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REVIEW ARTICLE

Outcomes of Different Wound Dressings and Offloading Combinations in Diabetic Foot Ulcers: A Systematic Review

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ABSTRAK

Kedua-dua pembalut luka dan pemunggahan adalah penting dalam menguruskan ulser kaki diabetik (DFU). Namun, kajian sistematik yang wujud hanya menilai keberkesanan kedua-dua intervensi secara berasingan. Oleh itu, kajian ini bertujuan untuk memberikan gambaran tentang keberkesanan gabungan antara kedua-dua teknik pembalut luka dan pemunggahan. Kajian sistematik ini dijalankan selaras dengan garis panduan Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) dan telah didaftarkan di PROSPERO (nombor pendaftaran: CRD42024624203) sebelum kajian dimulakan. Empat pangkalan data telah digunakan iaitu PubMed, ScienceDirect, Sage Journal dan Web of Science. Kata kunci yang digunakan termasuk "diabetic foot ulcer", "wound dressing" dan "offloading". Kajian terkawal rawak yang diterbitkan antara tahun 2015 hingga 2024 yang menyatakan jenis pembalut luka dan jenis pemunggahan telah dirangkumkan dalam kajian ini. Pengekstrakan data memberi tumpuan kepada jenis pembalut luka, kaedah pemunggahan dan hasil penyembuhan DFU. Sebanyak 21 kajian telah dirangkumkan. Semua kajian menunjukkan bahawa gabungan pembalut luka dan pemunggahan menghasilkan hasil penyembuhan yang baik dari segi masa penyembuhan, pengurangan saiz luka serta faktor lain seperti kualiti hidup. Kadar penyembuhan lengkap tertinggi (90%) dicapai melalui penggunaan hidrogel perak dan kasut ortotik; manakala masa penyembuhan paling singkat dicapai melalui penggunaan madu dan hidrogel secara alternatif bersama kasut ortotik ($p = 0.004$). Secara keseluruhan, gabungan pembalut luka dan pemunggahan memberi kesan positif kepada proses penyembuhan DFU. Walau bagaimanapun, batasan heterogeniti klinikal seperti perbezaan purata saiz ulser dan bilangan pesakit menyebabkan kesukaran untuk menentukan kombinasi terbaik pembalut luka dan pemunggahan yang paling berkesan.

Kata kunci: *Pemunggahan; teknik pembalut luka; ulser kaki diabetik*

ABSTRACT

Both wound dressings and offloading are important in managing diabetic foot ulcer (DFU). However previous systematic reviews only evaluate the effectiveness of each intervention separately. Therefore, we would like to provide an insight of the combined effectiveness of both wound dressing and offloading techniques. This systematic review is carried out in compliance with the Preferred Reporting

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in Systematic Reviews and Meta-Analyses (PRISMA) and was registered to PROSPERO (registration number: CRD42024624203) prior to starting the review. Four databases were utilised for the review: PubMed, ScienceDirect, Sage Journals and Web of Science. Keywords included "diabetic foot ulcer", "wound dressing" and "offloading". Randomised controlled trials between 2015 to 2024 that specified the type of dressing and type of offloading were included. Data extraction focused on the type of dressings, offloading and healing outcomes of DFUs. 21 studies were included. All studies showed that the combination of dressing and offloading created good healing outcomes in terms of healing time, reduction in wound size and other factors such as quality of life. The highest rate of complete healing (90%) was achieved by using silver hydrogel and orthotic shoes; while the shortest healing time was achieved by using honey and hydrogel alternatively with orthotic shoes (p=0.004). It is clear that the combination of wound dressings together with offloading positively impacts the healing process of DFU. However, as the clinical heterogeneity limitations such as different mean ulcer sizes, number of patients, it is hard to determine the best combination of dressings and offloading.
Keywords: Diabetic foot ulcer; offloading; wound dressings

INTRODUCTION

Diabetes mellitus is a growing global health challenge, with its prevalence projected to rise to 643 million by 2030 and further to 783 million by 2045 (Hossain et al. 2024). This epidemic brings along significant complications, including peripheral vascular disease and diabetic peripheral neuropathy, which contribute to the development of diabetic foot ulcers (DFUs) (Soyoye et al. 2021). According to the recent International Working Group on the Diabetic Foot (IWGDF) Guidelines, DFUs refers to foot ulcers in a person with current or previously diagnosed diabetes mellitus, and it is usually accompanied by peripheral neuropathy and/or peripheral artery disease in the lower extremity (Van Netten et al. 2023). A recent analysis revealed a high lifetime incidence of 19 ~ 34% for DFUs (Guo et al. 2023). DFUs often require extensive and costly treatment, and they are a major cause of morbidity. For example, in Malaysia, managing DFUs incurs annual costs of RM 5981 in public healthcare settings and RM 8581 in private care (Nair et al. 2022), reflecting the substantial economic burden. Furthermore, DFUs have a recurrence rate of 65% within five years and often take more than 3 months to heal, highlighting the chronic nature of the condition (Armstrong et al. 2023).

Current management of DFUs involves a multidisciplinary approach, including glycemic control, infection management, wound care and offloading techniques (Sidhu & Harbuzova 2024). However, despite well-established guidelines, patients face numerous challenges in adhering to treatment plans. These challenges include the complexity of wound care, frequent follow-up visits and loss of mobility, which can impact both patients and their caregivers (Nube et al. 2016). Additionally, diabetes itself impairs normal wound healing mechanisms, such as the hypoxia-inducible factor 1-alpha (HIF-1α)/vascular endothelial growth factor (VEGF) pathway for angiogenesis and the Wnt/β-catenin pathway for keratinocyte generation, further complicating the healing process (Jiang et al. 2023).

Offloadings are one of the cornerstones of the healing of DFUs, given the role of excessive mechanical stress in their development and delayed healing (Bus et al. 2020). Excessive mechanical stress results from the cumulative effects of ambulatory activity over time, shear stress and plantar pressure (Chatwin 2021). This leads to inflammation, ulcer formation and prolonged healing, which increases the risk of infection of the DFUs, hospitalisation and amputation (Lazzarini et al. 2019).

To offload DFUs that are located at the plantar forefoot or midfoot, a non removable knee-high offloading device is the first-choice recommended

treatment (Bus et al. 2020). The second option is a removable knee-high device, followed by a removable ankle-high device as the third choice. Properly fitting footwear combined with felted foam would be considered as a fourth option. If non-surgical offloading methods fail, surgical interventions may be required to heal ulcers on the metatarsal head and toes. Overall, total contact casting (TCC), a specialised offloading technique, has demonstrated superior healing rates, shorter healing times and a significant reduction in ulcer size compared to other devices (Fernando et al. 2022).

Wound dressings play a critical role in the management of DFUs, with conventional dressings, modern dressings and advanced therapies which offer various benefits. Conventional dressings, such as gauze pads and cotton bandages, are simple, cost-effective options commonly used for minor wounds (Shi et al. 2020). In contrast, modern dressings like hydrocolloid, hydrogel and foam dressings provide a more controlled healing environment, better managing moisture and promoting faster healing (Nuutila & Eriksson 2021). For more complex or chronic wounds, advanced therapies such as bioactive matrices and intelligent bandages are increasingly utilised. Bioactive matrices, like collagen-based dressings, stimulate tissue regeneration and aid in the remodelling of the wound bed, while intelligent bandages, equipped with sensors, monitor critical factors such as moisture levels and infection markers, offering real-time data to healthcare providers (Youn et al. 2024).

Despite the significant advancements in these individual modalities, most studies focused on comparing these modalities separately such as wound dressings only or offloadings only (Cai et al. 2024; Chen et al. 2024a; Chen et al. 2024b; de Sousa et al. 2023; Gauna et al. 2024; Jiang et al. 2023; Monami et al. 2024; Nuutila & Eriksson 2021; Racaru et al. 2022; Shi et al. 2020; Tanasescu et al. 2022; Vas et al. 2020; Velasco-Rodríguez-Rabadán et al. 2025; Zhang et al. 2019). There remains limited evidence on the combined use of these dressings and offloading therapies, highlighting a notable gap in the current literature on optimal wound care strategies for DFUs. This review aimed to systematically evaluate the combined effectiveness of wound dressings and offloading techniques in managing DFUs. Considering studies that included a combination of both therapies might be limited and we would like to focus not only the efficacy of the combinations, but also to explore study designs, target populations and common limitations across studies. A systematic review was chosen to explore the objectives instead of a meta-analysis. By exploring the synergy between these two modalities, we sought to highlight their potential to improve clinical outcomes and provide evidence-based recommendations for integrated treatment strategies, which will help to support adherence to the combination of both modalities. This approach could pave the way for more personalised and cost-effective DFU management, benefiting both patients and healthcare systems.

MATERIALS AND METHODS

Search Strategy

This systematic review was carried out in compliance with the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) and was registered to PROSPERO (registration number: CRD42024624203) prior to starting the review. The search was conducted in November 2024. Four databases were utilised in this review: PubMed, ScienceDirect, Sage Journals and Web of Science. Keywords and search strategy used were shown in Table 1.

Eligibility Criteria

The eligibility criteria wee as shown in Table 2, any articles that did not fulfill the criterias were eliminated from the review.

Data Extraction

One reviewer assessed all the identified studies

TABLE 1: The search strategy incorporated the following keywords and search terms, applied through the advanced search settings

Database	Keywords used	Type of articles	Range
Pubmed	(offloading) AND (wound dressing)) AND ((diabetic foot ulcer) OR (DFU))	Randomised controlled trials	10 years
	((total contact cast) OR (TCC)) AND (wound dressing)) AND ((diabetic foot ulcer) OR (DFU))		
Sage Journal	Diabetic foot ulcer AND offloading AND wound dressing		
Science Direct	Diabetic foot ulcer AND offloading AND wound dressing		
Web of Science	((ALL=(offload)) AND ALL=(diabetic foot ulcer)) AND ALL=(wound dressing)		
	(ALL=(total contact cast)) AND ALL=(wound dressing)		

TABLE 2: The inclusion and exclusion criteria for the review

Inclusion Criteria	Exclusion Criteria
Type of studies: Randomised controlled trials	Type of studies: Meta-analysis, systematic reviews, other review articles, non-clinical studies including in vitro studies, animal studies, case reports, clinical trials, research articles
Type of participants: Adults diagnosed with DFU, non-infected ulcers	Non-DFU related articles
Type of intervention: Wound dressing and offloading must be included and specified, not limited to any type	Did not include both dressings and offloading together, or either dressing or offloading not specified
Type of evaluation: The study must contain at least one of the following as an outcome: 1. Healing rates (%) 2. Complete healing time/ time taken for complete closure or epithelisation of ulcer	Others: Articles with no access or incomplete data Non-English articles Duplicated articles

DFU: Diabetic foot ulcers

from the databases by title and abstract to determine the possible eligibility, the data was listed out in an excel sheet and cross checked by two other reviewers. After the screening, the full copy of the articles were reviewed again by all three reviewers according to the inclusion and exclusion criteria. The complete findings were discussed among the reviewers to conclude the final studies included. No attempt was made to pool the result due to the heterogeneity of the articles, which included different study designs, duration of studies and interventions. Categorisation of the data was first done based on the type of dressings (including vacuum dressings topical oxygen therapy) and offloading, other standard of care measurements from the studies were also recorded such as sharp debridement the use of antibiotics.

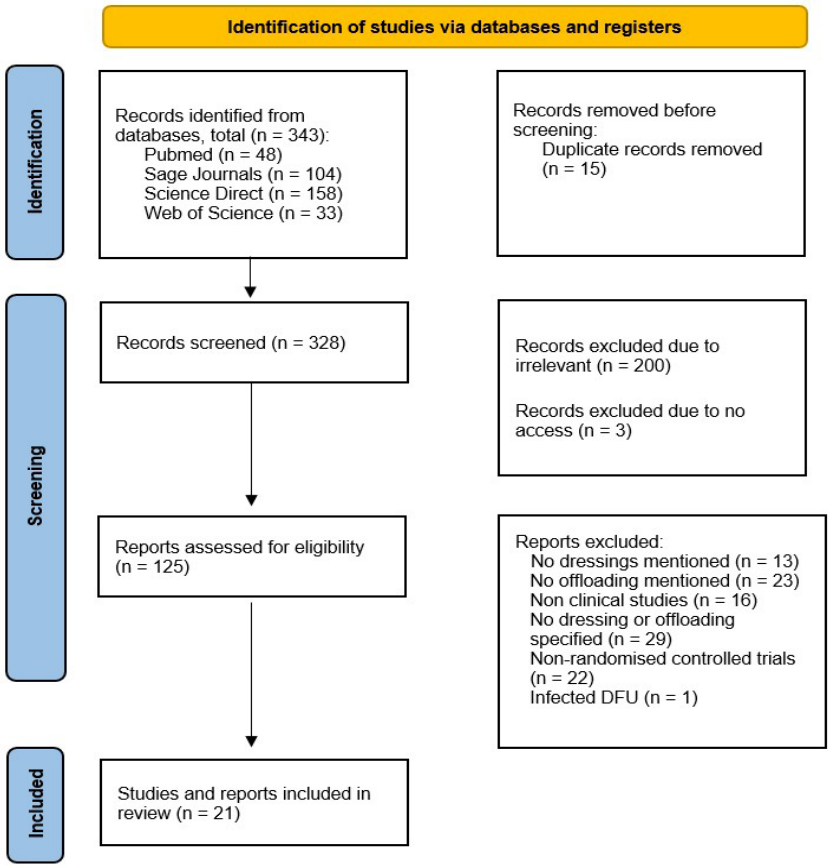

FIGURE 1: PRISMA flowchart

As shown in Figure 1, a total of 343 potential studies were identified from the selected databases, of which 15 studies were duplicates, 200 studies were not relevant. Among the remaining 125 studies, there were 16 non-clinical studies, 13 studies did not mention any type of dressings, 23 did not mention any offloading methods, while 29 studies did not specify the type of dressing and offloading they used. A total of 22 studies were not randomised controlled trials. Subsequently, 21 randomised controlled trials were included in this systematic review. The risk of bias and validity of all studies included were assessed based on the Cochrane risk of bias tool (RoB 2).

