	0.445	−0.222
DFSQ-UMA-En_15	0.032	0.583	−0.277
DFSQ-UMA-En_16	0.498	−0.015	0.287

literature, i.e., the Diabetes Foot-Self Care Behavior Scale (DFSBS) (32), which is a 7-item questionnaire with good psychometric properties available in the Chinese, Farsi and German languages (33, 34). However, a recent systematic review on PROMs in DFD patients recommends DFSQ-UMA over DFSBS, as the former meets the current recommendations to a greater extent compared to the latter (7, 35).

4.6 Strengths and weaknesses

One of the main strengths of this study is the adaptation of the DFSQ-UMA into English, which is the language that serves as the backbone for the dissemination of clinical and scientific knowledge worldwide. English is also the most widely spoken non-native language globally, thus this adaptation facilitates its use in

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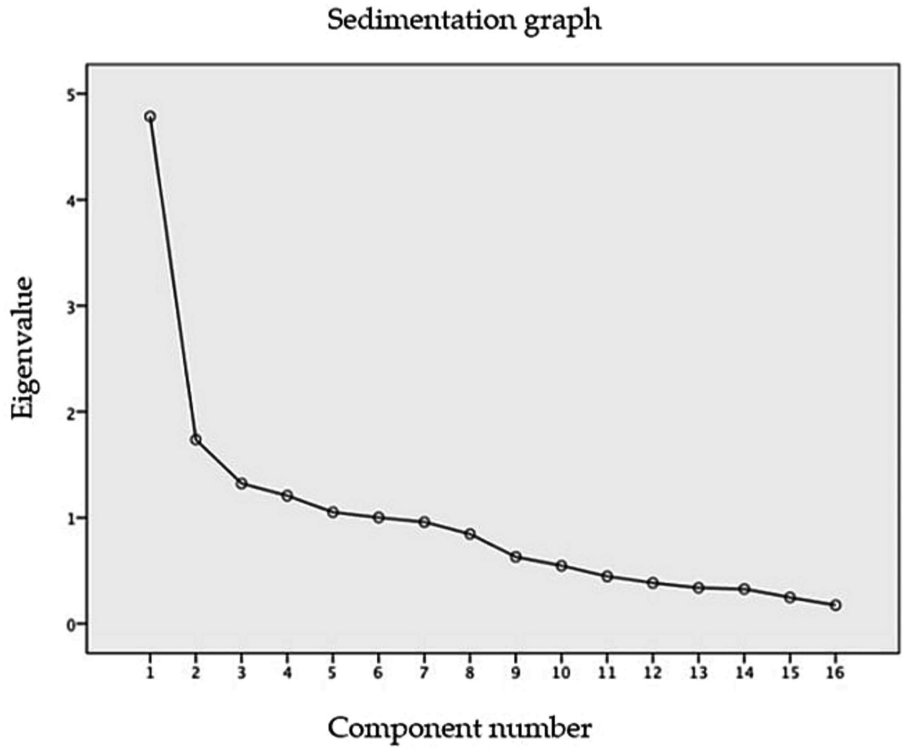

FIGURE 2
Sedimentation plot of the 16 items of the English version of DFSQ-UMA (DFSQ-UMA-En).

TABLE 6 Correlation between DFSQ-UMA-En and the instruments used to analyze criterion validity.

		DFSQ-UMA-En			
		Self-care	Self-assessment	Footwear and socks	Total
SF-12	Physical Function	0.557**	0.256**	0.354**	0.706**
	Role Physical	0.628**	0.202**	0.446**	0.802**
	Bodily Pain	0.425**	0.074	0.312**	0.475**
	General Health	0.401**	0.306**	0.208**	0.429**
	Vitality	0.646**	0.354**	0.443**	0.780**
	Social Functioning	0.594**	0.146*	0.422**	0.683**
	Role Emotional	0.486**	0.302**	0.302**	0.696**
	Mental Health	0.565**	0.325**	0.369**	0.727**
	Physical Component State	0.629**	0.186**	0.438**	0.676**
	Mental Component state	0.631**	0.215**	0.414**	0.801**
EuroQol VAS		0.858**	0.364**	0.482**	0.844**
EuroQol 5D		0.924**	0.372**	0.431**	0.744**
FFI	Pain	0.637**	0.215**	0.384**	0.646**
	Stiffness	0.667**	0.189**	0.356**	0.645**
	Difficulty	0.719**	0.253**	0.419**	0.642**
	Activity	0.537**	0.127	0.322**	0.565**
	Social	0.640**	0.181*	0.415**	0.685**
	Total	0.858**	0.275**	0.506**	0.831**

Significance of Pearson correlation coefficient *$p \leq 0.01$; **$p \leq 0.001$.

English-speaking population and research, increasing the visibility of this valuable tool. This, in turn, may encourage the translation and cross-cultural adaptation of this instrument into other languages to allow for result comparisons across different population groups.

Moreover, this validation study exceeded the minimum number recommended by the literature for the validation of assessment tools based on the number of items. In this case, 160 individuals were required, and the study was conducted on 193 patients (25).

This study has some limitations that should be taken into consideration. The English version of DFSQ-UMA was adapted using a sample of type 2 DM patients within a specific age range, excluding those under 18 years of age. Subsequent research could consider specific population profiles due to psycholinguistics differences, such as patients with associated comorbidities (36), as well as the design of studies to analyze psychometric variables related to longitudinal studies, such as responsiveness.

5 Conclusion

DFSQ-UMA-En is a valid and reliable tool with good readability and comprehension features. The Cross-cultural adaptation and validation of DFSQ-UMA into the English language were successful. This questionnaire addresses foot self-care behaviors in DFD patients, standing out as essential for early diagnosis and prevention strategies in clinical and research settings.

Data availability statement

The data presented in this paper will be available from the corresponding author upon reasonable request.

Ethics statement

The studies involving humans were approved by University of Malta Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MR-M: Conceptualization, Data curation, Investigation, Project administration, Validation, Writing – review & editing. RF-T: Investigation, Software, Validation, Writing – original draft. CF: Formal analysis, Funding acquisition, Writing – review & editing. AG: Formal analysis, Supervision, Writing – review & editing. GG-N: Resources, Visualization, Writing – review & editing. EN-F: Supervision, Writing – original draft. MG-S: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1326439/full#supplementary-material

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Does PAD and microcirculation status impact the tissue availability of intravenously administered antibiotics in patients with infected diabetic foot? Results of the DFIATIM substudy

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Aims/hypothesis: The aim of this substudy (Eudra CT No:2019-001997-27)was to assess ATB availability in patients with infected diabetic foot ulcers(IDFUs)in the context of microcirculation and macrocirculation status.

Methods: For this substudy, we enrolled 23 patients with IDFU. Patients were treated with boluses of amoxicillin/clavulanic acid(AMC)(12patients) or ceftazidime(CTZ)(11patients). After induction of a steady ATB state, microdialysis was performed near the IDFU. Tissue fluid samples from the foot and blood samples from peripheral blood were taken within 6 hours. ATB *potential* efficacy was *assessed by evaluating* the maximum serum and tissue ATB concentrations(C_{max} and $C_{max\text{-}tissue}$)and the percentage of time the unbound drug tissue concentration exceeds the minimum inhibitory concentration (MIC)($\geq$100% $_{tissue}$ and $\geq$50%/60% $_{tissue}$ fT>MIC). Vascular status was assessed by triplex ultrasound, ankle–brachial and toe–brachial index tests, occlusive plethysmography comprising two arterial flow phases, and transcutaneous oxygen pressure($TcPO_2$).

Results: Following bolus administration, the C_{max} of AMC was 91.8 $\pm$ 52.5 μgmL^{-1} and the $C_{max\text{-}tissue}$ of AMC was 7.25 $\pm$ 4.5 μgmL^{-1}(P<0.001). The C_{max} for CTZ was 186.8 $\pm$ 44.1 μgmL^{-1} and the $C_{max\text{-}tissue}$ of CTZ was 18.6 $\pm$ 7.4 μgmL^{-1}(P<0.0001). Additionally, 67% of patients treated with AMC and 55% of those treated with CTZ achieved tissue fT>MIC levels exceeding 50% and 60%, respectively. We observed positive correlations between both $C_{max\text{-}tissue}$ and AUC_{tissue} and

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arterial flow. Specifically, the correlation coefficient for the first phase was r=0.42; (P=0.045), and for the second phase, it was r=0.55(P=0.01)and r=0.5(P=0.021).

Conclusions: Bactericidal activity proved satisfactory in only half to two-thirds of patients with IDFUs, an outcome that appears to correlate primarily with arterial flow.

KEYWORDS

diabetic foot, antibiotic, infection, microdialysis, peripheral arterial disease

Introduction

Diabetic foot (DF) is a serious late complication of diabetes that dramatically increases the risk of lower limb amputations (1). More importantly, it increases patient morbidity and mortality (2). Infection is one of the key components of DF, contributing to unfavorable patient prognosis and poor podiatric outcomes (3). Early diagnosis of diabetic foot infection (DFI), followed by prompt and aggressive therapy, has the potential not only to slow disease progression, but also to delay or even reverse the above complications (4).

For DFI management, podiatrists have several treatment modalities at their disposal. In mild forms of DFI, antiseptics or local devices with anti-infective substances can be effective in certain cases (5). For mild and moderate stages of DFI, antibiotics (ATBs) administered in various oral or intravenous regimens are recommended (6). For severe forms of DFI accompanied by sepsis, parenteral ATB therapy is strictly indicated (7).

ATBs are selected based on causative microbial agents and microbial sensitivity. To ensure an adequate antibacterial response, it is essential to administer ATBs at levels conducive to optimal bactericidal activity in both serum and peripheral tissues (8). However, the efficacy of ATBs, particularly in peripheral tissues, can be affected by several factors. We hypothesize that macro- and microangiopathy are the most influential of these. However, researchers have yet to comprehensively address the serum and tissue concentrations of time-dependent ATBs, that are not routinely monitored in patients with DFI, especially those suffering from peripheral arterial disease (PAD). Therefore, the aim of our study was to assess the availability and bactericidal effect of ATBs in patients with infected diabetic foot ulcers (IDFUs) in the context of micro- and macrocirculation status.

