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Review Article

Collagen-based dressings for diabetic foot ulcers: A systematic review

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Abstract

Background: To evaluate the efficacy and safety of collagen-based dressings in the management of diabetic foot ulcers (DFUs), compared to standard wound care (SWC), human amniotic membrane allografts (hAMA), and decellularized extracellular matrix (dECM) products.

Methods: A systematic review of randomized controlled trials (RCTs) and cohort studies published between December 2013 and March 2025 was conducted using PubMed, Scopus, and Web of Science. Eligible studies assessed collagen-based dressings for DFUs, with primary outcomes including wound area reduction, closure rates, and healing time. Adverse events were considered secondary outcomes. Due to heterogeneity, findings were narratively synthesized by dressing type.

Results: Twenty-two studies (15 RCTs, 7 cohort studies) were included. Collagen-based dressings consistently outperformed SWC, achieving greater wound reduction (54.5–88.2%), higher closure rates (22.2–82.4%), and shorter healing times (21–83.5 days), with no serious treatment-related adverse events. Helicoll showed superior performance (wound reduction: 84–86.5%; closure: 50–71.4%). Comparisons with hAMA and dECM yielded mixed and heterogeneous results, without consistent evidence of superiority. RCTs favored hAMA over Apligraf, while some real-world studies reported the opposite. Findings on collagen/ORC/silver dressings versus dECM were also inconsistent.

Conclusions: Collagen-based dressings are safe and effective for improving DFU healing when compared with standard wound care. However, current evidence is insufficient and heterogeneous to establish superiority over other advanced biologic therapies. Further head-to-head randomized trials are warranted.

Keywords: Collagen-based dressings, Decellularized extracellular matrix, Diabetic foot ulcer, Human amniotic membrane, Standard wound care, Wound healing.

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Diabetes mellitus (DM) imposes a significant global health and economic burden, with projections estimating nearly 700 million affected individuals by 2045 (1, 2). Among its complications, diabetic foot ulcers (DFUs) are among the most debilitating, affecting 15–25% of patients and contributing to up to 85% of diabetes-related lower-limb amputations (3). DFUs are chronic, non-healing wounds resulting from hyperglycemia-associated factors such as impaired perfusion, persistent inflammation, dysfunctional cell signaling, and increased infection susceptibility.(4) Beyond their clinical severity, DFUs pose an enormous economic burden. In the United States alone, the direct costs of diabetic lower-limb complications surpass those of several major cancers, including breast and colorectal cancer (5). These ulcers also have a profound impact on patients' quality of life, contributing to pain, functional impairment, and social isolation (6). Standard wound care (SWC) , including debridement and dressings such as saline gauze, often falls short in managing DFUs due to the wounds' complexity and chronic nature (7) While such interventions help maintain a moist environment and reduce infection risk, they frequently fail to achieve complete healing, leaving patients at continued risk of amputation (8, 9).

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To address these challenges, advanced wound dressings have been developed that not only act as protective barriers but also interact dynamically with the wound microenvironment to promote repair (10). Effective DFU dressings should target key pathophysiologic features, including poor perfusion, unresolved inflammation, dysregulated cell signaling, and microbial burden (11). Emerging dressing technologies now leverage the intrinsic bioactivity of their constituent materials. Among the most promising materials are collagen-based biomaterials, due to their biocompatibility, low immunogenicity, biodegradability, and capacity to support tissue regeneration (12, 13). Collagen, the most abundant structural protein in the human body, plays a pivotal role in all phases of wound healing. It supports hemostasis, facilitates chemotaxis, and promotes the proliferation and migration of fibroblasts and keratinocytes through interactions with growth factors and extracellular matrix (ECM) proteins (14). Sourced from bovine, porcine, ovine, equine, or marine tissues, collagen dressings act as ECM analogs modulating matrix metalloproteinases (MMPs), stabilizing the wound bed, and facilitating cellular infiltration and regeneration (15-19). Given these regenerative properties and favorable safety profile, collagen has been incorporated into a wide range of advanced dressings, including native sheets, granules, bioengineered scaffolds, and composite materials. These formulations have shown promise in promoting wound closure in both preclinical and clinical settings (13, 20-22). This systematic review aimed to evaluate the clinical effectiveness of collagen-based dressings in the management of DFUs by synthesizing findings from the existing literature and assessing their therapeutic impact across different product types.