RESULTS

Characteristics of Included Studies

Table 3 showed the summarised data of 21 randomised controlled trials articles included in the systematic review. Studies included were published from 2015 to 2024. Majority of the studies were from the United States (12 studies), other studies were done in Australia, Egypt, Korea, Iran, Italy, India and Saudi Arabia. A total of 1971 patients were included from all the articles, with the range of 17 to 307 patients, mean of 89.59. The range of patients' ages were from 28 to 85 years old.

TABLE 3: Summarised intervention and outcomes for randomised controlled trails (RCTs)

Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Driver et al. (2015)	32 sites in USA	1. IDRT (dermal replacement layer, consisting of collagen and chondroitin-6-sulfate) (n = 153) 2. Sodium chloride gel (n = 154)	Active Offloading Walker, boot, and/ or shoe	Dressing-daily	1. Sharp debridement	Active group (51%; 79/154) Control group (32%; 49/153, p=0.001).	Median IDRT - 43 days Control - 78 days (no mean)	Not stated	The rate of reduction in wound size was 7.2% per week for the active group vs. 4.8% per week for the control group (p=0.012).
Gould et al. (2021)	USA	PMVT Collagen alginate	Diabetic cam boot	Dressings - weekly	Follow-up - weekly basis 1/ Wound cleansing with either sterile saline or water 2. Sharp debridement of the index ulcer with a scalpel and/ or curette when indicated 3. Secondary three-layer dressing with felt padding.	PMVT 74% vs Control 38%, p = 0.0003	Mean PWVT (n = 37) : 54 days Control (n = 19): 64 days p = 0.009	PMWT 76% (n = 50) Control 24% (n = 50)	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Tettelbach et al. (2018)	USA	dHACM/ chorion membrane allograft) SOC: Alginate absorbent non-adhesive hydropolymer secondary dressings gauze	Cam walker, offloading boot, shoe, or complete contact cast	Dressings - weekly unless they became wet or soiled. If additional dressing changes were required in the treatment group, only the outer dressings were changed.	2-week study run-in phase: alginate wound dressings and appropriate offloading. ≤25% wound closure after run-in: Randomly assigned to receive weekly dHACM application in addition to offloading or standard of care with alginate wound dressings, for 12 weeks.	70% (38/54) of dHACM vs 50% (28/56) of healed ulcers in the no-dHACM group (P = 0.0338)	Not stated	Not stated	Not stated
Rezaei-Nejad et al. (2023)	Tehran University of Medical Sciences, Iran	Freeze-dried human Amniotic Membrane Allograft Gel placebo: conventional dressing, using a gelatin scaffold without HAM, with the same appearance as the intervention group	Ankle motion walker boots	Follow-up- every 7 ± 2 days dressings - 3 times a week (home), weekly at follow-up after leaving the treatment to remain in place for 48 h.	1. Wound debridement, if required 2. Cleansed with normal saline solution	None	Mean time required for wound healing (> 50% reduction in wound size) LAMG 42 days	Mean reduction in wound sizes LAMG- 73.44% ±15.33% Placebo - 13.19% ±10.19% (P-value=0.008)	<75% LAMG: 66.6% Control 0% p = 0.0043 <50% LAMG: 100% Control: 0% p = 0.0039

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Author	Location	Intervention			Main Healing Outcomes				
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Tettelbach et al. (2019)	Multicentre (11), USA	Dehydrated human umbilical cord (EpiCord) allograft SOC: alginate non-adherent silicone dressing absorbent non-adhesive hydropolymer secondary dressing gauze bandage roll	1.Removable cast walker, if unsuitable and/or not conducive to treatment 2. Standardised TCC kit. **The active offloading walker (boot and/or shoe) or a similar device was used by all subjects throughout the screening/run-in and treatment phases of the study.	Follow-up -weekly . Dressings- minimum weekly or as clinically indicated. Eligible subjects were enrolled in a 14-day run-in period, and the DFU was treated with moist dressings and offloaded using an appropriate sponsor-approved device.	1. Sharp debridement weekly or as deemed necessary by the site investigator.	12 weeks EpiCord- 70% (71/101) Alginate - 48% (26/54) (p = 0.0089) 16 weeks EpiCord- 74 of 101 (73%) Alginat 29 of 54 (54%) (p = 0.0199)	Not stated	Not stated	Healing rates at 12weeks Epicord - 81% (70/86) Alginate 54% (26/48) (p = 0.0013).
Armstrong et al. (2021)	5 Centres, USA	Resorbable glass microfiber matrix (Mirragen) SOC: Collagen alginate dressing (Fibracol) padded three-layer dressing (Dynaflex)	Removable diabetic cam-walker/ TCC Dispensed diabetic shoes and insoles provided by the sponsor at the study exit.	Dressings Mirragen- weekly SOC- performed per indication and occurred on the weekly visits, and if the dressing was saturated, re-application was performed at that time.	1. Glucose monitoring 2. Weekly debridements when needed	14 of 20 wounds (70%) healed in the BBGFM group compared with 5 of 20 (25%) in the SOC group (unadjusted p = 0.004)	Not stated	Mean PAR at 12weeks was 79% in the BBGFM group compared with 37% in the SOC group (adjusted p = 0.027)	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Khalid et al. (2024)	Single centre, USA	Synthetic electrospun fiber matrix SOC: Heavily exudating wounds- alginate dressings minimal exudate - foam dressings	Run in period: DFU (DJO cam walker boot) Treatment: controlled ankle movement boot (or equivalent shoe) according to their instructions for use	Foam or alginate dressings- weekly	1. Sharp debridement 2.Wound cleaned: sterile saline	SEFM- 56 % (14/25) SOC - 29 % (6/21)	SEFM -6.6 3.0 weeks SOC - 7.0 2.7 weeks mean number of applications of SOC and SEFM required to achieve closure in the SEFM Group was 7.0 ± 3.7	Mean PAR SEFM- 65% SOC- 58 %	Not stated Reductions of wound area at 4 weeks posttreatment mean : 87%, median: 100%.
Alvarez et al. (2017)	Single centre, USA	Porcine urinary bladder-derived extracellular matrix (UBM) SOC: nonadherent (siliconised) medical-grade foam (Mepilex)	Traditional TCC : minimally padded, well-molded, and rigid (plaster plus fiberglass)	Dressing change and Recasting was applied at each visit (weekly) for 16 weeks or until healing was achieved.	No other SOC	Incidence of wound healing at 12 and 16 weeks was 90% and 100%, respectively, compared with 33% and 83.3% in the control (p = 0.062)	Mean time to healing in the UBM-treated group was 62.4 days compared with 92.8 days in the control group (p = 0.031)	Not stated	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Niederauer et al. (2018)	Single centre, USA	Topical oxygen therapy Foam Alginate	Offloading walker boots	Follow-up - weekly Between visits, the study device was used continuously (24 hours per day, 7 days per week) and dressings were changed as needed by the subjects themselves or a relative/friend	1. Surgically debridement - min weekly, but number not limited 2. wound cleansing	Full ulcer closure - CDO 46.2% -s Placebo - 22.6% Randomised in the study: 32.4% CDO and 16.7% placebo.	The time to 50% DFU closure was significantly shorter in patients that received CDO therapy (mean 18.4 versus 28.9 days, p = 0.001).	There was increasing significant beneficial effect of the CDO arm at 25%/40% PWAR (p=0.017) and 20%/30% PWAR (p = 0.008).	Not stated
Driver et al. (2017)	Multicentre (22), USA, Puero Rico, Canada	Topical oxygen therapy Hydrocolloid Alginate Foam	Offloading boots	Dressing - weekly Change of the spent TCOT device - every other week	1. Wound cleansing 2. Wound debridement	ITT TCOT - 35 out of 65 Control - 31 out of 63 (p = 0.4167) PP TCOT - 34 out of 61 (56%) Control - 31 out of 61 (49%)	Median time to complete closure in the PP group was 63 days for the TCOT and 77 days for the control group (p > 0.05).	Not stated	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Serena et al. (2021)	Multicenter (19), USA	Topical oxygen therapy hydrofibre alginate	TCC	Based on exudate level or clinical judgement.	SOC : 1. Wound cleansing with sterile water or saline solution, and gentle irrigation with warm tap water 2. Sharp debridement using a standardised protocol based on TIME principles for wound bed preparation 3. Offloading with a TCC twice in the first week and weekly thereafter (all exceptions had to be agreed by the lead investigator; a fixed ankle walker boot or similar device was acceptable as an alternative, but shoe inserts were not deemed to provide sufficient offloading) 4. Moisture balance with hydrofibre or alginate dressing.	18/64 (28.1%) patients healed in the SOC group at 12 weeks compared with 36/81 (44.4%) in the SOC plus TOT group (p = 0.044).	Not stated	Percentage reduction in ulcer area (cm^2) SOC vs SOC+TOT Mean ± SD 41.05 ± 69.82 46.38 ± 100.24 Minimum, maximum-160.38, 100-487.52, 100 A statistically significant reduction in wound area between the groups: SOC group mean reduction: 40% (SD 72.1); SOC plus TOT group mean reduction: 70% (SD 45.5); per protocol p = 0.005	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Lavert et al. (2019)	Multicenter (34), USA	Topical oxygen therapy vs placebo device single foam (XTRASORB Foam) calcium alginate (MAXORB extra wound dressing) for excessive exudate	DH offloading walker	Dressings - weekly	1. Wound cleansing 2. Moist wound care 3. Offloading 4. Aggressive surgical debridement.	A significantly higher proportion (204%) of ulcers healed in the CDO group compared with the placebo (46.2% vs. 22.6%, respectively; p = 0.016). The relative performance of active CDO over placebo became greater when frequent debridement was used (51.2% vs. 21.3%, respectively; p = 0.006).	Not stated	Not stated	Not stated
Vangaveti et al. (2023)	Single centre, Australia	ESWT SOC: Melipex® XT foam	Cushioning insoles and foam dressings with a hole on the ulcer site were applied	Not stated	Sharp debridement	At 6 weeks a total of 11 out of 48 ulcers were healed with 6 out of 23 (26.1%) in the SOC group and 5 out of 25 in the (20.0%) in the ESWT +SOC, p = 0.73.	Not stated	The average percentage reduction in wound surface area in the SOC group was 5.05 136.7 and 36.08 46.72 mm2 in the ESWT +SOC group, p = 0.33. reduction in ulcer size at 6 weeks ESWT 18 (86%) patients without ESWT. 14 (70%)	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Park et al. (2019)	Single center, Korea	Porcine type I collagen SOC: Foam	Offloading shoe with rigid-rocker sole Collagen 13 (76.5) SOC 10 (76.9) Splint Collagen 3 (17.6) SOC 2 (15.4) Wheelchair Collagen 1 (5.9) SOC 1 (7.7)	Dressing changes- two or three times per week	Wound cleaned with saline solution	The collagen group had a significantly higher proportion of patients who achieved complete healing compared with the control group (82.4% (14/17) versus 38.5% (5/13), respectively; P = .023,	The median time to complete ulcer healing was also significantly shorter in the collagen group compared with the control group (63 days versus not reached,	The mean size reduction was also greater in the collagen group compared to the control group (4.39 ± 4.95 cm^2 versus 2.24 ± 2.81 cm^2, respectively; p = 0.027	Mean ± SD (cm^2/week) Collagen 0.55 ± 0.44 Control 0.29 ± 0.42 p-value 0.001
Park et al. (2018)	Multicenter (6), Korea	Polyurethane foam dressings with sprays (Topical epidermal growth factor)	Offloading shoe with rigid-rocker sole rhEGF 64 (78.0) Placebo 65 (76.5) Splint rhEGF 14 (17.1) Placebo 15 (17.6) Wheelchair rhEGF 4 (4.9) Placebo 5 (5.9)	Offloading shoe with rigid-rocker sole rhEGF 64 (78.0) Placebo 65 (76.5) Splint rhEGF 14 (17.1) Placebo 15 (17.6) Wheelchair rhEGF 4 (4.9) Placebo 5 (5.9)	1. Wound debridement-weekly at the investigator's discretion.	rhEGF 73.2% (60/82) Control 50.6% (43/85)	median time to complete ulcer healing rhEGF group 56 days) placebo group (84 days) P < 0.001	Mean ulcer size reduction rhEGF group (2.47 ± 2.53 cm^2) placebo group (1.75 ± 2.91 cm^2 (p = 0.028)	rhEGF group compared with the placebo group (18.41 ± 13.09% per week versus 12.81 ± 13.86% per week, respectively; p = 0.029)

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Armstrong et al. (2022)	Multi-centre, USA	Cryopreserved bioactive split thickness skin allograft (BSA) (TheraSkin) SOC: Collagen alginate dressing padded three-layer dressing (Dynaflex)	None, Felt, Shoe, Shoe + felt, Camboot or equivalent, TCC, Wheelchair Screening: CAM boots or total contact casting (TCC) if the subject's foot is too large for a CAM	Not stated	1. Glucose monitoring 2. Weekly debridement's as appropriate	76% (38/50) of the BSA-treated DFUs healed compared with 36% (18/50) treated with SOC alone (adjusted p = 0.00056)	The average time for closure within the 12-week period BSA was 46.9 days (95% CI: 38.7 ± 55.1) closure with SOC was 65.3 days (95% CI: 57.7 ± 72.9). (p = 0.0019).	Mean PAR at 12 weeks was 77.8% in the BSA group compared with 49.6% in the SOC group (adjusted p = 0.0019)	Not stated
Essa etal. (2023)	General Surgery Department of Benha University Hospital, Egypt	SilvrSTAT Gel dressing wet-to-moist dressing with or without povidone-iodine	Shoe orthoses	SilvrSTAT Gel : every 72 hours. The dressing was done for up to 12 weeks or stopped if the ulcer healed. Wet gauze pads: daily	All patients were instructed to visit our clinic at scheduled sessions twice weekly for a maximum follow-up period of 12 weeks.	Group A 36 (90%) Group B 31 (77.5%) < 0.001	Not stated	Not stated	Ulcer healing rate per week (area over time) Group A 0.68 ± 0.07 Group B 0.47 ± 0.04 p-value < 0.0001