Research design and methods

Study participants

A total of 23 patients with type 2 diabetes mellitus (DM) and IDFUs, graded (2–3)–(0–3)–(2–3) according to the WIfI classification (9), were enrolled in a substudy of the DFIATIM *(Diabetic Foot Infection treated with ATBs and it's Impact on gut Microbiota)* single-center randomized prospective comparative trial (Table 1). DFU infection was determined based on the following parameters: clinical signs, including phlegmon, edema, redness, pathological ulcer secretion, deepening of the DFU, and fetor; laboratory markers of infection, such as CRP and leukocytosis; positive bacterial findings in tissue samples or swabs taken from the base of the IDFU after debridement; and in several cases positive probe-to-bone test (10) and/or positive bone biopsy results. DFI was categorized as mild, moderate, or severe based on the Infectious Diseases Society of America (IDSA) criteria (7). Patients aged 30 to 75 years suffering from moderate or severe DFI caused by Gram-positive or Gram-negative bacteria sensitive to either amoxicillin/clavulanic acid (AMC) or ceftazidime (CTZ) were enrolled in this substudy of the DFIATIM trial. Exclusion criteria included severe hepatic insufficiency, chronic renal insufficiency/failure corresponding to stages 4 and 5 of the Chronic kidney disease (CKD) classification, severe malnutrition, indication for emergent foot amputation, recent percutaneous transluminal angioplasty (within 2 weeks), indication for acute revascularization due to rapid progression of PAD or acute arterial ischemia, allergy to test ATBs, presence of a diagnosed neoplasm, pregnancy, lactation, septic shock, active Epstein–Barr virus, inflammatory bowel disease, celiac disease or any other malabsorption disease, and acute gastroenteritis.

Prior to enrolment in the study, all patients signed informed consent forms, which were approved by the ethics committees of the Institute for Clinical and Experimental Medicine and Thomayer University Hospital (both Prague, Czech Republic).

Vascular status assessment

Large vessel evaluation

During the inclusion visit, all study participants were evaluated for both macrocirculation (larger vessels) and microcirculation status. Assessment of peripheral arterial circulation consisted of foot pulse measurement and triplex ultrasound of the peripheral

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TABLE 1 Basal characteristics of study participants and their circulation status.

Evaluated parameters	Patients treated with bolus AMC therapy	Patients treated with bolus CTZ therapy	*P* value
Number of patients	12	11	
Age (years)	60.1 ± 6.9	65.3 ± 8.5	NS
Weight (kg)	99.1 ± 16.8	103.5 ± 18.4	NS
BMI (kg m^{-2})	30.1 ± 4.9	31 ± 4	NS
HbA1c (mmol mol^{-1})	59.7 ± 15.4	63.4 ± 16.2	NS
CRP (mg L^{-1})	17.3 ± 25.1	49.8 ± 65	NS
Serum albumin (g L^{-1})	40.23 ± 3.6	40.15 ± 5.3	NS
Serum creatinine (µmol L^{-1})	98.2 ± 40.8	90 ± 24.9	NS
Glomerular filtration (CKD-EPI) (mL s^{-1} × 1.73 m^{-2})	1.27 ± 0.5	1.29 ± 0.5	NS
ABI	1.03 ± 0.32	1.01 ± 0.38	NS
TBI	0.66 ± 0.19	0.7 ± 0.27	NS
PAD (% of study participants)	44%	70%	NS
Arterial flows in first phase (mL min^{-1})	78.3 ± 42.9	79.4 ± 27.4	NS
Arterial flows in second phase (mL min^{-1})	37.9 ± 18.2	48.5 ± 20.4	NS
Interarm distance (mm)	23.9 ± 4.1	25.6 ± 3.5	NS
$TcPO_2$ (mm Hg)	43 ± 12.6	47 ± 12.4	NS

All results are presented as means ± standard deviation; BMI, body mass index; HbA1c, glycated hemoglobin; CRP, C-reactive protein; AMC, amoxicillin/clavulanic acid; CTZ, ceftazidime; CKD, chronic kidney disease; NS, nonsignificant; ABI, ankle-brachial index; TBI, toe-brachial index; PAD, peripheral arterial disease; $TcPO_2$, transcutaneous oxygen pressure.

arteries (11, 12). Additionally, we measured systolic blood pressure in the peripheral arteries, including the dorsalis pedis artery, the posterior tibial artery, using a handheld Doppler ultrasound device (Edan SD3 Vascular Ultrasonic Pocket Doppler, EdanUSA, San Diego, CA) equipped with an 8 MHz probe. The same technique was used to evaluate the ankle–brachial index (ABI) and toe–brachial index (TBI) (12). See Table 1 for details.

Color-coded triplex ultrasound has emerged as the gold standard in the field of accurate PAD detection. For this purpose, we used the LOGIQ P7 ultrasound system (GE Healthcare) equipped with a 4 MHz or 8 MHz probe, operating at the factory default setting. To determine morphology and blood flow in the peripheral limb arteries, pulse wave correction was set to the standard angle of 70 degrees followed by appropriate adjustments to the pulse repetition frequency. Monophasic waves were used to identify the presence of hemodynamically significant stenosis or obliteration. Arterial lesions that modify pulse waveforms are considered to have clinical hemodynamic significance due to their ability to dramatically reduce peripheral perfusion.

Arterial flow volume

The volume of arterial flow in the treated lower limb was measured using occlusive plethysmography (OP), a noninvasive diagnostic tool for screening PAD and evaluating vessel functionality. Using air plethysmography and photoplethysmography, we are usually able to detect the quality of perfusion in the peripheral lower limb. During the arterial phase of OP, conducted using the VLab-4000 plethysmography device (Advanced Medical Solutions, Czech Republic), the volume of arterial flow was measured in two phases - first and second phase. We also evaluated another parameter, the interarm distance. If the interarm distance is found to be elongated during arterial flow measurement, this can indicate similarly as reduced first or second phase of arterial flow stenosis or obliteration of the proximal arteries (Table 1). The probability of PAD significantly increased with lengthening of the interarm distance. The interarm distance ≥ 20 mm is more reproducible, values greater than 25 mm attain a sufficiently high positive predictive value for PAD diagnosis. The detection of interarm distance of pulse wave together with the change of pulse wave shape are crucial for interpretation of the presence or absence of PAD detected by occlusive plethysmography. This interarm distance is counted based on Oliva-Roztočil index (it is defined as the distance between ascending and descending components of the arterial pulse wave, measured at two-thirds of the amplitude of the pulse; (13), the relatively old method described in 1983 (14). Based on angiology experts, this interarm distance is still used during the evaluation of different plethysmographic methods results (15).

The usage of occlusive plethysmography is relatively widely enlarged especially in angiology centres in middle Europe. This method belongs to time- (duration of plethysmography assessment is 15 minutes) and financially saving assessment (1/3 evaluation ultrasound cost) in contrast to ultrasound methods. There are no limitations to be performed in infected or ischemic feet.

Transcutaneous oxygen measurement

Microcirculation status was determined by measuring transcutaneous oxygen pressure ($TcPO_2$; Table 1). $TcPO_2$ was measured using the TINA TCM 400 transcutaneous monitoring system (Radiometer, Copenhagen) equipped with Clark electrode. We used this device to electrochemically determine the partial pressure of oxygen on the surface of the skin (12, 16). This method consisted of heating a standard probe featuring a small chamber containing silver and platinum electrodes with an oxygen-permeable membrane. The temperature was raised to 42 - 45°C for arterialized cutaneous flow, thus increasing oxygen diffusion through the skin via local vasodilation. The results obtained were automatically recalculated to 37°C (16).

DFIATIM clinical trial

This article provides data pertaining to a substudy of the DFIATIM clinical trial. In this single-center randomized

prospective comparative trial, 60 patients with infected DF meeting the inclusion and exclusion criteria will be enrolled for treatment with intravenous ATBs (sample size estimation see statistics). The cohort will be divided into two groups. The first group, comprising 30 patients with infections caused by pathogens sensitive to the CTZ, will receive intravenous CTZ treatment. The second group, consisting of 30 individuals infected with bacteria sensitive to AMC, will receive intravenous AMC treatment. After the initial inclusion visit, patients will be admitted to hospital. Parenteral administration of AMC (1.2 g every 8 hours) or CTZ (2.0 g every 8 hours) will be initiated using standard bolus regimens. This will induce a steady state of ATBs consisting of at least 5 applications. Randomization, performed in each study arm in a 1:1 ratio according to the prescribed scheme, will determine whether patients receive ATBs in bolus or continuous dosage patterns. Serum and tissue concentrations of ATBs will then be monitored via blood and microdialysis (MD) sampling. Until discharged from hospital, patients will be treated according to different ATB dosage regimens in line with the randomization scheme (Figure 1). The total duration of intravenous ATB therapy will last 6 - 7 days. After hospital discharge, patients will be followed and undergo standard treatment according to the study schedule (Figure 1). The DFIATIM trial has been approved by the ethics committees of the Institute for Clinical and Experimental Medicine and Thomayer University Hospital.

Only patients treated with intravenously administered ATBs using the bolus method were included in the substudy presented in this article. Of these, 12 patients received AMC treatment and 11 were treated with CTZ.

Microdialysis

After achieving a steady state of ATB administration involving 5 bolus applications while in hospital, patients underwent microdialysis. During this procedure, tissue fluid and blood samples were collected simultaneously over a period lasting a minimum of six hours. The aim of the procedure was to measure the concentrations of ATBs in tissue fluid.