Methods

Literature search strategy: This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered in the PROSPERO database (Registration No.: CRD420251035667) (23). A comprehensive search of PubMed, Scopus, and Web of Science was performed to identify studies published between December 1, 2013, and March 1, 2025.

Eligibility criteria: The inclusion criteria were as follows: (1) study design: RCTs or retrospective cohort studies; (2) population: adult patients with DFUs; (3) intervention: collagen-based dressings used as the primary treatment, including sheets, sponges, granules, engineered scaffolds, or composites where collagen was the predominant matrix; and (4) outcomes: at least one clinically relevant endpoint, including wound closure, time to healing, wound size reduction, or adverse events. The exclusion criteria were as follows: (1) studies without original clinical data; (2) review articles, case reports, case series, editorials, letters, commentaries, or conference abstracts; and (3) interventions in which collagen was not the main therapeutic component.

Study selection and data extraction: Following removal of duplicate records, all identified studies underwent a three-phase screening process. Two reviewers independently assessed titles and abstracts for relevance and eligibility. Full texts of potentially eligible studies were retrieved and reviewed in detail. Any disagreements between reviewers were resolved through consensus discussion. Data extraction was performed independently by the same reviewers using a standardized data collection form to ensure methodological consistency and minimize bias. Extracted variables included study design, sample size, participant demographics, and type of collagen dressing, comparator interventions, treatment duration, and primary clinical outcomes such as wound area reduction, closure rates, and time to healing.

In addition, baseline metabolic control and limb-related clinical characteristics, such as glycemic status, duration of diabetes, presence of peripheral neuropathy, degree of ischemia, and baseline infection status, were extracted where reported. Definitions of complete wound closure varied across studies, with some reporting closure at the time of full epithelialization and others requiring confirmation after a predefined follow-up period (e.g., one week). These differences were considered when interpreting healing outcomes. Where available, adverse event data were also recorded. Given the heterogeneity in study designs, interventions, and outcome measures, findings were synthesized narratively and categorized by collagen dressing type: living cell constructs, acellular scaffolds, purified type I collagen dressings, and collagen-based composites.

Risk of bias assessment: Risk of bias was assessed using validated tools appropriate to each study design. RCTs were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, assessing bias arising from the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result (24). Retrospective cohorts were assessed using the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool, which evaluates bias due to confounding,

selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selective reporting (25). Any disagreements in bias assessment between reviewers were discussed and resolved by consensus.

Results

Study selection: The initial database search yielded 4,959 records. After removing 905 duplicates, 4,054 records were screened by title and abstract, resulting in the exclusion of 3,979 articles that did not meet eligibility criteria. Seventy-five full-text articles were assessed, with 53 excluded for reasons such as non-English language, irrelevance to outcomes of interest, or use of dressings not primarily collagen-based. Ultimately, 22 studies met all inclusion criteria and were included in the qualitative synthesis. The study selection process is illustrated in the PRISMA flow diagram (figure 1). The complete search syntax for each database is provided in figure 2. The reference lists of relevant publications were also screened. Quality appraisal results are available in figures 2 and 3

Study characteristics: The 22 included studies, published between 2013 and 2025, and comprised 15 RCTs and 7 retrospective cohort studies. Total sample sizes ranged from 22 to 1,590 participants. Across studies, mean participant ages ranged from 49.4 to 76.1 years, with most cohorts comprising a higher proportion of male patients. Intervention durations spanned from 2 to 36 weeks, with follow-up periods ranging from none to 1 year. Baseline ulcer durations varied widely (2 weeks to over 1 year), and wound sizes ranged from as small as 0.5 cm² to over 67 cm².