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Motawea et al. (2019)	Mansoura diabetic foot clinic, Egypt	1. PHT-NLC-hydrogel - nanostructured lipid carriers (NLCs) of phenytoin (PHT) 2. Phenytoin hydrogel (0.5%w/v) 3. Blank hydrogel	Cast shoes	Dressings - weekly	1. Weekly sharp debridement 2. Wound cleansed with sterile isotonic saline.	Blank 34.91 ± 28.33 PHT 47.10 ± 4.23 NLC 95.82 ± 2.22	Not stated	Not stated	Not stated
Sahu et al. (2018)	outpatient department of VIMSAR, Burla, India	Povidone iodine soaked gauze pad (n = 16)	TCC (n = 15)	Dressing - every 2 days	1. Wound debridement 2. Wound cleansed with saline	Not stated	12 of 15 ulcers healed in 48 ± 7 days; in the TD group, 10 of 16 ulcers healed in 58 9 days.	Not stated	Not stated

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Author	Location	Intervention				Main Healing Outcomes			
		Dressing	Offloading	Frequency	Other standard of care mentioned	% of complete closure/ healing rates	Healing Time	Ulcer size reduced/ Percent wound area reduction	Rate of reduction/ healing velocity
Searan et al. (2024)	Diabetic Foot Center, King Fahad Specialist Hospital Al Qassim-KSA, Saudi Arabia	Fucidin (control) (n = 30) Hydrogel alone (n = 30) Honey alone (n = 37) Honey & Hydrogel (n = 37)	Local = wool felt foam 7 mm hypoallergenic adhesive sheet. Orthotic Medical Shoes = forefoot offloading healing shoes = Diabetic heel wedge healing shoes.	First, second, and fourth groups dressings- daily basis third group- alternately (1 day honey was applied, and on the second-day hydrogel was used).	1. Surgical debridement 2. Empiric antibiotic amoxicillin/ clavulanic acid (625 mg per os 8 h) based on the empiric antibiotic regime for diabetic foot infection until the results of wound culture.	Not stated	Mean healing times Total 12.76 +4.08 days honey alone 12.20, hydrogel alone 13.97 honey and hydrogel alternately 10.83 days control Fucidin ointment or cream 14.03 days (p= 0.004)	Not stated	Not stated
Piaggesi et al. (2024)	Multicentre (5), Italy	Inert hydrofiber dressing	1. TCC 2. Walking boot rendered irremovable 3. Removable walking boot	Dressing - weekly	Sharp debridement of the ulcer	19 (95%) - group A 18 (90%) - group B 16 (80%) - group C	37.0 + 21.6 days- group A 39.6 + 12.2 days - group B 43.2 + 15.1 days - group C (p = 0.5579)	Not stated	Not stated

BBGFM: Resorbable glass microfiber matrix; CDO: Continuous diffusion of oxygen; DFU: diabetic foot ulcer; dHACM: Dehydrated human amnion; HAM: Human amniotic membrane; ESWT: Extracorporeal shockwave therapy; IDRT: Integra dermal regeneration template; NLC: Nanostructured lipid carriers; PAR/PWAR: Percentage of wound area reduction; PHT: Phenytoin; PMVT: Processed microvascular tissue allograft; rhEFGF: Recombinant human epidermal growth factor; SD: Standard deviation; SEFM: Synthetic electrospun fiber matrix; SOC: Standard of care; TCC: Total contact casting; TD: Traditional dressing; TCOD/TCOT: Transdermal continuous oxygen delivery; TOT: Topical oxygen therapy; UBM: Urinary bladder-derived extracellular matrix

(A) Characteristics of DFU and Related Clinical Conditions

The DFU from the studies were categorised based on Wagner Classification and University of Texas Wound Classification System as seen in Figure 2. A total of 10 studies (45.45%) used Wagner classification for their ulcers, where seven studies involved both Grade 1 and 2, two studies for Grade 1 and one study for Grade 2. Seven studies (31.82%) utilised University of Texas Wound Classification System of DFU, with five studies involving DFU with Texas Grade 1A, one study used Texas IA or II A and one study used Texas IA or higher. Four studies (18.18%) did not specify the type of DFUs with any of the classifications. Therefore, the ulcers involved in the randomised control trials (RCTs) were mostly superficial ulcers, without exposure to bone or tendon; and without presence of gangrene, abscess or osteomyelitis.

Other descriptions of ulcers and clinical conditions involved in the studies were documented in Table 4. The mean surface area of the DFUs were relatively small, ranging from 1.12 cm^2 to 12.85cm^2. Only DFUs that were at least 4 weeks of duration were selected for the clinical trials. For studies that specified the location of ulcers, only ulcers at and below the level of malleoli were selected. However, not all duration of ulcer was documented in the studies as shown in Table 4. Plantar ulcers were more common than dorsum ulcers, while in most studies, forefoot ulcers had a higher prevalence than midfoot, hindfoot and ankle ulcers except for (Searan et al. 2024). Only one study reported the level of exudates into heavy, moderate low and described the types of exudates of the ulcers (Serena et al. 2021)

Any conditions that might cause a relatively suppressed immune system such as autoimmune disorders, history of immunosuppressants, radiotherapy, chemotherapy, Acquired Immunodeficiency Syndrome (AIDS) and malignancy were excluded in most of the studies. Adequate perfusion to the lower limb had been objectively defined by most of the studies as an inclusion criteria, which usually included one or more of the following: (i) ankle/brachial index (ABI) >0.7; (ii) Doppler ultrasound findings of biphasic or triphasic waveforms in the foot pulses; (iii) toe systolic pressure > 50 mm Hg;

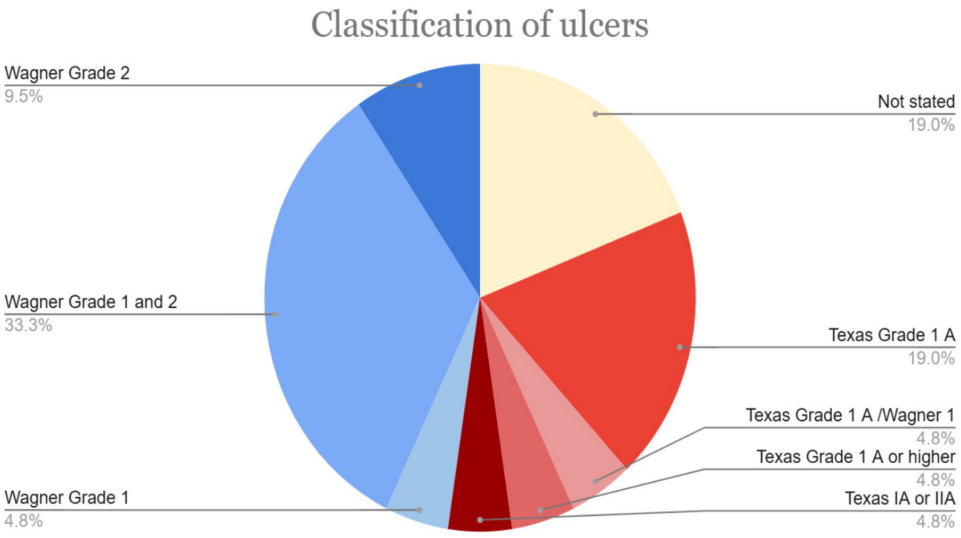

FIGURE 2: Classifications of ulcers involved in the study

TABLE 4: Patients and types of ulcers

Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Driver et al. (2015)	307 patients Mean age (SD): 55.8 (10.6)	Wagner Grade 1 and 2	Ulcer size (cm^2, SD) 1 to 12 cm^2 post debridement Ulcer duration: ≥30 days	Active/Control/Total Calcaneal (%) 0 /2(1.3)/2 (0.7) Forefoot (%) 109 (70.8)/93 (60.8)/202 (65.8) Midfoot (%) 33 (21.4)/40 (26.1)/73 (23.8) Hindfoot (%) 12 (7.8)/18 (11.7)/30 (9.8)	Adequate vascular perfusion as defined by ankle-brachial index ≥0.65 and ≤1.2 or toe pressure >50 mmHg or $TcPO_2$ >40 mmHg or doppler ultrasound consistent with adequate blood flow to the affected extremity	Not mentioned
Gould et al. (2022)	100 patients: Mean age (SD): PMVT: 59.4 (13.22) Control: 61.2 (9.79)	Wagner Grade 1 and 2 PMWT W1 n = 26 W2 n = 24 Control W1 n = 17 W2 n = 33	Ulcer size: (cm^2 SD) PMVT: 3.1 (3.4) Control: 3.5 (2.3) Ulcer duration: ≥4 and <52 weeks	Plantar: NPWT n= 41 Control n=35 NPWT: Toe 13 Forefoot 17 Midfoot 10 Hindfoot 1 Heel 8 Ankle 1 Control: Toe 7 Forefoot 14 Midfoot 13 Hindfoot 2 Heel 8 Ankle 6	Adequate circulation to the affected foot as demonstrated by a dorsal TCOM or a SPP measurement of ≥30 mmHg or an ankle brachial index (ABI) between 0.7 and 1.3, biphasic dorsalis and posterior tibial vessels on arterial Doppler ultrasound toe brachial index (TBI) >0.6 within three months prior to study enrollment	1. End stage renal disease as evidenced by a serum creatinine >3.0 mg/dL within last 120 days of randomisation. 2. Recent use of immunosuppressants

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Tettelbach et al. (2019a)	98 patients: Mean age (SD)/Range Overall 57.2 (10.5) /56.9 (34, 83) dHACM 57.4 (10.6)/55.9 (34, 80) Control 57.1 (10.5)/57.2 (34, 83)	Not stated	Ulcer size (cm^2, SD) dHACM 3.2 (2.8) Non dHACM 3.9 (3.8) Ulcer duration, weeks (SD) dHACM 20.8 (18.5) Non dHACM 21.4 (15.8)	dHACM: Toe 17 ForeF 27 MidF8 HindF 8 Control: Toe 4 ForeF 30 MidF 8 HindF 7	Adequate circulation to the affected extremity as demonstrated by dorsum transcutaneous oxygen test ($TcPO_2$) ≥30 mmHg, ABI between 0.7 and 1.2, or triphasic or biphasic Doppler arterial waveforms at the ankle of affected leg	1. Recent history of immunosuppressant, radiotherapy or chemotherapy treatment 2. Immune system related disorders such as autoimmune diseases 3. Pregnancy or breastfeeding
Rezaei-Nejad et al. (2023)	18 patients: Mean age (SD): control group 60.24 (1.83), Intervention group 58.19 (4.49) Range: 35 to 65 years old	Wagner Grade 2	Ulcer size (cm^2) LAMG group: 4.04 cm^2 Placebo group: 3.97 cm^2 Ulcer duration: ≥3 months, <12 months	Intervention: Plantar 5 Dorsum 4 Control: Plantar 4 Dorsum 5	Presence of dorsalis pedis and posterior tibialis pulses (ABI ≤0.90)	1. Major surgical intervention on the wound site (e.g. revascularisation procedure, tissue grafting) within the past 3 months 2. History of coagulation disorders, immunodeficiency, and allergies 3. Recent history of immunosuppressant, radiotherapy or chemotherapy treatment 4. Pregnancy or breastfeeding
Tettelbach et al. (2019b)	101 patients: Mean age (SD): EpiCord: 58.3 (10.9) Alginate: 56.3 (10.2) Age ≥65 years (n, %) EpiCord: 28 (27.7%) Alginate: 10 (18.5%)	Not stated	Ulcer size (cm^2), post-debridement EpiCord: 2.6 (SD: 2.2) Alginate: 2.8 (SD: 2.6) Ulcer duration Mean (SD) weeks Epicord 20.5 (13.7) Alginate 20.3 (13.2)	Located below ankle Epicord: Toe 12 ForeF 58 MidF 20 HindF 9 Alginate: Toe 12 ForeF 27 MidF 9 HindF 3	Adequate circulation to the affected extremity	1. Recent history of immunosuppressant, radiotherapy or chemotherapy treatment 2. End stage renal disease: on dialysis or planning to start dialysis 3. Immune system related disorders such as SLE and HIV

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Armstrong et al. (2022b)	40 patients: Mean age (SD) BBGFM 61.0 (13.81) SOC 64.3 (9.32)	Texas Grade 1 A/Wagner 1	Ulcer size (cm^2) BBGFM 3.5 (2.07) SOC 5.2 (4.67) Ulcer duration (weeks) BBGFM 23.0 (18.45) SOC 16.5 (16.73)	Below the malleoli of the ankle BBGFM: Toe 1 ForeF 5 MidF 9 HindF 5 SOC: Toe 1 ForeF 7 MidF 7 HindF 5	Subject has adequate circulation to the affected extremity, as demonstrated by one of the following within the past 90 days: Dorsum TCOM ≥30 mmHg; or ABI with results of ≥0.7 and ≤1.3 in conjunction with Doppler arterial waveforms, which are triphasic or biphasic at the ankle of affected leg	1. Recent history of immunosuppressant or local radiotherapy on ulcer site 2. Presence of any condition(s) which seriously compromises the subject's ability to complete this study or has a known history of poor adherence with medical treatment. 3. Pregnancy or breastfeeding
Husain et al. (2024)	37 patients: Mean age (SD) All: 66.9 (12.1) SEFM: 66 (13.5) SOC: 68.1 (10.4)	Not stated	Ulcer size (cm^2) Mean (SD): All : 6.3 (9.8) cm^2 SEFM: 3.9 (5.1) cm^2 SOC: 9.2 (13.1) cm^2 Ulcer duration (weeks) ≥ 28 days	At least in part on the foot or ankle	Patient has adequate circulation to the affected extremity as demonstrated by at least one of the following within 60 days prior to enrollment/ randomisation: (a) Dorsum Transcutaneous oxygen test ($TcPO_2$) of study leg with results ≥40 mmHg, OR (b) ABI of study leg with results of ≥0.7 OR (c) TBI of study extremity with results of >50 mmHg	1. Recent history of immunosuppressant, radiotherapy or chemotherapy 2. Known history of poor adherence with medical treatment. 3. Immune system related disorders such as autoimmune disorders 4. Active cancer 5. Known allergy to resorbable suture materials, e.g. Polyglactin 910, Polydioxanone 6. Pregnancy or breastfeeding