Microdialysis is a minimally invasive sampling technique designed primarily for *in vivo* monitoring of metabolic, biochemical, physiological, and pharmacological processes in living tissues and organs (17). It is widely used in pharmaceutical research, particularly for assessing drug pharmacokinetics and pharmacodynamics in peripheral tissues (17). Microdialysis enables *in vivo* monitoring of small water-soluble substances in the extracellular environment of tissues. Therefore, microdialysis serves as an ideal diagnostic tool for evaluating levels of tissue ATBs (18).

In this study, we employed the 63 Microdialysis Catheter (CMA Microdialysis AB, Stockholm, Sweden), which features a semipermeable hollow membrane. The catheter was connected to a syringe pump via an inlet tube for saline solution and an outlet tube for collecting microdialysate. In our patients with IDFUs, the probe was inserted into the subcutaneous tissue near the wound under antiseptic conditions and then flushed with perfusate solution at a constant flow rate of 0.5 to 5.0 µL min^{-1} (17). The microdialysis catheter was connected to a microperfusion pump and perfused with Ringer's solution. Briefly, the perfusate rinses the membrane from the inside and, as it flows through the probe, becomes enriched with ATBs, which are then transported from the tissue across the membrane into the perfusate based on their concentration gradient (19). The outflowing microdialysate was collected in an Eppendorf tube at intervals of 30 min. The catheter was then removed under aseptic conditions and discarded. All microdialysate samples were frozen immediately and stored at -80°C until analysis.

To optimize microdialysis recovery, expressed as the ratio between the concentration of the substance in the microdialysate and its concentration in the tissue, we used a microdialysis probe with a cut-off at least 4 times higher than the molecular weight of

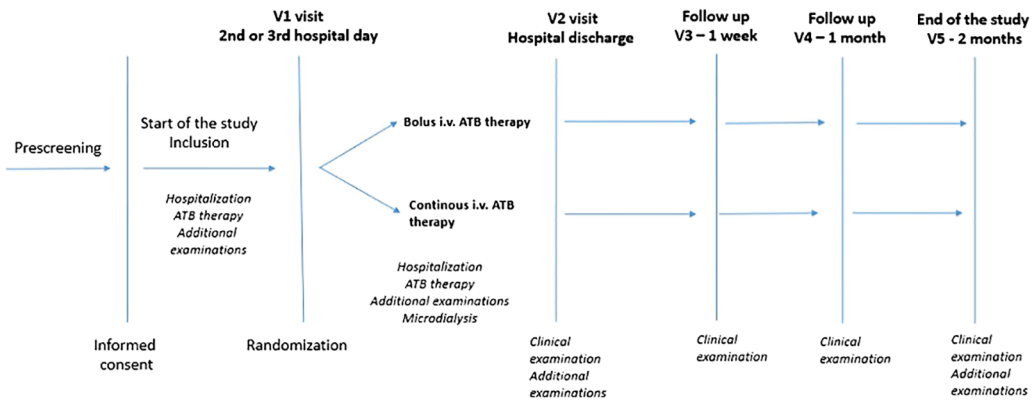

FIGURE 1
DFIATIM study scheme.

the ATBs (18). Ringer's solution was used as a perfusion medium to simulate the composition of extracellular fluid and minimize undesired transport of substances into and out of the membrane due to differences in osmolarity (20).

Before commencing this DFIATIM substudy, we performed retrodialysis to establish the technical recovery, or transition ability of ATBs across the microdialysis membrane (19). Measurements were carried out under laboratory conditions using samples of human serum obtained from healthy volunteers (21). We have chosen such perfusion rate based on previous in vitro and in vivo repeated tests with low interindividual variability to find optimal perfusion rate to recovery sufficient volume of tissue samples and achieve ATB molecules transmission into the microdialysis canula and collector. To achieve a high microdialysis recovery, expressed as the ratio between the concentration of the substance in the microdialysate versus the concentration in the tissue, it is necessary to use a cut-off that is 4 times higher compared to molecular weight (22).

In our study, approximately 0.5 mL of serum was spiked with AMC or CTZ at two concentration levels: 10 and 40 μg mL^{-1}. Next, the microdialysis probe was inserted into the spiked solution in a plastic vessel and rinsed with Ringer's solution at a flow rate of 2.5 μL min^{-1}. After attaining a steady-state flow rate, microdialysis samples were collected over a period of 30 min. The spiked serum samples obtained were then analyzed by capillary electrophoresis (CE). The relative concentration levels were used to calculate the microdialysis recovery, which were 76.2% for AMC and 81.1% for CTZ. Importantly, these values align with previously reported microdialysis yields of ATBs determined by retrodialysis using a probe inserted into the subcutaneous tissue (20). The values were used to recalculate the ATB levels detected in the microdialysis samples obtained from patients, adjusting them to reflect concentrations in subcutaneous tissue.

Capillary electrophoresis

The relatively small volumes of clinical samples available for analysis require the use of a suitable microanalytical technique (23–26) to allow sensitive quantitative monitoring of ATBs over short time intervals. The most common are highly selective biosensors or mass spectrometry methods combined with direct sample injection or high-performance liquid chromatography (HPLC). Since both serum and microdialysates of tissues are highly complex biological matrices, it is advisable to employ an efficient separation technique such as capillary electrophoresis (CE) (27–30). Due to the minimal requirements on the amount of clinical material and its laboratory processing, CE represents a suitable tool for the analysis of microliter quantities of collected microdialysates. These small volumes can be injected directly into the electrophoretic capillary after only a one-step dilution with organic solvent, providing an efficient sample pretreatment method.

The separation in CE is controlled by an electric field of high intensity up to 1 kV cm^{-1}, which results in relatively short ATB migration times lasting only a few minutes. In addition, in combination with universal contactless conductivity detection (C^4D) (31), the need for sample derivatisation is eliminated, and ATBs are determined directly in their native forms in which they are found in the human body.

For this study, CE-C^4D determination of AMC and CTZ was performed in off-line mode. This involved collecting serum and microdialysis samples at the clinical workplace, freezing them, and transporting them to the analytical laboratory. The thawed clinical samples, ranging in volume between 15 - 20 μL, were mixed with three times the volume of acetonitrile as an organic solvent that serves to deproteinise the clinical sample and simultaneously suppresses its electrical conductivity. After centrifugation, the supernatant is immediately analyzed by CE-C^4D; details are summarized in our recent publications (19, 21, 29).

Efficacy of ATB therapy

The efficacy of ATB therapy in patients with IDFUs depends on achieving a certain level of bactericidal activity. This is evaluated using the following parameters: maximum serum concentration (C_{max}) and maximum tissue concentration ($C_{max\text{-}tissue}$); the ratio of C_{max} or $C_{max\text{-}tissue}$ to the minimum inhibitory concentration (MIC) of the causative agents (C_{max}/MIC and $C_{max\text{-}tissue}$/MIC); the ratio of the area under the serum or tissue concentration–time curve (AUC or AUC_{tissue}) to the MIC (AUC/MIC and AUC_{tissue}/MIC); and the duration of the dosing interval during which plasma or tissue concentration exceeds the MIC (for AMC, ≥ 50% and ≥ 100% fT > MIC and ≥ 50% and ≥ 100% $_{tissue}$ fT > MIC; for CTZ, ≥ 60% and ≥ 100% fT > MIC and ≥ 60% and ≥ 100% $_{tissue}$ fT > MIC; 32). The measurements of 24 hours AUC were conducted using the trapezoid method over an extended eight-hour interval. It was counted in the following manner: based on pre-administration concentration C0 (C through), which was collected in a steady state, we determine 24 hours AUC using the rule of three since we assume that before the next administration, the concentration will remain stable.

The efficacy of ATB therapy depends on achieving effective ATB concentrations, when the levels of monitored ATBs at least reach, better exceed the MIC of the causative pathogens for at least half (in the case of AMC)/60% of the daily time (in the case of CTZ), preferable for 100% of the time when we administer ATB to a patient with infected diabetic foot. This is the most effective way how to prevent infection in diabetic foot.

The aim of this study was to establish the impact of various factors, including the presence of PAD defined by triplex ultrasound or facultatively by angiography, computed tomography angiography, magnetic resonance angiography, ABI, TBI, and occlusive plethysmography and microcirculation status, determined by $TcPO_2$ for key parameters such as bactericidal activity.

Statistical analysis

Data are expressed as the mean ± standard deviation or the median and range for continuous variables, and as relative frequencies for discrete variables. Data were tested for normality

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using the Shapiro-Wilk test. Parametric tests were used for normally distributed data, while nonparametric methods were used for data that were not normally distributed. Differences between the two groups were compared using the *t*-test for normal distribution or the Mann-Whitney test for other types of continuous distribution. Discrete variables were tested by χ^2-test. Pearson (normal) and Spearman (other) correlation coefficients were used to measure the associations between variables. Dependent samples were tested by the one-sample Wilcoxon signed rank test. All tests were two-sided and a P value < 0.05 was considered statistically significant. *Significance levels after Holm's correction for multiple testing (PH) are also presented.* Statistical analysis was performed using JMP®16.2.0 statistical software (SAS Institute, Cary, NC). Statistical processing was conducted using standard parametric and nonparametric methods in collaboration with statisticians at the Institute for Clinical and Experimental Medicine, Prague.

Results

The study cohorts did not differ significantly in basal characteristics, including circulation parameters (Table 1). DFUs were infected by 2 to 3 pathogens on average (2.5 ± 0.9 microorganisms per DFU in the AMC group vs. 2.5 ± 1.4 bacteria per DFU in the CTZ group; NS). However, there were variations in the MIC of the causative agents (0.54 ± 0.54 vs. 4.68 ± 3.2; P = 0.002; *(PH=0.008);* Table 2).