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Alvarez et al. (2017)	17 patients: Mean age: UBM 57.5 Control: 55.2	Texas Grade 1 A	Ulcer size (cm^2) Mean: 12.85 cm^2 Ulcer duration 5.2 months	Had to be on the plantar surface of the foot	The subject had to have adequate arterial circulation to the foot as determined by an ABI >0.75, TBI >0.65, or toe systolic pressure >50 mmHg.	1. History of other advanced wound therapy (e.g. autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, ECM) or received topical collagenase 2. Recent history of immunosuppressant, radiotherapy or chemotherapy 3. Active cancer 4. Pregnancy or breastfeeding
Niederauer et al. (2018)	146 patients: Mean age (SD) 56.3 (12.4) years	Texas Grade 1 A	Ulcer size (cm^2, SD) after debridement CDO 3.54 (1.68) Placebo 3.89 (2.02) Total 3.71 (1.85) Ulcer duration (days, SD) CDO 131.6 (89.2) Placebo 143.8 (97.7) Total 137.6 (93.4)	DFU at or below the malleoli	Adequate arterial perfusion defined as one or more of the following: - Transcutaneous oxygen measurements of the dorsum of the foot >30 mmHg with a skin perfusion pressure >30 mmHg - An ABI >0.7, with documented confirmation of adequate arterial perfusion - A Doppler waveform consistent with adequate flow in the foot (biphasic or triphasic waveforms) at screening - Absolute toe pressure of >30 mmHg	1. End stage renal disease 2. Recent history of immunosuppressant, radiotherapy or chemotherapy 3. Active cancer 4. Pregnancy or breastfeeding 5. History of alcohol or substance abuse within 6 months of screening

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Driver et al. (2017)	122 patients: Mean age: 59 years (range 28 - 85 years)	Texas Grade 1 A	Ulcer size (cm^2, SD) Control: 2.3 (1.7) cm^2 (range 0.4 - 8.9 cm^2) TCOT: 2.0 (1.7) cm^2 (range 0.6 - 8.7 cm^2) Ulcer duration: ≥4 and <52 weeks	At or below the malleoli	Patients with ABI ≥0.7 on the study limb; $TcPO_2$ >40 mmHg; a toe pressure 40 mmHg; or a Doppler waveform consistent with adequate flow in the foot (biphasic or triphasic waveforms) at screening also were included	1. Presence of charcot foot 2. History of antibiotics use within 48 hours of baseline 3. Recent history of immunosuppressant, radiotherapy or chemotherapy 4. History of other advanced wound therapy (e.g., autologous platelet-rich plasma gel, becaplermin, bilayered cell therapy, dermal substitute, ECM) 5. End stage renal disease 6. Pregnancy
Serena et al. (2021)	145 patients: Mean age (SD) SOC 62.69 (12.56) SOC + TOT 64.20 (14.15) Minimum, maximum age SOC 34, 91 SOC + TOT33, 93	Wagner Grade 1 and 2	Ulcer size (cm^2) Mean (SD) SOC: 3.47 (4.12) SOC + TOT: 0.5, 21.93 Ulcer duration: SOC: 23.77 (17.85) weeks SOC + TOT: 24.46 (22.62) weeks	SOC: Ankle 1 Dorsal 12 Heel 9 Hindfoot 1 Midfoot 5 Plantar 25 Toes 11 SOC + TOT: Ankle 2 Dorsal 16 Heel 9 HIndfoot 2 Midfoot 6 Plantar 34 Toes 12	Adequate circulation to the foot, defined as a dorsum TCOM or a SPP measurement of ≥30 mmHg, an ABI between 0.7 and 1.3, or a TBI of >0.6 within the three months before the first screening visit	1. Immune system related disorders such as autoimmune disorders 2. End stage renal disease and other significant medical conditions such as serious cardiovascular, renal, liver or pulmonary disease, palliative care or sickle cell anaemia 3. History of other advanced wound therapy (engineered tissue or other scaffold materials) 4. Recent history of immunosuppressant or chemotherapy

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Lavery et al. (2019)	146 patients: Mean age (SD): 56.3 (12.4) years	Texas Grade 1 A	Ulcer size (cm^2, SD) All = 3.71 (1.85) Site X (significantly less debridement): 4.39 (1.97) Other sites: 3.59 (1.82) Ulcer duration: 30 to 365 days	NIL	Adequate arterial perfusion defined as one or more of the following: - TCOM of the dorsum of the foot >30 mmHg with a skin perfusion pressure >30 mmHg - An ABI >0.7, with documented confirmation of adequate arterial perfusion - A Doppler waveform consistent with adequate flow in the foot (biphasic or triphasic waveforms) at screening - Absolute toe pressure of >30 mmHg	1. End stage renal disease 2. Recent history of immunosuppressant, radiotherapy or chemotherapy 3. Active cancer 4. Pregnancy or breastfeeding 5. History of alcohol or substance abuse within 6 months of screening
Vangaveti et al. (2023)	48 patients: Mean age (range) SOC: 62 (52-79) ESWT + SOC: 62 (52-78)	Texas Grade 1 A or higher	Ulcer size (mm^2) SOC 48 (20 - 408) ESWT + SOC 70 (25 - 226) Ulcer duration (weeks) Overall 8.5 (2.2 - 47.5) SOC 7.5 (1.7 - 47.5) ESWT + SOC 8.5 (3.7 - 55.2)	NIL	PVD was not an exclusion criteria. Seven patients (31.8%) of the intervention group and 8 patients (33.3%) from the control group had PVD, where two patients from each group underwent vascular surgery due to PVD	1. Immune system related disorders such as autoimmune disorders 2. End stage renal disease and other significant medical conditions such as serious cardiovascular, renal, liver or pulmonary disease, aplastic anemia, chronic inflammatory diseases 3. Active cancer 3. History of specific wound therapies: hyperbaric oxygen and enzymatic debridement

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Park et al. (2019)	39 patients: Mean age (SD) Collagen: 62.8 (13.0) SOC: 53.0 (14.7)	Wagner Grade I Collagen 16 (94.1) SOC 13 (1 0 0) Grade II Collagen 1 (5.9) SOC 0	Ulcer size (cm^2, SD) Collagen 4.98 (6.59) SOC: 4.49 (6.56) Ulcer duration: >6 weeks without any sign of healing	SIte Collagen Control Toe 3 (17.6) 2 (15.4) Interphalangeal area 1 (5.9) 1 (7.7) Sole 6 (35.3) 5 (38.4) Heel 4 (23.5) 3 (23.1) Malleolus 2 (5.9) 1 (7.7) Other 1 (5.9) 1 (7.7)	Adequate distal extremity arterial flow, defined as either transcutaneous partial pressure of oxygen (TcPO2) 30 mm Hg or palpable pulses at either the dorsalis pedis artery or posterior tibial artery of the ankle	1. Immune system related disorders such as autoimmune disorders 2. End stage renal disease and other significant medical conditions such as serious cardiovascular, renal, liver or pulmonary disease, malnutrition 3. Active Cancer 4. History of other advanced wound therapies(growth factors or bioengineered tissue products) 5. Recent history of immunosuppressant, radiotherapy or chemotherapy 6. Charcot arthopathy 7. Pregnancy
Park et al. (2018)	167 patients: Mean age (SD) rhEGF: 56.52 (12.71) Placebo: 59.31 (12.64)	Wagner Grade 1 and 2 rhEGF / Placebo Grade I : 46 (56.1)/ 45 (52.9) Grade II: 36 (43.9)/ 40 (47.1)	Ulcer size (cm^2) Mean (SD) rhEGF 2.80 (3.72) Placebo 2.35 (2.69) Ulcer duration: >4 weeks without any sign of healing	rhEGF vs Placebo Toe 34 (41.5) 36 (42.4) Interphalangeal area 3 (3.7) 2 (2.4) Sole 13 (15.9) 9 (10.6) Heel 3 (3.7) 12 (14.1) Malleolus 9 (11.0) 6 (7.1) Other 20 (24.4) 20 (23.5)	Adequate distal extremity arterial flow, defined as either transcutaneous partial pressure of oxygen (TcPO2) ≥30 mmHg or palpable pulses at either the dorsalis pedis artery or the posterior tibial artery of the ankle	1. Immune system related disorders such as autoimmune disorders 2. End stage renal disease and other significant medical conditions such as serious cardiovascular, renal, liver or pulmonary disease, malnutrition 3. Active cancer 4. History of other advanced wound therapies (growth factors or bioengineered tissue products) 5. Recent history of immunosuppressant, radiotherapy or chemotherapy 6. Charcot arthropathy 7. Pregnancy

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Armstrong et al. (2022a)	100 patients: Mean age (SD) BSA: 61.2 (12.55) SOC: 60.0 (10.99)	Wagner Grade 1	Ulcer size (cm^2) BSA: 4.2 (7.8) Median: 2.2; IQR: 3.4 SOC: 3.9 (5.22) Median: 1.9; IQR: 3.1 Ulcer duration (weeks) BSA: 17.5 (11.06) SOC: 15.5 (13.20	BSA vs SOC Plantar 35 (70) vs 45 (90) Dorsal 15 (30) vs 5 (10) DFU location Toe 8 (16) vs 5 (10) Forefoot 18 (36) vs 22 (44) Midfoot 15 (30) vs 17 (34) Heel 7 (14) vs 5 (10) Ankle 2 (4) vs 1 (2)	Adequate circulation to the affected foot as documented by a dorsal TCOM or a SPP measurement of ≥30 mmHg or an ABI between 0.7 and 1.3 within 3 month old of screening using the affected study extremity. As an alternative, arterial Doppler ultrasound can be performed evaluating for biphasic dorsalis pedis and posterior tibial vessels at the level of the ankle or a TBI of >0.6 is acceptable	1. Recent history of immunosuppressant, radiotherapy or chemotherapy 2. End stage renal disease: evidenced by a serum creatinine ≥3.0 mg/dL within 6 months of randomisations. 3. Pregnancy or breastfeeding
Essa et al. (2023)	80 patients: Mean age SD (range) SilvrSTAT 55.8 (2.38) (52-60) Conventional 54.64 (3.54) (50-60)	Wagner Grade 1 and 2	Ulcer size (cm^2), mean (SD) SilvrSTAT 7.8 (1.3) Conventional 7.21 (1.16) Volume of the ulcers (cm^3), mean (SD) SilvrSTAT 1.952 (0.67) Conventional 1.91 (0.38) Ulcer duration (weeks): > 6 weeks	Silver vs conventional Dorsum mid-foot 9 5 Dorsum fore foot 9 15 Planter hind foot 5 3 Planter fore foot 4 2 Planter mid-foot 13 1	Presence of revascularized nonischemic DFUs after successful bypass surgery or endovascular intervention are accepted	1. Recent history of immunosuppressant, radiotherapy or chemotherapy 2. End stage renal disease and other significant medical conditions such as serious cardiovascular, renal, liver or pulmonary disease, malnutrition 3. Known allergy to silver 4. Active cancer
Motawea et al. (2019)	27 patients: Mean age (SD): 58 (8.7) years	Not stated	Ulcer size (cm^2, SD) Blank 5.36 (2.14) PHT 3.94 (1.86) NLC 5.50 (3.66) Ulcer duration: Not stated	below the metatarsal heads	Ankle brachial pressure index <0.9 were excluded	Chronic kidney disease, immunosuppression and serious coagulopathies

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Authors (year)	Patients	Classification of ulcers	Ulcer mean size and duration	Location of ulcer	Vascular status	Other clinical conditions
Sahu et al. (2018)	31 patients: Mean age: 60 ± 7.52 years.	Wagner Grade 1 and 2	Ulcer size (cm^2) Not stated Ulcer duration: Not stated	NIL	Not mentioned, but vascular assessment was done for patients	No ambulation
Searan et al. (2024)	120 patients: Mean age (SD): 59.65 (7.10) Range: 29 and 58 years Patients <60 years: n=87 (47.8%)	Wagner Grade 2	Ulcer size (cm^2) Mean 1.12 (1.27) Ulcer duration: Not stated	NIL	No peripheral vascular disease	1. Unstable or severe conditions that require hospitalisation 2. Charcot arthropathy
Piaggesi et al. (2016)	60 patients: Mean age (SD) TCC: 61.4 (9.7) i-RWD: 59.8 (7.9) RWD : 62.3 (9.2)	Texas IA or IIA	Ulcer size (cm^2) TCC: 2.6 (0.8) cm^2 I-RWD: 2.1 (0.8) cm^2 RWD: 2.3 (0.9) cm^2 Ulcer duration: > 6 weeks	Location of ulcers (first toe/toes/ MTH) TCC (7/2/11) i-RWD (6/1/13) RWD (6/2/12)	Ankle-brachial pressure index ≥0.9 with two palpable pulses in the affected foot	1. Immune system related disorders such as autoimmune disorders 2. Chronic kidney disease and other significant medical conditions that impact tissue repair 3. Active cancer 4. Visual impairment 5. Lower limb oedema 6. Charcot arthropathy 7. HIV-positive

ABI: Ankle brachial index; BBGFM: Resorbable glass microfiber matrix; CDO: Continuous diffusion of oxygen; BSA: Bioactive split thickness skin; DFU: Diabetic foot ulcer; dHACM: Dehydrated human amnion; HIV: Human immunodeficiency virus; IQR: Interquartile range; LAMG: Lyophilised amniotic membrane gel; NPWT: Negative pressure therapy; PMVT: Processed microvascular tissue allograft; PVD: Peripheral vascular disease; rhEFGF: Recombinant human epidermal growth factor; RWD: Removable walking device/ removable walking boot; SD: Standard deviation; SPP: Skin perfusion pressure; SLE: Systemic lupus erythematosus; SOC: Standard of care; TBI: Toe branchial index; TCC: Total contact casting; TCOM: Transcutaneous oxygen measurement; $TcPO_2$: Transcutaneous partial pressure of oxygen; UBM: Urinary bladder-derived extracellular matrix

(iv) transcutaneous oxygen of the dorsum of the foot > 30mmHg with a skin perfusion pressure > 30mmHg; and (v) absolute toe pressure of > 30 mmHg. End stage renal disease was also excluded in half of the studies.

(B) Study Design

(i) Run-in period

Figure 3 showed that nearly half of the studies followed this protocol: After screening through the inclusion and exclusion criteria, a 14 week run-in period was carried out, where standard care of care was provided; followed by a treatment period of 12 weeks, where the interventions were given to the patients; and a variable follow up period (from 4 weeks to 1 year) depending on the study, was usually done to monitor the recurrence of ulcers. Only one study had a short run-in period of 1 week, 10 studies did not have run-in-periods. For the treatment phase, there were two studies for 16 weeks, one study for 9 weeks and two studies for 6 weeks.

According to Niederauer et al. (2018), the purpose of the run-in period was to make sure that the wounds were chronic in nature. During this period, the standard of care for DFUs was given to all patients prior to starting the intervention of the study, which included standard of care dressings (choice of dressings varies for studies), offloading devices and debridement (usually sharp debridement), some included the use of secondary dressings, as shown in Table 5. There was no standardisation for the "standard of care dressings", some studies gave a vague statement such as "moist dressing" or "standard of care dressing". The most frequently mentioned dressing in the run-in-period was alginate or collagen alginate dressing. Other dressings mentioned included foam, hydrofiber and saline dressings. Types of offloading also varied from studies, where offloading boots were most frequently mentioned. Other than that, sharp debridement, wound cleansing and other secondary dressings were also given to patients as part of the standard of care.

Since patients of HbA1c >12% were excluded from the study, the intent-to-treat population can be considered not having poorly controlled diabetes, excluding glycemic control from the standard of care. Thus this run in period acted as an evidence to prove that the wounds did not heal well despite two weeks of optimised standard of care. After the run-in period, wounds that did not reach a certain target of closure or epithelisation was included in the clinical trials. There was no standardisation of this target, it ranged from 20 to 50% of reduction in ulcer area after run-in-period. One of the studies further divided the target for percentage of wound area reduction (PAR) into 2 weeks, having a target each for both weeks together and either of the 2 weeks.

FIGURE 3: Common study design in included randomised controlled trials (RCTs)

(ii) Randomisation and blinding

Most of the studies used the computer or software algorithm for randomisation, as seen in Figure 4. Seven studies used the sealed envelope method while four studies did not mention the method of randomisation. Six studies were double-blinded, seven studies were not blinded, the rest were single blinded. Table 6 gave a more detailed description of the randomisation and blinding methods, including the ratio for control and active treatment and blinding methods such as computerised planimetry and blinding of wound assessment.

TABLE 5: Run-in period, treatment phase and follow up phase of studies

Author (year)	Run in phase						Treatment phase	Follow-up phase
	Dressings	Offloading	Debridement	Secondary dressings mentioned	Wound cleansing mentioned	PAR target		
Driver et al. (2015)	0.9% sodium chloride gel	Active Offloading Walker, boot, and/or shoe	None	Yes	None	<30%	16 weeks	12 weeks
Gould et al. (2022)	Collagen Calcium Alginate	Diabetic cam boot	Yes	Three-layer dressing with felt padding	Yes	<20%	12 weeks	None
Tettelbach et al. (2019a)	Alginate dressings	Cam walker, offloading boot, shoe, or complete contact cast)	Yes	Absorbent non-adhesive hydropolymer secondary dressings, gauze	Yes	<25%	12 weeks	4 weeks
Rezaei-Nejad et al. (2023)	None	None	None	None	None	None	9 weeks	9 weeks
Tettelbach et al. (2019b)	Moist dressings	ankle motion walker boots	Yes	None	None	30%	12 weeks	4 weeks
Armstrong et al. (2022b)	Collagen Calcium Alginate	Diabetic cam boot	Yes	Three-layer dressing	None	<20%	12 weeks	2 weeks
Husain et al., (2024)	Foam Alginate	Diabetic cam boot	None	None	None	None	12 weeks	None
Alvarez et al. (2017)	None	None	None	None	None	None	16 weeks	52 weeks
Niederauer et al. (2018)	Standard of care dressings	Offloading Walker boots	Yes	None	None	either week of 1st 2 weeks: 25% 2 weeks: < 40%	12 weeks	12 weeks
Driver et al. (2017)	Moist dressings	Offloading boots	Yes	None	Yes	<30%	12 weeks	None

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Author (year)	Run in phase						Treatment phase	Follow-up phase
	Dressings	Offloading	Debridement	Secondary dressings mentioned	Wound cleansing mentioned	PAR target		
Serena et al. (2021)	Hydrofibre/ alginate dressing	TCC/fixed ankle walker boot	Yes	None	Yes	<20%	12 weeks	None
Lavery et al. (2019)	Standard of care dressings	DH Offloading Walker	Yes	None	None	<50%	12 weeks	None
Vangaveti et al. (2023)	None	None	None	None	None	None	6 weeks	6 weeks
Park et al. (2019)	None	None	None	None	None	None	12 weeks	None
Park et al. (2018)	None	None	None	None	None	None	12 weeks	None
Armstrong et al. (2022a)	None	CAM boots TCC	Yes	None	None	<20%	12 weeks	None
Essa et al. (2023)	None	None	None	None	None	None	12 weeks	None
Motawea et al. (2019)	None	None	None	None	None	None	8 weeks	None
Sahu et al. (2018)	None	None	None	None	None	None	6 weeks	None
Searan et al. (2024)	None	None	None	None	None	None	12 weeks	None
Piaggesi et al. (2016)	None	None	None	None	None	None	12 weeks	None

CAM: Controlled ankle motion; TCC: Total contact casting

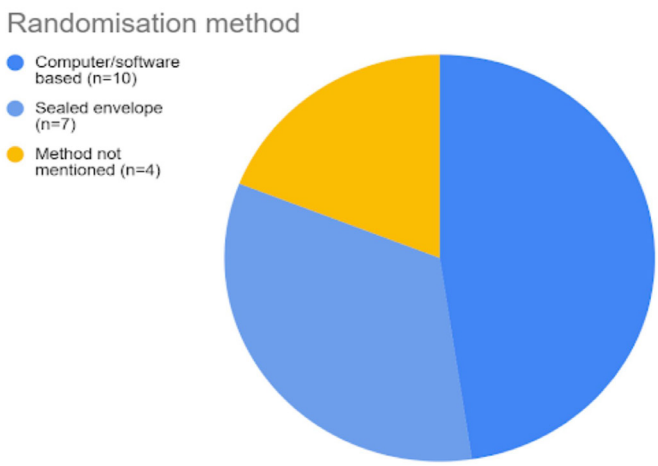

FIGURE 4: Randomisation of studies computer/software based (n = 10), sealed envelope and method not mentiuned (n = 4)

Wound Dressings

There was a wide range of wound dressings involved in the studies, the type of dressings were listed out in Table 7, including both intervention dressings and control group dressings. Advanced therapies used were dermal replacement layer, allografts, matrices and collagen products. The dermal replacement layer, Integra Dermal Regeneration Template (IDRT), as described by Driver et al. (2015), was develop using Integra's Dermal Regeneration Matrix (IDRM) technology. It was a bilayer acellular matrix made from collagen, glycosaminoglycan and chondroitin-6-sulfate, and it had a temporary epidermal silicone layer as protection. Allografts from the studies were derived from different sources, some contained placenta-related products such as dehydrated human umbilical cord and dehydrated or freeze-dried human amniotic membrane; others were processed from microvascular tissue and cryopreserved bioactive split thickness skin. The matrices were made from bioactive materials (Armstrong et al. 2022b), such as resorbable electrospun fibers that mimicked the scale, structure and architecture of native human tissue and animal products such as porcine urinary bladder (Husain et al. 2024). The collagen dressings used were either a combination of collagen and alginate (such as 3M Fibracol ™) or porcine based type I collagen. For growth factors, the efficacy of topical recombinant human epidermal growth factor (rhEGF) as a spray for DFUs was used by Park et al. (2018) with foam dressings.

Modern dressings were the most commonly used dressings, with alginate dressings being the most frequently used dressings as the standard of care dressing, followed by foam. The choice between foam and alginate was based on the level of exudates, where DFUs with heavy exudates were given alginate dressings and foam was provided for milder exudates. Hydrocolloid, hydrogel, hydrofiber and silver dressings were also used in the studies. Conventional dressings, although old-fashioned, were used in three studies too, where some were normal saline dressings and some were povidone iodine soaked dressings. Phenytoin, despite being an epileptic medication was given topically with nanostructured lipid carrier hydrogel by Motawea et al. (2019) as a new organic solvent-free formula for wound healing, as experimental studies showed that it can improve the healing process via mechanisms such as enhancing collagen deposition and decreasing wound exudates.

TABLE 6: Randomisation and blinding methods of studies

Author (year)	Randomisation method	Blinding
Driver et al. (2015)	Software algorithm at a central location in mixed blocks of 2 and 4 in a 1:1 ratio to the active or control treatment. Randomisation was stratified by study site and wound size (≤3 cm^2 vs. >3 cm^2).	Computerised planimetry was conducted in a blinded manner by a central laboratory (not double-blinded)
Gould et al. (2022)	A sealed envelope technique, in which the envelopes contained a random allocation sequence, was used to perform a 1:1 randomisation of eligible subjects to the control arm or PMVT. Randomisation was performed in 10-subject blocks to achieve balanced assignment of treatments, and clinical investigators were only informed of the randomisation assignment at the time of each individual patient's initial treatment visit.	The investigator and a physician blinded to the subject's care made the initial determination of wound closure, followed by adjudication and confirmation of closure by a panel of three independent blinded plastic surgeons with >10 years of experience in wound care. In order to avoid the introduction of bias, the adjudicators only saw blinded images of the "closed" wound and evaluated them based on the four criteria. If an image was unclear, adjudicators could request additional images because several were taken at each visit.
Tettelbach et al. (2019a)	Randomisation was conducted at each study site through sequentially numbered and sealed opaque envelopes. Group assignments were verified and monitored by the study sponsor (MiMedx Group Inc.).	Neither the treating physician nor the patient was blinded to group assignment, but study adjudicators who examined photographic images for validation of healing at completion of the study were blinded as to group assignment.
Rezaei-Nejad et al. (2023)	The participants were assigned into 2 groups (n = 9) using computer-based randomisation.	(i) The control group, receiving a placebo treatment consisting of conventional dressing, using a gelatin scaffold without HAM, with the same appearance as the intervention group; (ii) The intervention group, receiving the LAMG dressing. Three wound care physicians (two plastic surgeons and a dermatologist) who were blinded to the group assigned to evaluate the wounds. A pathologist blinded to the study's procedure examined the specimens to assess the preservation of ECM and the complete removal of cellular components.
Tettelbach et al. 2019b)	Randomisation to the study assignment was generated via sealed envelope group assignment. Envelopes containing the random group assignment were sequentially numbered, opaque and sealed by the study sponsor prior to being delivered to the study site. At the point of entering a qualified subject into the study after signature was obtained acknowledging informed consent, site staff opened the next envelope in the sequential order indicating the study group assignment.	Neither patient nor provider was blinded to group assignment.

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Author (year)	Randomisation method	Blinding
Armstrong et al. (2022b)	A block size of 10 was used for randomisation achieved by using five sheets of paper with an SOC assignment and five with a BBGFM assignment, with each assignment placed in an opaque envelope, which was then sealed, and the envelopes shuffled by the study coordinator before being labelled 1 through 10. This process was repeated to obtain a sufficient number of assignments and was observed by the principal investigator and study staff, before envelopes were distributed to study sites. Site investigators had to open the envelopes in order and could only open the next envelope in order after a subject was ready to be randomised, thus accomplishing allocation concealment.	Lack of investigator blinding. Final adjudication of healing was conducted by a panel composed of three plastic surgery wound experts blinded to the study assignment.
Husain et al. (2024)	Subjects were stratified by wound size, then randomised 1:1 to one of two treatments: SEFM or SOC. The sequence of enrollment was randomly generated utilising a website program (www.randomisation.com), and subject assignment was determined via sealed envelope. Subjects were stratified by wound size in an effort to recruit subjects with a wide range of initial ulcer sizes and randomised at a 1:1 allocation ratio. Sealed envelopes were prepared by the sponsor and provided to the wound care center at the beginning of the study. Once the subject was enrolled, an envelope was opened, and the randomisation form was completed by study personnel.	Single-blind trial. The participant remained blinded until the end of treatment. During weekly treatment, a drape was placed between the participant and the study limb while treatment was applied. During treatment applications, no branded or labelled materials were brought into the patient room.
Alvarez et al. (2017)	The subjects were randomised (2:1 ratio) into 1 of 2 arms (UBM plus TCC or TCC alone [control]).	nil
Niederauer et al. (2018)	Randomisation lists were made by the statistician for each clinical site in blocks of size four with SAS. Devices were labelled by the statistician before shipping to the sites. The sites assigned devices to patients sequentially at randomisation.	The only difference was that the placebo devices did not have any oxygen flowing out of the oxygen supply port. Since the oxygen flow rate (3ml/ hour) was low enough that it cannot be felt by the subjects or physicians, the devices all appeared identical. Similarly, the dressings and offloading boots in each arm were limited and identical. The result was that the patients, doctors, evaluators, sponsor and statistician were all fully-blinded to the treatment arms until the data had been collected and verified, thereby eliminating the placebo effect.