Concerning the assessment of pharmacokinetic parameters for AMC, the maximum serum levels of AMC (C_{max}) after bolus administration peaked at around 91.8 ± 52.5 μg mL^{-1}. AMC concentrations in peripheral tissues ($C_{max\text{-}tissue}$) reached approximately 9 – 31% of serum levels (ranging from 0.78 ± 0.97 to 7.3 ± 4.5 μg mL^{-1}; P = 0.0001 - 0.036; *(PH=0.0004 - >0.1;* Figure 2A).

When examining the area under the concentration–time curve for plasma or tissue, these microbicidal parameters proved relatively satisfactory. Similarly, when comparing the same parameters with MIC values, their ratios were within an acceptable range (Table 2). *To treat DFI effectively*, more than half of the daily tissue ATB concentrations must be greater than the MIC of the causative microbial agent. Among AMC-treated patients, only 67% had tissue concentrations that were above the MIC for at least 50% of the time (≥ 50% $_{tissue}$ fT > MIC*;* Figure 3A*)*. In contrast, only 33% of patients with IDFUs maintained tissue concentrations above the MIC for at least 100% of the time (≥ 100% $_{tissue}$ fT > MIC).

Patients treated with CTZ reached maximum serum CTZ levels of almost 187 μg mL^{-1}. In patients with IDFUs treated with CTZ, the maximum peripheral tissue concentration was 18.6 ± 7.4 μg mL^{-1}. Compared to serum levels, tissue CTZ levels ranged between 4.8 ± 2.1 and 18.6 ± 7.4 μg mL^{-1}; P = 0.0001; *(PH=0.0004);* Figure 2B), reaching approximately 9 – 22% of serum CTZ concentrations. Other pharmacological parameters detected in patients from the CTZ group are given in Table 2. Similar to the study participants treated with AMC, only 55% patients achieved more than half of the daily tissue CTZ concentrations higher than the MIC of pathogens (Figure 3B). Of the CTZ-treated patients, 45% had ≥ 100% $_{tissue}$ fT > MIC.

TABLE 2 *Pharmacokinetic parameters* in relation to bactericidal activity.

Evaluated parameters	Patients treated with bolus AMC therapy	Patients treated with bolus CTZ therapy
Number of patients	12	11
C_{max} (μg mL^{-1})	91.8 ± 52.5	186.8 ± 44.1
$C_{max\text{-}tissue}$ (μg mL^{-1})	7.25 ± 4.5 *	18.6 ± 7.4**
24 hours AUC	238.7 ± 78.7	1077 ± 344
24 hours AUC_{tissue}	65.5 ± 34.8	226.2 ± 79.1
MIC of causative microbial agent	0.54 ± 0.54	4.68 ± 3.2***
AUC/MIC	1170 ± 1304	556 ± 580
AUC_{tissue}/MIC	334 ± 351	113.3 ± 114.3

All results are presented as means ± standard deviation; *Comparison between C_{max} and $C_{max\text{-}tissue}$ AMC values (P = 0.0001–0.036; PH=0.0004 - >0.1). **Comparison between C_{max} and $C_{max\text{-}tissue}$ CTZ values (P = 0.0001; PH=0.0004). ***Comparison between MIC values of causative agents detected in the group of patients treated with AMC and those treated with CTZ (P = 0.002; PH=0.008). C_{max}, maximum concentration; AUC, area under the curve; MIC, minimum inhibitory concentration.

We identified positive and negative correlations of ATB bactericidal activity markers with some patient characteristics, particularly renal functions and body weight (Table 3). Regarding circulation parameters, only arterial flow correlated significantly with tissue ATB concentrations. The correlation coefficient for the first arterial phase was r = 0.42 (P = 0.045; *(PH - >0.1)*), and for the second phase, it was r = 0.44 – 0.55 (P = 0.0463 - 0.01*; PH>0.1 - >0.1*). Other macro- and microcirculation determinants *(including plethysmographic interarm difference with cut-point of 25 mm*, Figures 4A, B*)* did not correlate significantly with *pharmacokinetic parameters.*

Conclusions

The maximum effect of ATB therapy in iDFUs depends on achieving serum and tissue concentrations that provide effective bactericidal action. The efficacy of ATB therapy is typically assessed based on clinical evaluation during podiatric care, rarely using diagnostic methods. Serum ATB levels are usually only monitored for dose-dependent ATBs such as amikacin and gentamicin. However, time-dependent ATBs used to treat DFIs, including beta-lactams and cephalosporins (32), are not routinely assessed in the laboratory. In fact, there are almost no data on the pharmacokinetic and pharmacodynamic effects of these ATBs on the serum and peripheral tissues of DF patients (33).

The DFIATIM study aims not only to fill this knowledge gap, but also to test a number of clinical hypotheses. One of these is that PAD or microcirculatory impairment significantly affects the bactericidal activity and tissue availability of administered ATBs, especially in the DF. The potential influence of PAD on the

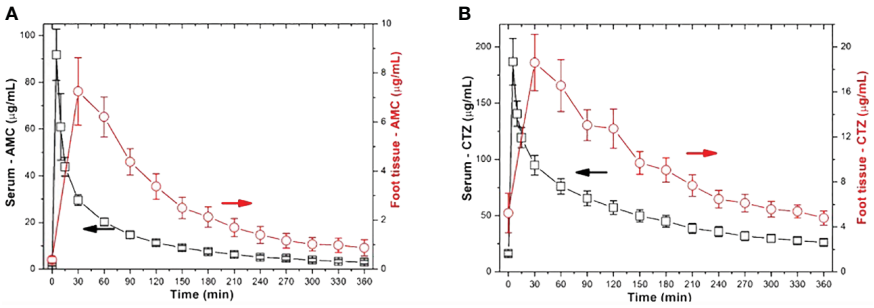

FIGURE 2
Comparison of serum and tissue ATB concentrations in study participants with IDFUs (**A** – AMC; **B** -CTZ).

accessibility of time-dependent ATBs in the lower limbs has yet to be addressed in the literature. Microdialysis is the most suitable method for clearly determining tissue concentrations of ATBs, monitoring their pharmacokinetic and pharmacodynamic properties, and ensuring the efficacy of intravenous ATB administration in patients with infected DF and PAD (29, 34). Before the introduction of microdialysis into clinical research, ATBs were detectable only in samples obtained from surgical resections or amputations, including even bone material (34, 35). Microdialysis facilitates real-time *in vivo* monitoring of ATBs (34). This is largely due to the use of a porous catheter membrane, which allows ATBs to diffuse across the membrane into the catheter according to the concentration gradient and the molecular weight of ATBs. We have previously validated this technique using our own *in vitro* and *in vivo* experiments (19).

Several methods, each with its own advantages and disadvantages, can be used to determine the concentrations of ATBs in serum and tissue. For our ongoing DFIATIM trial, we use a modern analytical method based on CE–C^4D (23) to sensitively determine ATBs in microdialysis samples (35). Compared to conventional HPLC techniques, CE approaches to ATB monitoring in microdialysis offer greater insights for several reasons (36). The amount of the sample injected into the separation capillary varies in nanoliter volumes, forming a complementary technique intended for tissue sampling by microdialysis. CE–C^4D enables direct measurement of a wide range of ATBs in their native

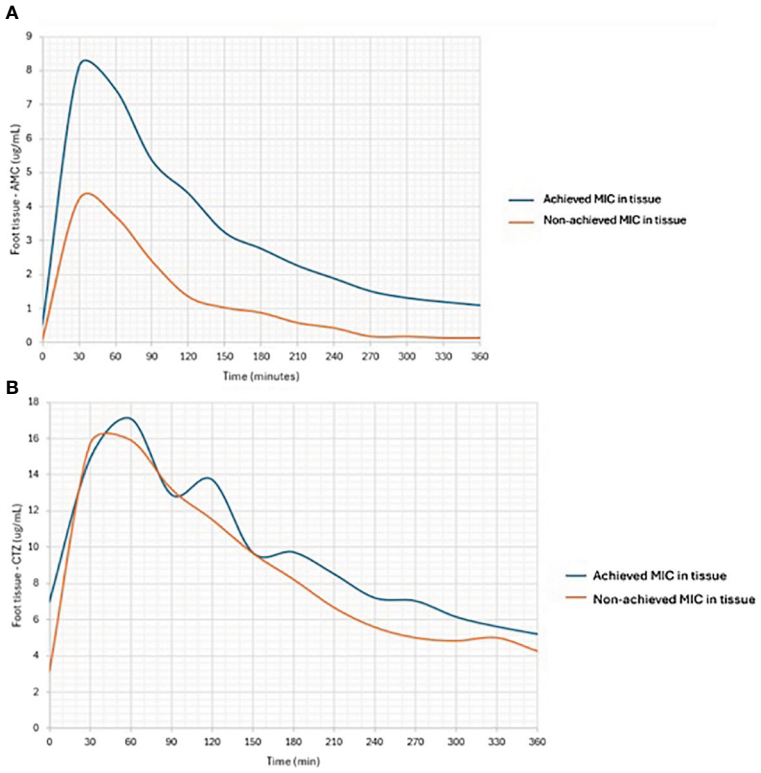

FIGURE 3
Comparison of tissue concentrations of AMC **(A)** and CTZ **(B)** in subjects achieving or non-achieving MIC in foot tissue samples.

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TABLE 3 Correlations between markers of ATB bactericidal activity and patient characteristics, including vascular parameters.