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Author (year)	Randomisation method	Blinding
Driver et al. (2017)	Study participants who continued to meet the inclusion criteria were enrolled into the study by the site investigator or coordinator and randomised to 1 of the 2 treatment groups. The randomisation was centralised with a 1:1 ratio (active treatment group: control treatment group), and 2 stratification factors were used: (i) wound size at baseline ($\geq$1 cm^2 to $\leq$5 cm^2 and >5 cm^2 to 10 cm^2) and (ii) patient age at baseline (<65 years, $\geq$65 years). These stratification factors also were used in analysing the results of the trial. The randomisation schedule was prepared by Precision Sciences Inc (Phoenix, AZ). The actual randomisation assignment was made via a web-based centralised system (WebView, Zifo Technologies, Lindenhurst, IL).	All study participants, the investigators, and site staff were blinded to the treatment. In addition, the evaluators who processed the tracings and photographs also were blinded. The active treatment group received the TCOT device, and the control group received a sham "device." TCOT treatment consisted of continuous administration of 98+% oxygen to the wound site using a 15-day device changed every 15 days. Sham units were prepared by assembling the "device" without the oxygen-generating fuel cell assembly. This was done by Sparton Corporation (blinded for review), which received a copy of the 1:1 randomisation schedule to enable the company to prepare kits with either working device units or sham units. The sponsor also was blinded to this randomisation process. Allocation concealment was successfully achieved because the devices looked the same regardless of assignment (for example, A or B).
Serena et al. (2021)	A computer-generated randomisation list was used to randomise patients across all sites in a 1:1 ratio; an envelope system was used to allocate to groups based on the next available envelope in the sequence. Based on performance in previous trials with a similar intervention period, an anticipated dropout rate of 10% was built into the recruitment plan. For an anticipated healing rate of 30% in the SOC and a 55% healing rate in the SOC plus TOT group, with 80% power, alpha set at 0.05 and a dichotomous endpoint (healed versus not healed), 60 subjects were required in each group- giving a target of 120 evaluable subjects. Consequently, the study aimed to recruit 132 subjects in order to achieve 120 evaluable subjects at the end of the study; withdrawal rates were closely monitored to allow for additional recruitment to ensure a balanced number of participants across the groups.	Open label.
Lavery et al. (2019)	Patients were then randomised to either the treatment arm with an active CDO device (henceforth, the active arm) or the control arm using a placebo CDO device (henceforth, the placebo arm). All devices in both arms were set to 3 mL/hour of oxygen flow and were functional in that they produced oxygen and displayed the oxygen flow rate. The only difference was the placebo device did not have any oxygen flowing out of the oxygen supply port.	The primary efficacy outcome was complete wound closure defined as complete reepithelialisation with no drainage as assessed by the treating clinician and confirmed by a blinded observer.the strengths of the study include the high-quality design with blinding of patients and physicians.

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Author (year)	Randomisation method	Blinding
Vangaveti et al. (2023)	The study aimed to enroll 50 patients diagnosed with DFU prospectively and randomised using a web based online program (20) in a 1:1 ratio to either ESWT + standard wound care (n = 25) or standard wound care (n = 25) for 6 weeks. The randomisation sequence was then placed in sealed envelopes with research nurse being the only person having access to the envelopes to enable allocation of participants to the 2 arms of the study after the initial screening.	The treatment group was not blinded.
Park et al. (2019)	After informed consent for participation was obtained by the clinical research coordinator, enrolled patients were randomised to the two study groups in a 1:1 ratio. The randomisation code was generated using a permuted-block method with a block size of four or six implemented using the SAS system. Randomisation was stratified by clinical center.	Clinical staff performing DFU evaluations were blinded to study group allocation.
Park et al. (2018)	After informed consent for participation was obtained by clinical research coordinator, enrolled patients were randomised to one of the two study groups in a 1:1 ratio. The randomisation code was generated using a permuted-block method with a block size of four or six implemented using the SAS system. Randomisation was stratified by clinical center.	Both spray solutions were distributed in identical packaging, with the same label to ensure double-blinding. Clinical staff performing DFU evaluations were blinded to treatment group allocations.
Armstrong et al. (2022a)	A patient allocation system was employed based on a random sequence of block sizes of 10 designed to achieve a balanced design. The system used concealed envelopes at each site with allocation on a slip of paper within each envelope. All subjects were randomised if they continued to meet inclusion/exclusion criteria to one of the two arms, both of which received the following routine procedures as part of the SOC	A blinded adjudication panel performed wound assessments of the images to confirm investigator's assessment of closure lack of investigator blinding.
Essa et al. (2023)	A Microsoft Excel sheet was used to create a randomisation sequence with a 1:1 allocation using random block sizes of 2 and 4 by an independent doctor. Each eligible patient was subjected to 1 of the 2 dressing groups: SilvrSTAT Gel group or conventional dressing group. Patients received the next available successive randomisation number and dressing type based on the randomisation schedule.	The first surgeon (blind one) selected the eligible patients, prepared ulcers by excision debris and necrotic tissue, documented the site, length, width, depth, and grades of the ulcers, and was responsible for the follow-up of the ulcers during outpatient clinic visits with documentation of the size of the ulcers. The first surgeon was blind to dressing type. The second participating surgeon (unblind one) knew the number of the patients and each patient's group according to a randomisation schedule electronically generated. He also knew the type of dressing used and prepared dressings for the patients.

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Author (year)	Randomisation method	Blinding
Motawea et al. (2019)	All patients were randomly assigned to one of the three groups by randomised block design based on age group, body mass index and sex.	Patients were blinded regarding type of the used dressing and they were instructed on guidelines for wound dressing and were asked to dress his/her ulcer daily and come back to the outpatient clinic every week for clinical evaluation and follow-up.
Sahu et al. (2018)	The patients were randomly assigned to the TCC group or to the TD group.	nil
Searan et al. (2024)	The algorithm randomisation method was employed in this clinical trial study to allocate participants in 4 groups in a way that ensures lanced representation and minimises bias. This was accomplished by utilising a statistical software program using spreadsheet software to ensure that the random number covers the range from 1 to 120 without repetition. This program was adapted based on age, gender, and type of diabetes treatment (diet, oral medication, or insulin).	nil
Piaggesi et al. (2016)	The patients were then randomised, by means of a remote telephone computer-generated randomisation into one of the following 3 groups: group A, which was offloaded with a TCC; group B, to which the i-RWD was applied; and group C, which received the RWD as an offloading device.	The patients were evaluated by an investigator blinded to the offloading device adopted for the patient. The study mentioned the impossibility of blinding the patients to the treatment.

BBGFM: Resorbable glass microfiber matrix; CDO: Continuous diffusion of oxygen; DFU: Diabetic foot ulcer; ECM: Extracellular membrane; ESWT: Extracorporeal shockwave therapy; HAM: Human amniotic membrane; LAMG: Lyophilised amniotic membrane gel; PMVT: Processed microvascular tissue allograft; RWD: Removable walking device/ removable walking boot; SAS: SEFM: SOC: TCC: Total contact casting; TCOD/TCOT: Transdermal continuous oxygen delivery; TD: Traditional dressing; UBM: Urinary bladder-derived extracellular matrix

TABLE 7: Dressings involved in studies

	Dressings Involved in Studies		
	Advanced therapies	Frequency	
1	Dermal replacement layer (IDRT)	1	
2	Allograft	5	
	Amnion/chorion membrane allograft (Rezaei-Nejad et al. 2023; Tettelbach et al. 2019b) - Dehydrated human amnion/chorion membrane allograft (dHACM) - Freeze-dried human amniotic membrane allograft gel/ Lyophilized amniotic membrane gel (LAMG)		2
	Dehydrated human umbilical cord (EpiCord) allograft (Tettelbach et al. 2019b)		1
	Processed microvascular tissue allograft (PMVT) (Gould et al., 2022)		1
	Cryopreserved bioactive split thickness skin allograft (Armstrong et al. 2022a)		1
3	Matrix	3	
	Synthetic electrospun fiber matrix (SEFM)(Husain et al. 2024)		1
	Resorbable glass microfiber matrix (Mirragen/BBGFM) (Armstrong et al. 2022b)		1
	Porcine urinary bladder-derived extracellular matrix (UBM)		1
4	Other Advanced Therapy	4	
	Collagen - Collagen alginate (Armstrong 2022a; Armstrong et al. 2022b; Gould et al. 2022) - Porcine based collagen (Park et al. 2019)		4
	Topical recombinant human EGF (rhEGF) (Park et al. 2018)		1
	Modern dressing	24	
1	Alginate (Driver et al. 2017; Husain et al. 2024; Lavery et al. 2019; Niederauer et al. 2018; Serena et al. 2021; Tettelbach et al. 2019a; Tettelbach et al. 2019b) *3 collagen alginate		10
2	Foam (Alvarez et al. 2017; Driver et al. 2017; Husain et al. 2024; Lavery et al. 2019; Niederauer et al. 2018; Park et al. 2018; Park et al. 2019; Vangaveti et al. 2023)		8
3	Hydrocolloid (Driver et al. 2017)		1
4	Hydrofiber (Piaggesi et al. 2016; Serena et al. 2021)		2
5	Hydrogel (Motawea et al. 2019; Searan et al. 2024)		2
6	Silver (Essa et al. 2023)		1
	Adjuncts	6	
1	Topical oxygen therapy (Driver et al. 2017; Lavery et al. 2019; Niederauer et al. 2018; Serena et al. 2021)		4
2	Extracorporeal Shockwave Therapy (ESWT) (Vangaveti et al., 2023)		1
3	Honey (Searan et al.)		1
	Conventional dressing		
1	Iodine (Essa et al. 2023; Sahu et al. 2018)		2
2	Saline gauze/ wet to dry dressing (Driver et al. 2015; Essa et al. 2023)		2
	Miscellaneous		
1	Phenytoin (Motawea et al. 2019)		1

Clinical trials with adjunct therapies like topical oxygen therapy, extracorporeal shockwave therapy (ESWT) and honey dressings were also included, with topical oxygen therapy being the most popular adjunct, four studies conducted different offloading methods against sham/placebo devices. Traditionally used for renal calculi, ESWT was found to help with angiogenesis for wound healing with its high energy mechanical waves, thus Vangaveti et al. (2023) assessed its efficacy against standard of care for DFUs. Honey dressings in DFU had been widely investigated recently, and Searan et al. (2024) had evaluated the impact on healing between fucidin (the control group) versus honey and hydrogel (individually and combined effect).

Offloading Involved

Aside from studies that focused on comparing efficacy of different offloading, studies that compared wound dressing were less specific on the type of offloading devices they used. Thus, Table 8 included the type of devices that were mentioned in the articles. Some of the studies also did not specify whether the device was removable or non removable. The most commonly used offloading method in the studies was offloading shoes, with nine studies applying it for patients, followed by diabetic controlled ankle movement walkers of various brands (eight studies), while the least was walking aids like splint or crutches.

Some studies only mentioned that these devices were given to patients with education on the importance of offloading, the compliance was recorded by the investigators but not shown in the articles. Only Gould et al. (2022) reported the compliance of offloading at both run-in period and treatment phase, where the mean duration of offloading at screening 16.0 ± 14.8 weeks and 14.0 ± 11.4 weeks for processed microvascular tissue allograft (PMVT) and alginate group respectively, while the mean percent time wound

TABLE 8: Offloading involved in studies

Non removable offloading device	**Frequency**	
Total contact cast (TCC) (Alvarez et al. 2017; Armstrong et al. 2022a; Armstrong et al. 2022b; Piaggesi et al. 2016; Sahu et al. 2018; Serena et al. 2021; Tettelbach et al. 2019a; Tettelbach et al. 2019b)		8
Irremovable offloading boot (Piaggesi et al. 2016)		1
Removable offloading device	13	
Offloading boots (Driver et al. 2017; Lavery et al. 2019; Niederauer et al. 2018; Tettelbach et al. 2019a; Tettelbach et al. 2019b)		5
Diabetic cam boot/ cam walker/Controlled ankle movement walker/Diabetic walker boot (Armstrong et al. 2022a; Armstrong et al. 2022b; Driver et al. 2015; Gould et al. 2022; Husain et al. 2024; Piaggesi et al. 2016; Rezaei-Nejad et al. 2023; Tettelbach et al. 2019a)		8
Footwear	11	
Offloading shoes (Armstrong et al. 2022a; Driver et al. 2015; Essa et al. 2023; Motawea et al. 2019; Park et al. 2018; Park et al. 2019; Searan et al. 2024; Tettelbach et al. 2019a; Tettelbach et al. 2019a)		9
Cushioning insoles (Armstrong et al. 2022b; Vangaveti et al. 2023)		2
Other offloading methods	6	
Wheelchair (Armstrong et al. 2022a; Park et al. 2018; Park et al. 2019)		3
Splint/walking aids/crutches (Park et al. 2018; Park et al. 2019)		2
Felt foam (Armstrong et al. 2022a; Gould et al. 2022; Searan et al. 2024)		3

offloaded during study were 82.1 ± 11.1 weeks and 81.1 ± 9.1 weeks for PMVT and alginate group respectively.

Healing Outcomes

As individual studies assessed different endpoints, studies compared based on the healing outcomes as recorded in Table 9.

(A) Complete wound healing

Complete wound healing referred to the complete re-epithelialisation or closure of the wound. Only two RCTs did not record this outcome. The combination of the highest healing rate was achieved by two studies. Complete wound healing of 90% at 12 weeks and 100% at 16 weeks for 11 patients by Alvarez et al. (2017), with porcine urinary bladder-derived extracellular matrix and total contact cast, however the results were not statistically significant ($p = 0.062$). The second study by Essa et al. (2023) was statistically significant ($p < 0.0001$), with a complete healing rate of 90% in 12 weeks for a cohort of 40 patients using the combination of SilvrSTAT Gel, a hydrogel containing silver nanoparticles and shoe orthoses.

Both Lavery et al. (2019) and Niederauer et al. (2018) showed that the combination of placebo device with foam or alginate dressing plus offloading walker boots had lower complete wound healing rates (22.6%, $p= 0.016$). Five out of 25 patients (20.0%) in the ESWT with foam and cushioning insoles had an even lower rate, but it was statistically insignificant ($p = 0.73$).

(B) Time to Healing

Time to complete healing is time taken for complete re-epithelialisation or closure of the wound. It was recorded in median and mean for different studies, eight RCTs did not record this outcome. For studies that recorded the mean, the shortest duration of 10.83 days was obtained by Searan et al. (2024) done by applying honey and hydrogel alternatively ($p=0.004$), and offloading with both felt foam and orthosis shoes. For studies that recorded the median time of healing, Driver et al. (2015)achieved a median of 43 days with IDRT and active offloading walker. There were also studies that record the time to 50% DFU closure, Niederauer et al. (2018) showed that patients that received continuous diffusion of oxygen (CDO) therapy with foam or alginate dressings and offloading walker boots had significantly shorter time to 50% DFU closure (mean 18.4 versus 28.9 days for placebo, $p=0.001$).

(C) Reduction in Wound Area

Reduction in wound area was recorded based on the initial and final size of the ulcer, we identified 11 RCTs that reported this outcome in the form of percentage or surface area (cm^2). Six RCTs recorded the PAR, Armstrong et al. (2022b) had the highest mean PAR at 12 weeks of 79% in a group of 20 patients by using resorbable glass microfiber matrix, a three layer compression dressing and removable diabetic cam-walker or total contact cast. Four studies reported the average reduction of ulcer size in cm^2, Serena et al. (2021) achieved the largest mean of wound area reduced, 46.38 cm^2 with topical oxygen therapy, hydrofiber or alginate dressings and total contact cast (Park et al. 2018; Park et al. 2019; Serena et al. 2021; Vangaveti et al. 2023).

(D) Rate of Healing

The rate of healing or reduction of wound size was reported either per area week or in percentage. Rezaei-Nejad et al. (2023) reported that 100% of patients can achieve a rate of 50% reduction of wound size in nine weeks using lyophilised amniotic membrane gel (LAMG) along with ankle motion walker boots. Park et al. (2018) used recombinant human epidermal growth factor (rhEGF) and various offloading methods: Offloading shoes with rigid-rocker sole, splint or wheelchair to get a healing rate as high as 18.41% per week ($p = 0.029$).

TABLE 9: Healing outcomes

Author (year)	Dressings (Active/ control)	Offloadings	% of complete closure/ healing rates	Time to healing	Ulcer size reduced/ PAR	Rate of reduction/ healing velocity
Driver et al. (2015)	IDRT/ Sodium chloride gel	Active offloading walker, boot, and/ or shoe	Active group - 51%; 79/154) control group - 32%; 49/153) (p=0.001)	Median IDRT - 43 days Control - 78 days	None	IDRT: 7.2% per week Control: 4.8% per week (p=0.012).
Gould et al. (2022)	PMVT/ Collagen alginate	Diabetic cam boot	PMVT 74% Control 38% P = 0.0003	Mean PWVT (n = 37) : 54 days Control (n = 19): 64 days (p = 0.009)	PMWT 76% (n = 50) Control 24% (n = 50)	None
Tettelbach et al. (2019a)	dHACM / Alginate	Cam walker, offloading boot, shoe, or complete contact cast	dHACM - 70% (38/54) Non-dHACM: 50% (28/56) (P = 0.0338)	None	None	None
Rezaei-Nejad et al. (2023)	Freeze-dried human amniotic membrane allograft gel/placebo: conventional dressing, Gelatin scaffold without HAM	Ankle motion walker boots	None	Mean time required for wound healing (> 50% reduction in wound size) LAMG 42 days	Mean LAMG- 73.44%±15.33% Placebo - 13.19%±10.19% (P=0.008).	<75% Closure LAMG: 66.6% Control : 0% p = 0.0043 <50% Closure LAMG: 100% Control: 0% p = 0.0039
Tettelbach et al. (2019b)	EpiCord allograft/ alginate	1.Removable cast walker, if unsuitable and/or not conducive to treatment 2. standardised TCC kit	12 weeks EpiCord- 70% (71/101) Alginate - 48% (26/54) (P = 0.0089) 16 weeks EpiCord- 74 / 101 (73%) Alginate- 29 /54 (54%) (p = 0.0199)	None	None	12weeks Epicord - 81% (70/86) Alginate 54% (26/48) (P = 0.0013

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Author (year)	Dressings (Active/ control)	Offloadings	% of complete closure/ healing rates	Time to healing	Ulcer size reduced/ PAR	Rate of reduction/ healing velocity
Armstrong et al. (2022b)	Mirragen/ Collagen alginate dressing	No type of offloading during tx Dispensed diabetic shoes and insoles provided by the sponsor at the study exit.	BBGFM - 14/20 (70%) SOC - 5/20 (25%) (unadjusted P = 0.004)	None	Mean PAR BBGFM - 79% group SOC - 37% (adjusted P = 0.027)	None
Husain et al. (2024)	Synthetic electrospun fiber matrix/ alginate or foam dressings	Run in period: DFU (DJO cam walker boot) Treatement: controlled ankle movement boot (or equivalent shoe) according to their instructions for use	SEFM - 56% (14/25) SOC - 29% (6/21)	SEFM - 6.6 $\pm$ 3.0 weeks SOC - 7.0 $\pm$ 2.7 weeks	Mean PAR SEFM - 65% SOC - 58 %	Reductions of wound area at 4 weeks post treatment mean : 87%, median: 100%
Alvarez et al. (2017)	UBM/ foam	Traditional TCC: minimally padded, well-molded, and rigid (plaster plus fiberglass)	UBM: 12 weeks - 90% 16 weeks - 100%, Control: 12 weeks - 33% 16 weeks - 83.3% (P = .062)	UBM - 62.4 days Control 92.8 days (P = 0.031)	None	None
Niederauer et al. (2018)	Foam or alginate with topical oxygen therapy/ placebo device	Offloading walker boots	Full ulcer closure CDO 46.2% Placebo - 22.6% Randomised in the study: 32.4% CDO and 16.7% placebo	Mean time to 50% DFU closure CDO therapy -18.4 days Control - 28.9 days, (p=0.001)	There was increasing significant beneficial effect of the CDO arm at 25%/40% PWAR (p=0.017) and 20%/30% PWAR (p=0.008).	None

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Author (year)	Dressings (Active/ control)	Offloadings	% of complete closure/ healing rates	Time to healing	Ulcer size reduced/ PAR	Rate of reduction/ healing velocity
Driver et al. (2017)	Hydrocolloid or alginate or foam with topical oxygen therapy/ placebo device	Offloading boots	ITT: TCOT - 35/65 (53.8%) Control - 31/ 63 (49.2%) (P = 0.4167) PP: TCOT - 34 out of 61 (56%) Control - 31 out of 61 (49%)	Median time to complete closure TCOT - 63 days Control - 77 days (P > 0.05)	None	None
Serena et al. (2021)	Hydrofibre or alginate with topical oxygen therapy/ placebo device	TCC	SOC - 18/64 (28.1%) SOC plus TOT - 36/81 (44.4%) (p=0.044).	None	PAR (cm^2) Mean ± SD SOC 41.05 ± 69.82 SOC + TOT 46.38 ± 100.24 Mean reduction SOC - : 40% (SD) 72.1) SOC plus TOT -70% (SD 45.5) (p = 0.005).	None
Lavery et al. (2019)	Foam or alginate with Topical Oxygen therapy/ placebo device	DH Offloading Walker	CDO group - 46.2% placebo. 22.6%, (P = 0.016). The relative performance of active CDO over placebo became greater when frequent debridement was used (51.2% vs. 21.3%, respectively; P = 0.006).	None	None	None
Vangaveti et al. (2023)	Foam with/ without ESWT	Cushioning insoles and foam dressings with a hole on the ulcer site	Total - 11/48 healed SOC - 6 /23 (26.1%) ESWT + SOC: 5/25 (20.0%) (p = 0.73)	None	Mean PAR SOC - 5.05 ± 136.7 mm^2 ESWT + SOC - 36.08 ± 46.72 mm^2 (p = 0.33) Reduction in ulcer size at 6 weeks ESWT 18 (86%) SOC - 0.14 (70%)	

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Author (year)	Dressings (Active/ control)	Offloadings	% of complete closure/ healing rates	Time to healing	Ulcer size reduced/ PAR	Rate of reduction/ healing velocity
Park et al. (2019)	Porcine type I collagen/ Foam	Offloading shoe with rigid-rocker sole: Collagen 13 (76.5) SOC 10 (76.9) Splint: Collagen 3 (17.6) SOC 2 (15.4) Wheelchair: Collagen 1 (5.9) SOC 1 (7.7)	Collagen - 82.4% (14/17) Control - 38.5% (5/13), (p = 0.023)	Median Collagen- 63 days Control - not reached	Mean size reduction collagen - 4.39 ± 4.95 cm^2 control -2.24 ± 2.81 cm^2, (p = 0.027)	Mean ± SD (cm^2/week) Collagen: 0.55 ± 0.44 Control: 0.29 ± 0.42 (p = 0.001)
Park et al. (2018)	Polyurethane foam dressings with rhEGF spray/placebo	Offloading shoe with rigid-rocker sole rhEGF 64 (78.0) Placebo 65 (76.5) Splint: rhEGF 14 (17.1) Placebo 15 (17.6) Wheelchair: rhEGF 4 (4.9) Placebo 5 (5.9)	rhEGF 73.2% (60/82) Control 50.6% (43/85)	Median time to complete ulcer healing rhEGF group 56 days) placebo group (84 days) (p < .001)	Mean ulcer size reduction rhEGF - 2.47 ± 2.53 cm^2 placebo - 1.75 ± 2.91 cm^2 (P = 0.028)	rhEGF: 18.41 ± 13.09% per week placebo: -12.81 ± 13.86% per week (p = 0.029)
Armstrong et al. (2022a)	Cryopreserved bioactive split thickness skin allograft (BSA) (TheraSkin) SOC: Collagen alginate dressing padded three-layer dressing (Dynaflex)	Tx: None, Felt, Shoe, Shoe + felt, Camboot or equivalent, TCC, Wheelchair Screening: CAM boots or total contact casting [TCC] if the subject's foot is too large for a CAM	BSA- 76% (38/50) SOC- 36% (18/50) (adjusted p = 0.00056)	Mean BSA - 46.9 days SOC - 65.3 days (p =0.0019).	Mean PAR BSA - 77.8% SOC - 49.6% (adjusted P =0.0019)	Not clearly stated
Essa et al. (2023)	SilvrSTAT Gel dressing wet-to-moist dressing with or without povidone-iodine	Shoe orthoses	Group A 36 (90%) Group B 31 (77.5%) (p < 0.001)	None	None	Ulcer healing rate per week (area over time) Group A 0.68 ± 0.07 Group B 0.47 ± 0.04 (p < 0.0001)

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Author (year)	Dressings (Active/ control)	Offloadings	% of complete closure/ healing rates	Time to healing	Ulcer size reduced/ PAR	Rate of reduction/ healing velocity
Motawea et al. (2019)	1. PHT-NLC-hydrogel - nanostructured lipid carriers (NLCs) of phenytoin (PHT) 2. phenytoin hydrogel (0.5%w/v) 3. blank hydrogel	Cast shoes	Blank - 34.91 + 28.33 PHT 47.10 + 4.23 NLC 95.82 + 2.22	None	Percentage wound areas compared to initial size PHT-NLC: 4.18 + 2.22, PHT: 52.90 + 4.23 and Blank - 134.91 + 28.33% ($p< 0.001$)	None
Sahu et al. (2018)	Povidone iodine soaked gauze pad (n=16) traditional dressing with povidone iodine solution	TCC (n=15)	TD - 80% (12 /15) Control - 62.5% (10/16)	TD - 48 + 7 days Control - 58 + 9 days	None	None
Searan et al. (2024)	Fucidin (control) (n = 30) Hydrogel alone (n = 30) Honey alone (n = 37) Honey & hydrogel (n = 37)	Local = wool felt foam 7 mm hypoallergenic adhesive sheet. Orthotic medical shoes = forefoot offloading healing shoes = Diabetic heel wedge healing shoes	None	Mean healing times Total 12.76 + 4.08 days honey alone 12.20, hydrogel alone 13.97 honey and hydrogel alternately 10.83 days control Fucidin ointment or cream 14.03 days (P = 0.004)	None	None
Piaggesi et al. (2016)	Inert hydrofiber dressing	1. TCC 2. walking boot rendered irremovable 3. removable walking boot	TCC- 19 (95%) i-RWD- 18 (90%) RWD- 16 (80%)	TCC- 37.0 + 21.6 days i-RWD- 39.6 + 12.2 days RWD - 43.2 + 15.1 days (P = 0.5579)	None	None

BSA: Bioactive split thickness skin allograft; CAM: Controlled ankle motion; CDO: Continuous diffusion of oxygen; DFU: Diabetic foot ulcer; dHACM: Dehydrated human amnion; ESWT: Extracorporeal shockwave therapy; HAM: Human amniotic membrane; IDRT: Integra dermal regeneration template/ dermal replacement layer; ITT: Intent-to-treat; LAMG: Lyophilised amniotic membrane gel; NLC: Nanostructured lipid carriers; PAR: Percent wound area reduction; PMVT: Processed microvascular tissue allograft; PHT: Phenytoin; SEFM: Synthetic electrospun fiber matrix; rhEFGF: Recombinant human epidermal growth; RWD: Removable walking device/removable walking boot; SD: Standard deviation; SOC: Standard of care; TCC: Total contact casting; TCOT: Transdermal continuous oxygen delivery; TD: Traditional dressing; Tx: Treatment; UBM: Urinary bladder-derived extracellular matrix

(e) Other Outcomes

(i) Recurrence of ulcer

Six studies have investigated the recurrence of DFU. The best record was reported by Husain et al. (2024), where two weeks following wound closure, all 14 closed wounds did not recur in the synthetic electrospun fiber matrix (SEFM) group with controlled ankle movement boot. The longest duration for assessment was done by Alvarez et al. (2017) where the 1-year ulcer recurrence rate was 10% (1/11) in the urinary bladder-derived extracellular matrix (UBM)-treated group and 50% (3/6) in the control group. The rest of the studies had a recurrence rate of less than 20%, but with different follow-up durations. Driver et al. (2015) reported that the ulcer recurrence rate at the completion of the 12-week follow-up phase was 19% for the IDRT group and 26% for the sodium chloride gel group ($p=0.32$), both with an active offloading walker. Tettelbach et al. (2019a) found that 36 of 38 (95%) wounds treated with dehydrated human amnion (dHACM) remained closed at the week 16 follow-up, while 24 of the 28 wounds healed with the control while alginate dressings (86%) had remained closed. Another study with the same primary author found that 68 of 71 (96%) wounds treated with EpiCord remained closed at week 16 follow-up, and 22 of the 26 ulcers (85%) treated with alginate dressings remained closed (Tettelbach et al. 2019b). Interestingly, Niederauer et al. (2018) found that more ulcers remained closed (90.0% ,10 ulcers) at follow-up in the placebo group with foam, alginate and offloading boots when compared to the group with add-on topical oxygen therapy (87.5%, 24 ulcers). They attributed it to the location of the ulcer, as they reported the re-open ulcers in the oxygen therapy group were ulcers at weight bearing sites. Nevertheless, this finding was not statistically significant ($p = 0.83$).