Markers of ATB bactericidal activity	Patient characteristics	Spearman r (95% CI), Pearson r value	p-value
C_{max}	Age	0.135	NS
C_{max}	BMI	0.046	NS
C_{max}	Weight	-0.031	NS
C_{max}	HbA1c	-0.137	NS
C_{max}	ABI	0.062	NS
C_{max}	TBI	0.211	NS
C_{max}	TcPO2	0.403	NS
C_{max}	First phase of arterial flow	-0.009	NS
C_{max}	Second phase of arterial flow	0.088	NS
C_{max}	Interarm distance	0.251	NS
C_{max}	Serum creatinine	0.141	NS
C_{max}	GF	-0.171	NS
$C_{max\text{-}tissue}$	Age	0.062	NS
$C_{max\text{-}tissue}$	BMI†	-0.557	p=0.06
$C_{max\text{-}tissue}$	Weight	-0.195	NS
$C_{max\text{-}tissue}$	HbA1c	0.012	NS
$C_{max\text{-}tissue}$	ABI	0.217	NS
$C_{max\text{-}tissue}$	TBI	-0.056	NS
$C_{max\text{-}tissue}$	TcPO2	-0.056	NS
$C_{max\text{-}tissue}$	First phase of arterial flow§	0.421(0.0111 to 0.71)	p=0.045
$C_{max\text{-}tissue}$	Second phase of arterial flow§	0.548(0.152 to 0.792)	p=0.01
$C_{max\text{-}tissue}$	Interarm distance	0.199	NS
$C_{max\text{-}tissue}$	Serum creatinine	0.136	NS
$C_{max\text{-}tissue}$	GF	-0.115	NS
24 hours AUC	Age	0.33	NS
24 hours AUC	BMI†	-0.55	p=0.06
24 hours AUC	Weight†	-0.557	p=0.06
24 hours AUC	HbA1c	0.09	NS
24 hours AUC	ABI	0.13	NS
24 hours AUC	TBI	-0.023	NS
24 hours AUC	TcPO2	0.105	NS
24 hours AUC	First phase of arterial flow	0.171	NS
24 hours AUC	Second phase of arterial flow§	0.439 (0.0095 to 0.732)	p=0.046
24 hours AUC	Interarm distance§	0.407	p=0.06
24 hours AUC	Serum creatinine†	0.923 (0.743 to 0.979)	p<0.001
24 hours AUC	GF†‡	-0.825 (-0.949 to -0.477)	p=0.001
24 hours AUC_{tissue}	Age	0.307	NS
24 hours AUC_{tissue}	BMI†	-0.585(-0.868 to -0.0166)	p=0.046
24 hours AUC_{tissue}	Weight	-0.079	NS
24 hours AUC_{tissue}	HbA1c	0.063	NS
24 hours AUC_{tissue}	ABI	0.151	NS
24 hours AUC_{tissue}	TBI	-0.063	NS
24 hours AUC_{tissue}	TcPO2	0.062	NS
24 hours AUC_{tissue}	First phase of arterial flow	0.286	NS
24 hours AUC_{tissue}	Second phase of arterial flow§	0.501(0.0886 to 0.767)	p=0.046
24 hours AUC_{tissue}	Interarm distance	0.346	NS
24 hours AUC_{tissue}	Serum creatinine	0.204	NS
24 hours AUC_{tissue}	GF	-0.217	NS
AUC/MIC	Age	-0.007	NS
AUC/MIC	BMI	-0.27	NS
AUC/MIC	Weight	-0.407	NS
AUC/MIC	HbA1c	0.003	NS
AUC/MIC	ABI	0.319	NS
AUC/MIC	TBI	-0.418	NS
AUC/MIC	TcPO2	-0.024	NS
AUC/MIC	First phase of arterial flow	0.038	NS
AUC/MIC	Second phase of arterial flow	0.0492	NS
AUC/MIC	Interarm distance	0.249	NS
AUC/MIC	Serum creatinine	0.107	NS
AUC/MIC	GF	-0.039	NS
AUC_{tissue}/MIC	Age	0.035	NS
AUC_{tissue}/MIC	BMI†	-0.815 (-0.955 to -0.38)	p=0.004
AUC_{tissue}/MIC	Weight†§	-0.6687 (-0.914 to -0.068)	p=0.035
AUC_{tissue}/MIC	HbA1c	-0.034	NS
AUC_{tissue}/MIC	ABI	0.35	NS

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TABLE 3 Continued

Markers of ATB bacteri-cidal activity	Patient characteristics	Spearman r (95% CI), Pearson r value	p-value
AUC_{tissue}/MIC	TBI	-0.359	NS
AUC_{tissue}/MIC	TcPO2	-0.102	NS
AUC_{tissue}/MIC	First phase of arterial flow	0.057	NS
AUC_{tissue}/MIC	Second phase of arterial flow	0.041	NS
AUC_{tissue}/MIC	Interarm distance	0.187	NS
AUC_{tissue}/MIC	Serum creatinine	0.112	NS
AUC_{tissue}/MIC	GF	-0.034	NS

†Significant correlations only in the AMC group. ‡ Significant correlations only in the CTZ group. § Significant correlations in all patients treated with AMC or CTZ. C_{max}, maximum concentration; AUC, area under the curve; BMI, body mass index; MIC, minimum inhibitory concentration; GF, glomerular filtration.

states, bypassing the need for complex derivatization reactions (37) or sample treatments that are difficult to perform in microliter amounts. The short migration times of electrophoretic analysis (38) are essential for continuous monitoring of microdialysates, particularly in pharmacological and physiological studies (39). Our previous study clearly demonstrated that the electrophoretic stacking technique is suitable for accurate determination of cephalosporin CTZ and beta-lactam AMC in the blood plasma and microdialysate of foot tissue after ATB administration (19). The concentrations we obtained were in close agreement with a conventional HPLC technique (40).

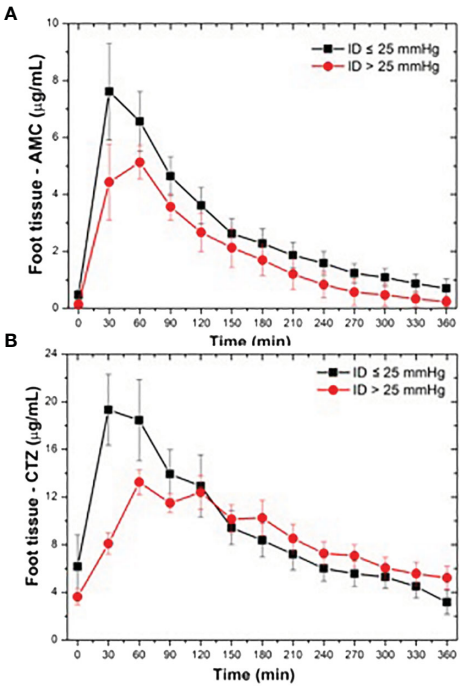

FIGURE 4
Comparison of tissue concentrations of AMC **(A)** and CTZ **(B)** in study subjects based on achieved Interarm distance detected during occlusive plethysmography (with cut-point 25 mm Hg).

After incorporating new microdialysis and CE methods within our podiatric practice, we decided to carry out the prospective DFIATIM trial to elucidate the time-dependent concentrations of ATBs in serum and tissue as well as their bactericidal activities. We were particularly interested to discover in one substudy of mentioned trial how the vascular status of the study participants could influence these parameters.

Our results revealed that bolus intravenous administration of both AMC and CTZ yielded satisfactory serum ATB levels. Similarly, Gariani et al. confirmed the satisfactory clinical impact of oral AMC on DFI, similar to clinical outcomes for other antimicrobial regimens (41). However, data on CTZ are practically non-existent in the literature. The bactericidal activity of ATBs are determined by the time interval over which ATB concentrations in tissue exceed the MIC. For AMC, tissue concentration must be ≥ 50% fT > MIC, and for CTZ, the tissue concentration must be ≥ 60% fT > MIC. In our study, these criteria were met in only 67% of patients treated with AMC and 55% of patients with CTZ. However, it was very difficult from the point of macro- and microcirculation parameters to subanalyse patients achieving or non-achieving appropriate MIC of ATBs in peripheral tissue. The subgroups were very small ((8 patients treated by AMC achieved MIC for more than 50% of evaluation time vs. 4 patients non-achieving these levels/similarly 6 patients treated by CTZ achieved MIC for more than 60% of evaluation time vs. 5 patients without sufficient tissue concentrations), and it was impossible to perform appropriate statistical power analyses. Similar situation is when we would like to compare patients achieving or not appropriate plethysmographic parameters including interarm distance.

In our study, ATB levels in serum and tissue, particularly in the AMC group, positively correlated with serum creatinine levels and negatively with weight, BMI, albumin, and glomerular filtration. Similar correlations in connection to AMC treatment were recently documented by Brazil experts (42). Therefore, it is imperative to highlight the importance, during DFI therapy, of tailoring ATB dosage schemes based on factors such as patient weight, BMI, drug distribution, nutrition, and renal functions.

Regarding the relationship between PAD, microcirculatory impairment, ATB availability, and bactericidal activity, we noted significant positive correlations solely between maximum ATB tissue levels and their AUC with arterial flow, as detected in the treated lower limb by OP. Interestingly, neither ABI, TBI, nor $TcPO_2$ correlated significantly with measured pharmacokinetic and pharmacodynamic parameters. These original findings on the interconnection between vascular status, ATB availability, and bactericidal activity have yet to be reported in the literature. A study by Raymakers et al. underscored the importance of tissue perfusion ($TcPO_2$) in the penetration of CTZ into the skin, muscles, and bones. However, this study did not follow ATB concentrations in real time, and results were based on immediate ATB levels detected from tissue obtained during amputation procedures (33).

In our study, TcPO2, like ABI and TBI, did not correlate with real-time pharmacology data in either AMC or CTZ. This indicates that the macrocirculation status represented by ABI and TBI and the microcirculation status represented by $TcPO_2$, are not as important as the volume of blood that reaches the treated foot through the native arterial network and pre-existing capillaries. Our results clearly demonstrate the important role of plethysmography in the diagnosis of vascular changes (exhibiting sensitivity of 73% to 90% and specificity of 77% to 96% for PAD diagnosis) in patients with IDFUs, reinforcing the need for comprehensive vascular examination in podiatric patients at all times (43).

One of the limitations of this study is the small number of patients enrolled. However, microdialysis studies are technically and logistically demanding to perform and generally involve small numbers of participants. Additionally, patients with critical limb-threatening ischemia were excluded from the study, since these patients typically require urgent revascularization procedures or even major amputations.

In summary, ATB treatment of patients with IDFUs proved satisfactory in only half to two-thirds of study participants. The availability and bactericidal activity of ATBs appear to be impaired by vascular changes, particularly by the volume of arterial flow in the treated lower limbs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The ethics committees of the Institute for Clinical and Experimental Medicine and Thomayer University Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VF: Writing – original draft. RJ: Investigation, Writing – review & editing. SA: Methodology, Writing – review & editing. JH: Investigation, Writing – review & editing. VW: Investigation, Writing – review & editing. PB: Methodology, Writing – review & editing. JM: Supervision, Writing – review & editing. PT: Investigation, Methodology, Supervision, Writing – original draft. JP: Methodology, Supervision, Writing – review & editing. MD: Supervision, Writing – review & editing. DS: Supervision, Writing – review & editing. VL: Investigation, Writing – review & editing. MP: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Vascular service provision during the COVID-19 pandemic worsened major amputation rates in socially deprived diabetic populations

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Introduction: The Coronavirus Disease – 2019 (COVID-19) pandemic significantly impacted healthcare service provision and put diabetic patients at increased risk of adverse health outcomes. We aimed to assess the impact of the COVID-19 pandemic on the incidence and demographic shift of major lower-limb amputation in diabetic patients.

Methods: We performed a retrospective analysis of diabetic patient records undergoing major lower-limb amputation between 01/03/2019 and 01/03/2021 at the Royal Sussex County Hospital, the regional arterial hub for Sussex. Primary outcomes were amputation incidence rates and patient demographics compared between the prepandemic and pandemic cohorts.

Results: The incidence rate ratio of major lower-limb amputations shows a drop in amputations during the pandemic compared to pre-pandemic (IRR 0.82; 95% CI 0.57–1.18). Data suggests a shift in the social deprivation background of patients receiving amputations to disproportionately affect those in the more deprived 50% of the population (p=0.038). Younger patients received more amputations during the pandemic compared to prepandemic levels (p=0.001).

Conclusion: Results suggest that during the COVID-19 pandemic there was a paradoxical reduction in amputations compared to prepandemic levels. However, changes to the demographic makeup of patient's receiving amputations are alarming as younger, and more deprived patients have been disproportionately affected by the pandemic.

KEYWORDS

diabetic foot, social deprivation, COVID-19, amputation, surgical, public health

Introduction

In March 2020, the World Health Organization (WHO) declared the coronavirus (COVID-19) outbreak a pandemic which triggered an immediate change in National Health Service (NHS) care processes (1). The impact of the pandemic and the associated changes on patient outcomes is largely unknown, particularly in chronic diseases where long term management and follow-up is essential. Diabetic foot care outcomes are heavily associated with service provision making them especially vulnerable to decline within the context of COVID-19 (2). Negative diabetic foot outcomes such as major lower-limb amputation contribute a significant portion of the burden of diabetes mellitus (DM) on healthcare systems (3, 4).

Our local organization, the Sussex Vascular Network (SVN) provides vascular surgery services to the population of the counties of East Sussex and West Sussex, acting as the central arterial hub for six 'spoke' hospitals within the region. The SVN provides vascular footcare services to a population of 1.7 million, of which 99,065 are registered diabetics with general practice surgeries (5–8). The SVN has an interest in reducing the incidence of lower-limb amputations to improve patient outcomes and reduce associated costs. Therefore, it is essential to understand the impact the COVID-19 pandemic has had on care delivery within the SVN to better guide implementation of guidelines and development of the post COVID-19 care strategy.

The primary aim was to assess the impact of the COVID-19 pandemic on DM-related major lower-limb amputations. The secondary aim was to investigate a potential relationship between the Index of Multiple Deprivation (IMD) and DM-related major lower-limb amputation in the context of COVID-19 policy changes.

Methods

Study design

We designed an exploratory retrospective cohort study drawing from a previous quality improvement audit and reviewed data spanning the period of 1 March 2019 to 1 March 2021. This period corresponds to the years pre- and post- the publication of "COVID-19 'Battle Plan'" on 1 March 2020, which was the first active public policy measure from the United Kingdom (UK) government on COVID-19 that affected NHS care provision (1). We reviewed all cases of DM-related major lower-limb amputations to assess incidence rates as compared to the national average. No sample size calculations were conducted as the data reflects the entire population of DM-related major lower limb amputations. We examined the differences in incidence rates prior to and during the period of COVID-19 policy changes to assess the impact of the pandemic on DM-related major lower-limb amputations within the SVN. We analyzed the relevant demographic data including age, sex, and deprivation to examine associations with DM-related major lower-limb amputations incidence and the impact of the COVID-19 pandemic on demographics.

Abbreviations: COVID-19, Coronavirus Disease 2019; WHO, World Health Organization; NHS, National Health Service; DM, Diabetes Mellitus; SVN, Sussex Vascular Network; IMD, Index of Multiple Deprivation; UK, United Kingdom; OPCS-4, Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4; ICD-10, International Statistical Classification of Diseases and Health Related Problems 10th Revision; IBM SPSS, International Business Machines Statistical Product and Service Solutions; SD, Standard Deviation; IQR, Interquartile Range; CI, Confidence Interval; DALY, Disability Adjusted Life Year; DFD, Diabetic Foot Diseases.

Inclusion criteria

Included cases were all major lower-limb amputations in patients with diabetic foot diseases conducted at the Royal Sussex County Hospital – the SVN major arterial hub – between 1 March 2019 and 1 March 2021. All major lower-limb amputations for diabetic foot disease for the entire region are performed at the vascular hub, as advocated in the service provision document by the Vascular Society (9). Major lower-limb amputations are defined as amputation of the lower-limb above the ankle and corresponding to codes X09.3, X09.4, and X09.5 of OPCS-4 Classification of Interventions and Procedures (10). Diabetic patients are defined as being diagnosed with type I, type II, malnutrition-related, other specified, and unspecified DM corresponding to ICD-10 codes E10-E14 (11).

Cases were obtained by requesting patient details corresponding to all operations classified as X09.3-X09.5 performed in the specified period and cross referencing against all patients with a recorded E10-E14 diagnosis. All cases of major lower-limb amputation with a recognized preceding diabetic foot complication were included. Patients with diabetic foot complications were defined as patients suffering from critical limb ischemia, diabetic foot ulcer, diabetic foot infection, diabetic foot osteomyelitis, and/or Charcot's foot (12). Cases of bilateral amputations were included as separate cases while revisions of previous amputations were not included. Identification of the target population within these parameters was done by requesting patient details from the hospital theatre management software Bluespier and cross referencing against relevant parameters with the assistance of a data analyst.

Exclusion criteria

Non-diabetic patients who underwent major lower-limb amputation were excluded, as were diabetic patients without coded diabetic foot disease.

Data abstraction

A data abstraction tool was designed to capture relevant details. Sources of information included physical patient notes and electronic records. Collected data was anonymized by a unique identification number for each case. Demographic details captured included date of birth, sex, and residential postcode. Ethnicity was

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excluded from the demographic details captured due to inconsistent recording of ethnic origin on patient notes. Patient factors covered the relevant details of the admission including affected limb, procedure performed, date of procedure, and diabetes diagnosis.

IBM SPSS version 26 was used for processing and analysis. Age in years at the date of procedure was calculated using the date of birth, and date of procedure, and then sub-stratified into age groups: <40; 40–49; 50–59; 60–69; 70–79; and ≥80. Index of Multiple Deprivation (IMD) was captured by cross referencing residential postcodes against the English Indices of Deprivation 2019 worksheet (13). IMD was recorded by sorting data according to decile of deprivation where the 1st decile represents the 10% most deprived neighborhoods in England while the 10th decile represents the 10% least deprived neighborhoods.

Data analysis

Data was dichotomized by creating pre-COVID-19 and COVID-19 cohorts, based on whether the date of procedure fell before or after 1 March 2020. Missing data were omitted from analysis. Statistical analyses were conducted using IBM SPSS version 26. Distribution of the data was determined using visual assessment of histogram distribution which showed that age was normally distributed with some left skew. Other metrics were not seen to be normally distributed. Mean (standard deviation (SD)) were reported for normally distributed data; otherwise, median (interquartile range (IQR)) was reported. The population of patients with a DM diagnosis (ICD-10 codes E10-E14) falling within the SVN catchment was calculated from General Practice surgeries registration data published in the National Diabetes Audit (14, 15). The population data was used to calculate crude incidence rates within each cohort. 95% confidence intervals (CI) for the crude incidence rates were determined using Byar's confidence interval calculation method as recommended by Public Health England standards for the reporting of key public health measures (16). Incidence rate ratio was calculated between the two cohorts and a Wald method based approximate 95% CI was calculated (16). IMD decile data was dichotomized into deprived and non-deprived status based on falling within the 50% most deprived and 50% least deprived neighborhoods, respectively. Differences in deprivation status and sex between the cohorts were assessed using Pearson Chi-Square tests due to the data being categorical in nature. An independent samples T-Test was used to assess difference in age between the cohorts. A line graph by COVID-19 exposure was then created to map the variation of incidence over time. Bar charts were created to show variations in incidence per age group, sex, and IMD decile. Table 1 provides a summary of all results. Data and methods were reviewed by a statistician.

Results

Demographics

A total of 129 potential DM-related major lower-limb amputations occurring between 1 March 2019 and 1 March 2021 were found. 115 (89%) cases were included while 14 (11%) cases were excluded based on inclusion and exclusion criteria respectively. There were no missing data. 20 (17%) were female and 95 (83%) were male. All DM-related major lower-limb amputations were in adults with a mean age of 67(± 11) years (range of 33–93). Mean age within the pre-COVID-19 cohort was 69 (± 11). Mean age within the COVID-19 cohort was 63 (± 9). Median IMD lies within the 5th (IQR 4) decile. There were 16 (14%) Type I diabetics and 99(86%) Type II diabetics. Of which were 6 (10%) Type I diabetics and 57 (90%) Type II diabetics within the pre-COVID-19 cohort, while there were 10 (19%) Type I diabetics and 42 (81%) Type II diabetics within the COVID-19 cohort. No other types of DM were recorded.