(ii) Quality of life

Quality of life, including physical functioning, pain was measured using different instruments by five studies. Driver et al. (2015) and Rezaei-Nejad et al. (2023) used the Short Form Health Survey (SF-36) to assess the quality of life metrics.Driver et al. (2015) reported an improvement on physical functioning ($p=0.047$) and bodily pain ($p=0.033$) by using IDRT, active offloading walker and sharp debridement. However, the scoring details were not recorded. Rezaei-Nejad et al. (2023) assessed a positive impact of physical functioning via the SF-32 instrument (79.996 ± 11.966, $p<0.05$) and bodily pain (85.55 ± 3.33, $p<0.001$) in the LAMG group with ankle motion walker boots. Armstrong et al. (2022b) used the Wound Quality of Life (w-QoL) questionnaire and found an insignificant mean change of w-QoL score in the both resorbable glass microfiber matrix (BBGFM) (0.3) and collagen alginate group (control) (0.33) with removable diabetic cam-walker or TCC (unadjusted $p = 0.43$; adjusted $p = 0.86$). The mean change in pain score was also statistically insignificant (0.39 for BBGFM and 0.24 for collagen alginate, $p = 0.84$; adjusted $p = 0.86$). Serena et al. (2021) assessed the change in pain using the Visual Analog Scale. However, there was no statistical difference between the standard of care, which was total contact cast with hydrofiber or alginate versus adding on topical oxygen therapy.

(iii) Improvements in diabetic neuropathy and local perfusion

Three RCTs assessed improvements in diabetic neuropathy by conducting the 10-point Semmes-Weinstein monofilament (SWM) exam. Gould et al. (2022) found a greater mean reduction in area of peripheral neuropathy in the PMVT group with diabetic cam boot than the control group ($62 \pm 31\%$), with a 118% increase in the SWM test ($p = 0.028$). Armstrong et al. (2022b) found that with BBFGM and removable diabetic cam-walker or TCC, the mean change from baseline SWM score was 2.0, while the control group had a mean drop in the score by -0.6 (adjusted $p = 0.008$). According to Armstrong et al. (2022a), the improvement in neuropathy for the bioactive split thickness skin (BSA) and various offloading

methods (felt, shoe, TCC, cam boot and wheelchair) was insignificant. Gould et al. (2022) carried out indocyanine green fluorescence angiography (ICGFA) to assess wound perfusion. For patients on PMVT and diabetic cam boot, there was an increase in perfusion of 60% seen.

(iv) Cost of treatment

Only two studies reported the cost of treatment of DFU, and it was focused on the intervention dressings. Tettelbach et al. (2019a) reported that the median cost per dHACM healed ulcer was $2252.33 (range $306.95 - 12,394.02) while in Tettelbach et al. (2019b), they reported the average cost per EpiCord-healed ulcer was $3250.99 ± $2898.48.

Issue and limitations of studies

There were some study related adverse events reported. For example, four cases of adverse events using collagen dressings in Park et al. (2019), which were pain, discomfort and skin sensitisation, and three adverse events in the control group including odour, with skin sensitisation, pain and discomfort. Driver et al. (2017) reported four study related events which were: one wound directly from the offloading boot and three wounds possibly caused by the transdermal continuous oxygen delivery (TCOT) device. Besides that, Tettelbach et al. (2019a) reported inadequate debridement in both intervention and control groups, nine of 54 (17%) and six of 50 (11%), respectively) which might interfere with the results. Withdrawal rates were also a concern for the RCTs. Serena et al. (2021) reported a high withdrawal rate (18.6%, 27 patients) and attributed abortion of the withdrawal to the multiple comorbidities in patients with diabetes. Sahu et al. (2018) and Armstrong et al. (2022a) also reported withdrawals due to secondary infection. Furthermore, five RCTs admitted having a small sample size, with a total of 37 patients (Husain et al. 2024), 39 patients (Park et al. 2019), 17 patients (Alvarez et al. 2017), 27 patients (Motawea et al. 2019), 31 patients (Sahu et al. 2018) and 60 patients (Piaggesi et al. 2016), leaving 20 patient in each of the three intervention groups. On the other hand, some studies had multiple choices of offloading given. Among six studies that used more than one offloading intervention, three of them did not record the number of patients using the specific offloading methods. Even for the two studies that listed out the number of patients using the offloading, the healing outcomes reported was based on the dressing interventions, thus it was unknown on the combination of which offloading and dressing can produce the most optimal effect for healing.

DISCUSSION

This systematic review provides an insight to evaluate the combined efficacy of wound dressing and offloading on DFU. After filtering 343 articles, the 21 randomised controlled trials we reviewed were all based on patients with a HbA1c <12 % and have superficial DFU (Wagner Grade 1 to 2, or University of Texas Classification IA to IIA) with duration of at least 14 days to 4 weeks. Majority of the studies included patients with adequate perfusion to the lower limb, proven with either the ankle-brachial pressure index, Doppler ultrasound and other investigations; only one study included patients with peripheral vascular disease. Asides diabetes mellitus, the patients in this review do not have other conditions that might cause immunosuppression. Therefore, this recruitment creates a relatively stable patient population where their DFU healing was not affected by these factors. Most randomised controlled trials had a similar study design, where they followed the sequence of a run-in period, treatment phase and follow up phase. This study design highlights the efficiency of the related interventions in tackling hard-to heal DFUs, as they excluded wounds that achieve a certain degree of healing in the run-in period where the patients received the complete standard of care with dressings, offloading and debridement. They had also managed to provide the short term outcome with the follow up phase to observe for

recurrence of ulcers. In general, the combination of dressing and offloading together created good healing outcomes in terms of healing time, reduction in wound size and other factors such as quality of life.

There is an emergence of more advanced, bioengineered therapy such as amnion or placenta based products, synthetic electrospun matrix and many more. As these are new products made with cutting edge technology, cost effectiveness would be a great consideration because from what we observed, examples like dHACM used by Tettelbach et al. (2019a) costs a patient from $306.95 to 12,394.02, while in EpiCord used by Tettelbach et al. (2019b) costs $3250.99 on average. Nevertheless, regardless of the type of wound dressing, the nature of wound dressing as a consumable but dominant component in the healing of DFUs will inevitably make cost as a primary consideration that will influence, or even limit the choice of treatment. Therefore as Woods et al. (2020) suggested, economic evaluation should be done while carrying out clinical interventions to aid a more cost-effective treatment course for DFU.

Topical oxygen therapy is the most frequently involved adjunct therapy, with sham devices that do not have oxygen flow as a placebo device. Since topical oxygen therapy is always given with a type of modern dressing, these RCTs provide a good view of treatment that consists of dressings, offloadings and adjuncts. All four studies showed that the add on topical oxygen therapy had a positive impact on wound healing, with three of them being statistically significant (Driver et al. 2017; Lavery et al. 2019; Niederauer et al. 2018; Serena et al. 2021). Motawea et al. (2019), being the only RCT that utilised hydrogel with nanostructured lipid carriers (NLCs) of phenytoin (PHT), has shown that this antiepileptic has good healing outcomes (complete healing rate: $95.82 \pm 2.22\%$) while delivered in small particles sizes, perhaps in the future direct comparison with other types of modern dressings can help to further evaluate its effectiveness.

Moisture retaining dressings are popular dressing options, which includes alginate or collagen alginate, hydrofiber and foam dressings. Studies with hydrogel was found to have remarkable outcomes, where Essa et al. (2023) achieve the highest rate of complete healing of 90% with silver hydrogel and Searan et al. (2024) had the shortest mean duration of complete healing of 10.83 days by applying honey and hydrogel alternatively ($p = 0.004$). However, the results could also be the synergy effect of the silver nanoparticles or the honey with hydrogel, perhaps direct comparison of different modern dressings like honey versus silver would be useful to find an effective combination of the dressings. These two studies both utilised orthotic shoes, which is also one of the popular options for offloading in the other RCTs. It is interesting to note that Searan et al. (2024) has used a combination of felt foam and diabetic heel wedge healing shoes for offloading, which is not mentioned in other studies that used orthotic shoes except for Armstrong et al. (2022a). Negative pressure therapy (NPWT) has been a remarkable noninvasive adjunct therapy along with wound dressing, where Dalmedico et al. (2024) reported its potential benefits in reduction of amputation and wound area, however at the time being we did not encounter a study that utilises both NPWT and offloading at the same time. The potential synergy effect of the two therapies along with wound dressing on DFU could be explored in the future.

In general, we do see that removable devices and footwear are more frequently used than the traditional total contact cast, where studies that combined footwear with dressings has the shortest healing time as mentioned earlier. However, the offloading of ulcers was often not well-described in all studies. For example, not all studies with orthotic shoes and orthotic boots specify which type of orthotic shoes or boots they were using, but those with diabetic cam boots (controlled ankle motion) and total contact cast described well regarding the offloading process. We also cannot determine the efficacy of offloading in studies that have multiple choices of offloading used, as the results were focused based on the wound dressings except for Piaggesi et al. (2016). Piaggesi et al. (2016) was able to provide

the healing outcome of a specific combination of offloading and dressings, as the study was primarily focused on the efficacy of offloading methods. Besides that, we also noticed that the compliance of offloading was hard to monitor in the studies. This is a common limitation of offloading, where adherence is a huge issue to be tackled by targeting not only biological such as postural instability, high body mass index, but also psychosocial factors like stigma and dissatisfaction towards wearing offloading devices in public (Racaru et al. 2022). Future RCTs could work on documenting more details of the offloading process and ensuring compliance of offloading such as Gould et al. (2022).

Besides wound dressings and offloading, we found that sharp debridement was also carried out as a standard of care in most studies, as recommended by guidelines. It is great that this was reported, because with adequate debridement, not only accelerates formation of tissue granulation and re-epithelialisation, the removal of necrotic tissue or biofilms helps in infection control of DFU (Jiang et al. 2023). Reporting the frequency of debridement in future studies will help in standardising the healing outcomes of interventions such as dressings and offloadings. Patients that eventually require further mechanical debridement, amputation or the use of antibiotics were mostly withdrawn from these studies, such as Sahu et al. (2018) and Armstrong (2022a), therefore it would be uncertain to determine which of the combinations along with standard of care will lead to the need of further interventions. However, presenting cases of poor outcomes might guide the choice of treatment for clinicians in the future.

Although many studies showed a good short-term outcome for 12 to 16 weeks of treatment, there is lacking of long-term outcome from these studies, only Alvarez et al. (2017) reported the recurrence of ulcer in a year, but the study had a small sample size. Besides that, only studies with newly invented dressings showed the cost of dressings they used. It would be better if both the cost of dressings and offloading are included, because they are considered consumables throughout the long journey of wound healing (also depends on type of offloading). In terms of quality of life, it would be useful if more studies report this outcome because pain and physical functioning will influence a patient's adherence to the treatment. A few RCTs assessed the effect of treatment for DFUs on local neuropathy and even perfusion status of the affected feet. This area could be explored further as it has great potential if these interventions could create a positive impact for foot care in patients with diabetes.

As we only included relatively uncomplicated DFUs in this review, there is a need to look into the effect of dressing in combination with offloading in more serious or infected DFUs, such as those with exposed tendon or bone, or ulcers with tunneling or pockets. There is also a gap for DFUs involving patients with uncontrolled diabetes, where glycemic control could be included as part of the intervention. This could show more realistic results because in the real life situation, patients might walk in with DFUs without knowing their diabetes status, or the disease was not optimised in the first place. Poorly controlled diabetes would heavily influence the healing outcome of patients, thus it would be nice to explore and document how the multidisciplinary team handles this situation and the patients' compliance to such a comprehensive treatment.

CONCLUSION

From 21 RCTs included, it is clear that the combination of wound dressings together with offloading positively impacts the healing process of DFU. However, as the clinical heterogeneity limitations such as different mean ulcer sizes and number of patients, it is hard to determine the best combination of dressings and offloading. Perhaps a meta-analysis of RCTs that include these two interventions could be done when they are more related studies published. Nevertheless, the choice of interventions should be tailored to each individual based on their condition. We hope to see more RCTs that involve both interventions and there would be a standardised protocol for

the combination of dressings with offloading in the future.

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