TABLE 1 Summary of findings.

Metric	Pre-COVID-19	COVID-19	p Values
Incidence	63	52	N/A
Incidence Rate	6.4 per 10,000 (95% CI 4.9–8.2)	5.2 per 10,000 (95% CI 3.9–6.9)	N/A
Incidence Rate Ratio	0.82 (95% CI 0.57–1.18)		N/A
Mean Age	69 (± 11)	63 (± 9)	p=0.001
Sex	Male (55) Female (8)	Male (40) Female (12)	p=0.114
Median Deprivation	6th Decile (IQR 5)	5th Decile (IQR 2)	p=0.038

Overview of incidence

Incidence of DM-related major lower-limb amputations in the pre-COVID-19 cohort was 63. Incidence of DM-related major lower-limb amputations in the COVID-19 cohort was 52. This corresponds to an incidence rate of 6.4 per 10,000 (95% CI 4.9–8.2) pre-COVID-19 and an incidence rate of 5.2 per 10,000 (95% CI 3.9–6.9). Incidence rate ratio between pre-COVID-19 and COVID-19 cohorts was 0.82 (95% CI 0.57–1.18). Distribution of incidence over time per month of procedure by COVID-19 exposure is shown in Figure 1. Figure 1 demonstrates an initial spike in number of procedures during COVID-19 in April. This elevation is followed by a large drop in May through July compared to pre-COVID-19 counts, before the number of procedures generally normalized and followed the pre-COVID-19 trends.

Age

Mean age at time of amputation within the pre-COVID-19 cohort was 69 (± 11). Mean age at time of amputation within the COVID-19 cohort was 63 (± 9). Distribution of amputation procedures per age group is shown in Figure 2. Figure 2 demonstrates a shift in the distribution in the number of procedures from older age groups pre-COVID-19 to younger age groups during COVID-19 (p=0.001). Distribution of procedures

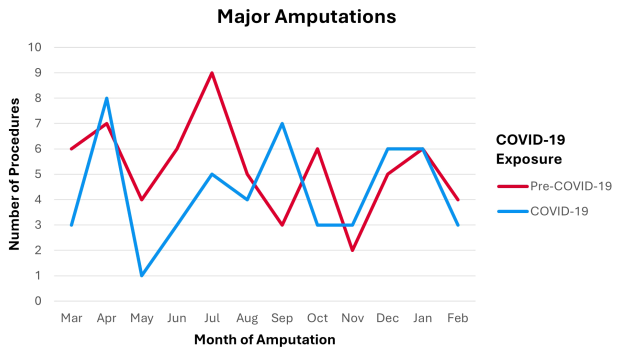

FIGURE 1
Number of DM-Related Major Lower-Limb Amputations per Month of Procedure by Cohort.

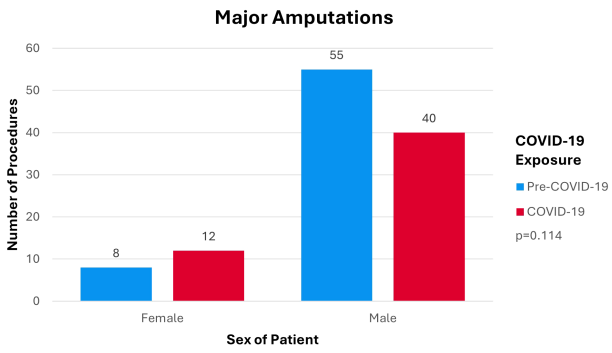

FIGURE 3
Number of DM-Related Major Lower-Limb Amputations by Sex by Cohort.

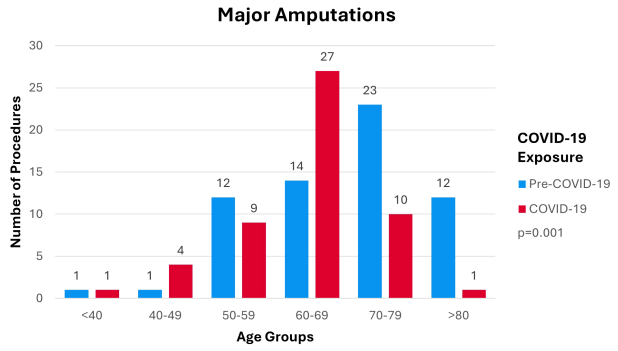

FIGURE 2
Number of DM-Related Major Lower-Limb Amputations per Age Group by Cohort.

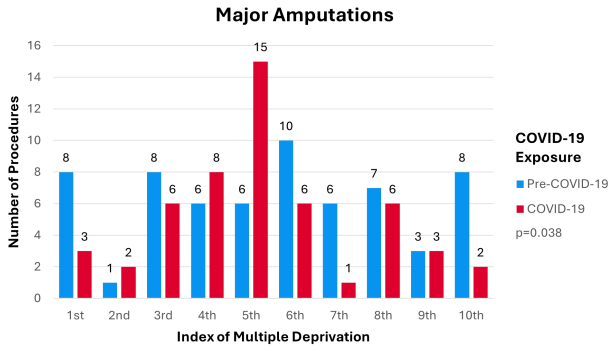

FIGURE 4
Number of DM-Related Major Lower-Limb Amputations per IMD Decile by Cohort.

performed pre-COVID-19 centers on the over 70 age groups with greater spread over all categories. Distribution of procedures performed during COVID-19 follow a more concentrated pattern centered on the 60–69 age group.

Sex

Distribution of amputation procedures by sex of patient by COVID-19 exposure is shown in Figure 3. Figure 3 demonstrated no major differences in the distribution of amputations by sex between the pre-COVID-19 cohort and the COVID-19 cohort (p=0.114). The outcome of major lower-limb amputations mostly affected males as opposed to females.

Deprivation

Pre-COVID-19 median amputation incidence by IMD decile lies within the 6th (IQR 5) decile. During COVID-19 median amputation incidence by IMD decile lies within the 5th (IQR 2) decile. Distribution of amputation procedures per IMD deciles by COVID-19 exposure is shown in Figure 4. Figure 4 demonstrates a shift in the number of procedures towards the 50% most deprived members of the population during COVID-19 compared to pre-COVID-19 (p=0.038). Distribution of the data across the IMD deciles pre-COVID-19 was more evenly spread amongst the different deciles. During COVID-19 the number of procedures performed became more concentrated in the 5th and 4th IMD deciles.

Discussion

DM represents the 8th leading cause of disability adjusted life years (DALYs) globally (17). Accounting for 2.8% of DALYs across all ages globally in 2019, it is a global public health challenge whose burden has grown by 147.9% since the 1990s (17). Within England, DM affects approximately 3.5 million individuals, costing 10% (£10 billion) of the NHS budget (4, 5, 18). Approximately 90% of the expenditure on DM patients goes to the management of associated complications such as lower limb amputations secondary to diabetic foot disease (DFD) (4). Lower-limb amputation is a preventable outcome which has a negative lifelong impact on patient quality of life and associated burden of disease on healthcare systems (19, 20). Lower-limb amputations in diabetic

patients are estimated to cost the NHS £65 million spread across peri- and postoperative care excluding costs of community and prosthesis related costs (4, 18).

Many risk factors predispose patients to the development of diabetic foot ulcers and consequently to major lower-limb amputation. Clinical risk factors feature more prominently in current guidelines and literature compared to wider determinants of health (21). These wider determinants including financial insecurity, education, access to services, amongst others represent fewer collective resources within a community and are known under the umbrella of social deprivation (22). Social deprivation forms an independent risk factor for the development and subsequent prognosis of DFD (22). Literature suggests that social deprivation contributes to the development of DFD as highly as the presence of comorbid cardiovascular disease (23). Despite the high impact of social factors, they are often overlooked by clinicians and policymakers alike when approaching the question of planning diabetic care. The COVID-19 pandemic is thought to have exacerbated the role these factors play in DFD.

As the first global health emergency of the modern era, the COVID-19 pandemic has already revealed significant vulnerabilities in national healthcare systems. Global trends of diabetic lower-limb amputations increased during the pandemic which is consistent with the apparent reduced care processes seen in the NHS (24, 25). Current evidence demonstrates that some of the indirect effects of COVID-19 were seen in major reduction of primary care contacts, especially for diabetic emergencies (odds ratio 0.35) (26). Consequently, rates of health checks dropped by 76%-88% across the UK and subsequently only partially recovered (27). This manifested in reduced DM-related primary care processes including early diagnosis, monitoring, and prescribing (27). Impacts of the pandemic also included major modifications in the management approach to several vascular pathologies including DFD compared to prepandemic standards. In 4.9% of cases, these modifications lead to amputation/palliation of patients that would have been offered salvage and revascularization opportunities in prepandemic settings (28). Paradoxically, an England population wide study showed a reduction in amputation rates during the first few months following the changes associated with the pandemic (29). This is alarming given that current guidelines have not been fully implemented across the UK in the past and the extent to which this is exacerbated by COVID-19 is unknown.

The incidence of DM-related major lower-limb amputations undertaken by the SVN between 1 March 2019 to 1 March 2021 was consistently lower than the latest reported national average of 8.1 per 10,000 (7). The incidence is also lower than the previous reported statistic from the SVN of 7.2 per 10,000 (7) suggesting that diabetic footcare service provision within the SVN is better than the diabetic footcare service provision across England and is improving compared to previous years. The comparison of incidence shows a 18% drop between pre-COVID-19 and COVID-19 cohorts. Figure 1 shows that the drop occurred within the first few months of the COVID-19 cohort before returning to previous trends. This finding is consistent with Valabhji et al's (29) England-wide study yet inconsistent with global trends for the same period (24, 25).

The incidence of DM-related major lower-limb amputation shifted to a younger age group during COVID-19 compared to pre-COVID-19 (p=0.001). This is concerning as the COVID-19 cohort would experience more DALY's compared to the pre-COVID-19 cohort. Figure 3 shows incidence of DM-related lower-limb amputations predominantly in the male population compared to females in both the pre-COVID-19 and COVID-19 cohort which is consistent with the current literature (30). The dispersion of procedures shifted from a relatively equal distribution across all IMD deciles pre-COVID-19 to an increase in procedures being performed within the 50% most deprived deciles during COVID-19. This shows that during COVID-19 more deprived areas were disproportionately affected by the impact of COVID-19 on lower-limb amputation rates (p=0.038).

Amputation incidence

Incidence of amputations from May through July during COVID-19 fell compared to the same period pre-COVID-19 levels as shown in Figure 1. This period contributes the most towards the decreased incidence rate ratio between the two cohorts. While this finding is consistent with the findings of Valabhji et al. (29), it is not in keeping with the available literature. Incidence was expected to increase due to decreased primary care contacts and screening of type II DM during the pandemic (26, 27). This was expected to delay diagnosis and specialist management of diabetic foot diseases resulting in more severe disease, unsalvageable limbs, and ultimately major amputations. Additionally, global trends within the same period consistently showed increased incidence of DM-related major lower-limb amputations and the UK was expected to follow the same trend (24, 25).

Age groups and incidence

The impact of COVID-19 on DM-related major lower-limb amputations incidence within the different age groups is alarming. The shift in the dispersion of amputation incidence to a younger age group during COVID-19 as seen in Figure 2 leads to an increase in DALYs for patients treated throughout the pandemic. This contributes negatively to the burden of DM and the burden of COVID-19 on the NHS. Those in the above 70 age groups might not have presented to services as frequently as younger age groups due to COVID-19 infection being a competing end point for morbidity and mortality in the elderly as suggested by Valabhji et al. (29). This therefore presents a confounding variable as older patients were more likely to succumb to a COVID-19 infection, and died with comorbid critical limb ischemia or diabetic foot related sepsis. Alternatively, the decreased amputation incidence might be due to those over 70 staying at home hoping to avoid COVID-19 infections at the hospital as supported by the 25.3% decreased attendance rates to emergency departments (31). The demonstrated shift in amputation incidence to age groups under 70 maybe due to a relative shift in availability of theatres for younger patients for

limb saving procedures as older patients succumbed to COVID-19 or did not present to hospitals. However, absence of data to include in our analysis meant that we are unable to comment further.

Deprivation and incidence

The correlation between IMD and DM-related major lower-limb amputations is well documented within the current literature (30). Figure 4 demonstrates changes in the dispersion of amputation incidence towards the most deprived 50%. During COVID-19, utilization of elective admissions dropped more consistently across the different deciles while utilization of emergency admissions dropped predominantly in less deprived deciles (32). Government and healthcare responses to COVID-19, which aimed to reduce strain on services via lockdown orders and postponing elective interventions, led to an overall decrease in attendance (31, 32). Economic reports show that the COVID-19 pandemic negatively altered social determinants of health within more deprived deciles (33). These pandemic related changes may have led to increased supply of clinical resources with coinciding decreased demand for services within less deprived populations. These shifts in supply and demand characteristics are likely to have favored intervention in those falling within more deprived IMD deciles.

Summary of COVID-19 driven trends

The COVID-19 pandemic was a novel event in modern times which allowed for real-time learning of pandemics and their effects on healthcare. Alongside the pandemic implementation of several programs such as e-consultations and telemedicine were accelerated (34). The aim of these programs was to streamline care in the context of social distancing and healthcare avoidance behaviors. The most tangible impact of COVID-19 and associated healthcare responses demonstrated by this study has been on the decreased incidence of DM-related major lower-limb amputation, especially, in the early months of the pandemic. While this may reflect that the initial efforts to decrease healthcare strain were successful, it may ultimately reveal a more negative impact on DM outcomes in the later phases of the pandemic. Despite the seemingly positive finding of decreased incidence, we have identified concerning shifts in the underlying population demographics because of COVID-19. The pandemic has disproportionately affected younger more deprived populations by altering population behaviors and healthcare provision. This is particularly pronounced as during the pandemic all-cause mortality was shown to be doubled in more deprived areas compared to equivalent populations in less deprived areas, likely as a result of the underlying health inequalities exacerbated by the onset of the pandemic (35). Whether behavioral changes will persist beyond the pandemic is yet to be seen. While the more direct impacts of COVID-19 predominantly affected morbidity and mortality in the elderly, the indirect impacts on non-COVID-19 related pathology are unclear.

Equity and outcomes

As a wider determinant of health, deprivation plays a key role in forecasting patient outcomes at the population level. It is important to acknowledge that deprivation extends beyond low income, to encompass a lack of socioeconomic resources and adverse environmental circumstances to good living. The latest data from the Office for National Statistics suggests that differences in healthy life expectancy at birth between individuals living in the least and most deprived areas amounts to approximately two decades (36). The statistics also show that while overall life expectancy at birth is increasing, the inequality gap between individuals living in the least deprived and most deprived areas is widening as well (36). This is especially alarming for patients suffering from diabetic foot problems as current literature indicates that individuals living in the most deprived areas are at higher risk of receiving a major lower-limb amputation compared to those in the least deprived areas (37). Despite this information, the impact of deprivation is compounded by lower service access and utilization inequities even in countries with established universal healthcare (38).

The current state of diabetic foot care necessitates a renewed and more equitable approach that can adapt to the ever-changing characteristics of the population. Given the rise in amputations amongst the younger and more deprived during the pandemic, this study suggests that current pathways failed to adapt to shifts in healthcare demand. The future brings increasing population demands and patient complexity which requires dynamic care pathways that can respond to the challenges of the time. The current NICE diabetic foot guidelines establish the foundational structures, and processes for services and treatment thresholds for patients while leaving implementation details to the individual partnerships (21). Therefore, it falls upon the partnerships to generate services that go beyond the clinical details and can stratify patients according to wider determinants of health in pursuit of optimal and equitable outcomes for all.

Strengths and limitations

This study sat within a wider desire to expand the understanding of footcare service provision within the SVN and the unique demographic characteristics of the target population in the context of COVID-19. Due to the fact all relevant operations were undertaken at the Royal Sussex County Hospital, it was possible to include all cases of DM-related major lower-limb amputations within the specified period. This eliminates any associated sampling bias thereby improving the internal validity of the results. Findings are likely to be representative of trends within the wider population of England and the UK at large as the data captures all DM-related major lower limb amputations from a population of 1.7 million (8). As the data captures the entire population of patients receiving major lower limb amputation secondary to DFD no sample size calculation was completed. This opens potential for type 2 errors to be present within the findings. This limits the generalizability of the findings to the wider

population as a whole. However, given the congruence of findings from this study and others exploring pandemic related outcomes within the same respective timeframe. The findings are limited to the trends occurring within a year of the COVID-19 pandemic starting. The impact of the COVID-19 pandemic on DM-related major lower-limb amputations would likely extend beyond this period potentially leading to short-sighted findings, however, it is important to note that this study is among the few that investigate the effects of COVID-19 on a specific healthcare outcome alongside underlying trends in demographic data.

Implications

The changes in amputation incidence across age groups and IMD deciles prompts further investigation to develop an understanding of the underlying causes. This should ideally include ethnicity as a confounder to explore its impact. It is also important to explore the impact of the changes to healthcare provision that may have been beneficial to guide future provision. Variation in trends over time also warrants further research of a future period to assess the external validity of this study's findings over time and the impacts of COVID-19 deeper into the pandemic period.

Conclusion

We have demonstrated decreased incidence rates of DM-related major lower-limb amputations within the SVN prior to and during the COVID-19 pandemic compared to previous local and national statistics. COVID-19 driven trends in age group and deprivation characteristics of the reference population highlight the impact of the pandemic on DM footcare service provision. Demographic changes were notably concerning and warrant further investigation into the longer-term impacts of COVID-19. The finding of inequal outcomes between groups of varying deprivation requires specific investigation to ensure equitable provision of services.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

AA: Writing – original draft, Writing – review & editing, Investigation, Resources, Software, Visualization. TR: Writing – review & editing, Data curation, Formal analysis, Supervision. SY: Supervision, Writing – review & editing, Conceptualization. BT: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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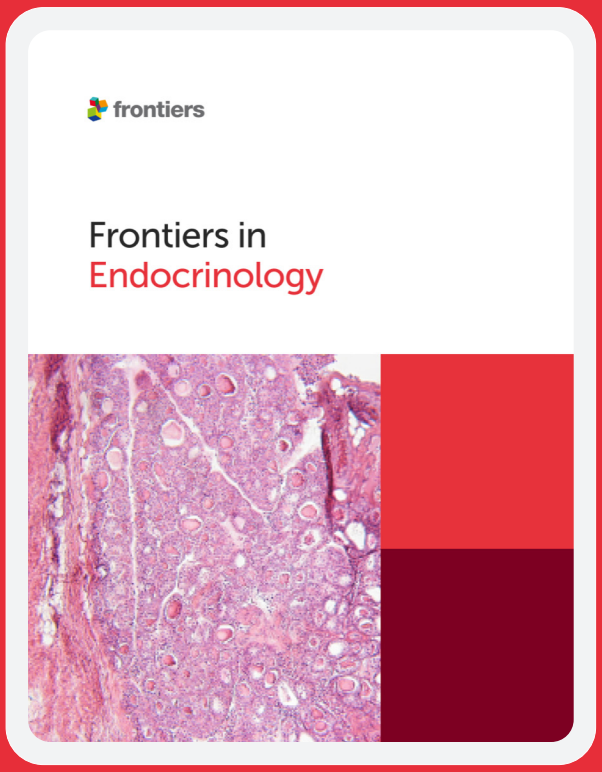

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