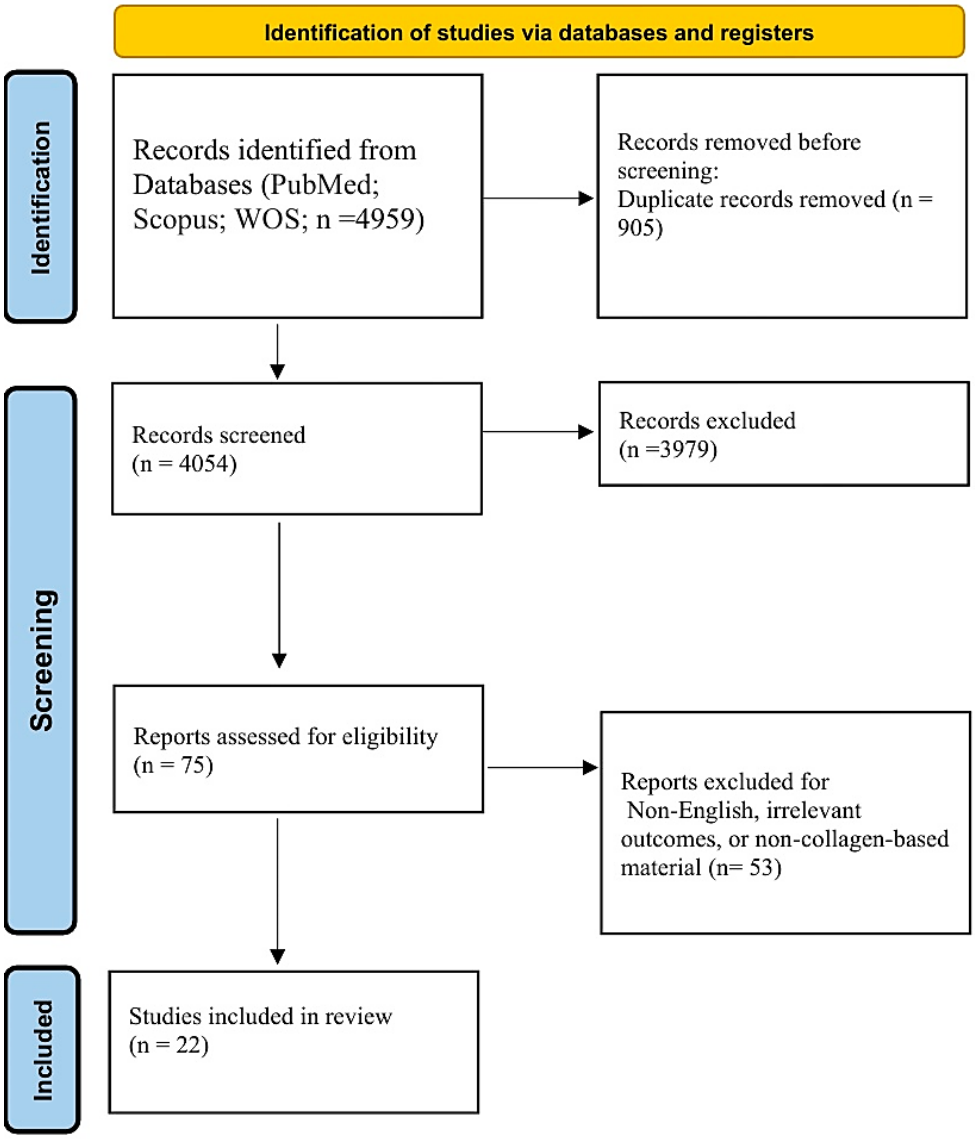

Figure 1. The PRISMA flow diagram of the study selection process

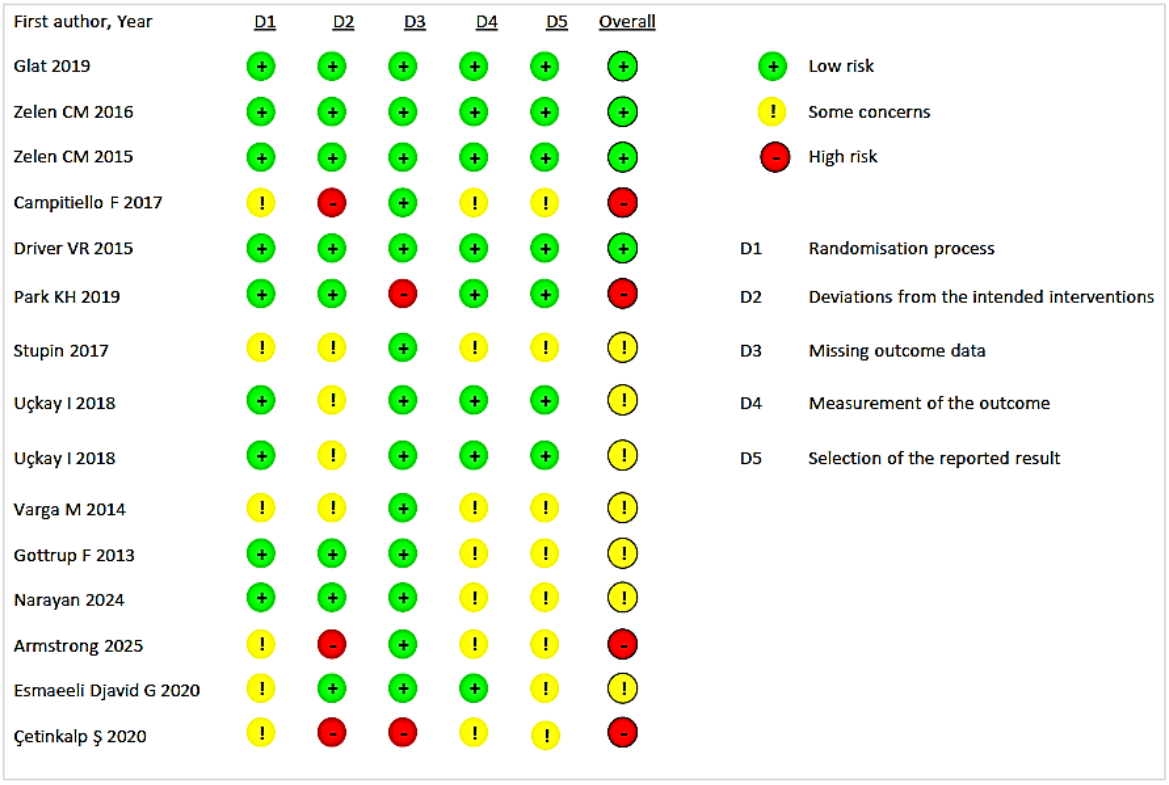

Figure 1. Search syntax for each database

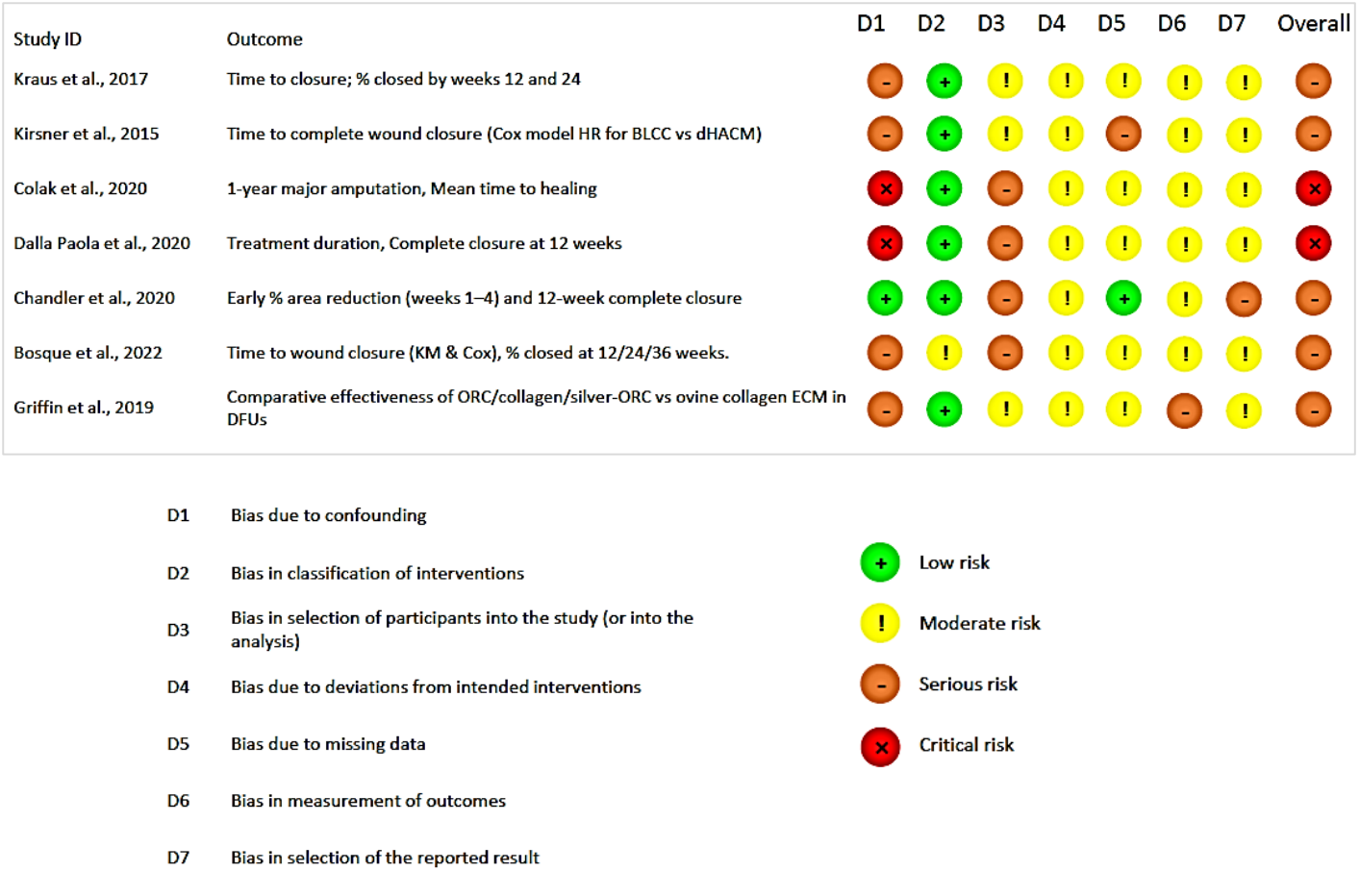

Figure 2. Quality appraisal results

The majority of ulcers were classified as Wagner Grade 1 or 2, although some studies included Grade 3 ulcers in advanced cases. Collagen-based dressings evaluated included:

- Apligraf: Bilayered Living Cellular Construct (BLCC)
- Acellular Collagen-Based Bioengineered Scaffolds (High-Purity Type-I Collagen (HPTC) and Integra)
- Purified Type I Collagen Dressings
- Collagen-Based Composite Dressings (Promogran Prisma, Antibacterial Collagen Dressings, and Bioactive Polymer Composites)

Comparators primarily involved SWC such as saline-moistened gauze or foam dressings. Outcomes reported across studies included wound area reduction, complete closure rate, time to closure, and safety profiles. These data are detailed in tables 1 and 2.

Ulcer severity and ulcer type: Across the included studies, ulcer severity and phenotype were variably reported, most commonly using the Wagner classification. A narrative subgroup analysis was therefore conducted based on available data. Wagner Grade 1 ulcers were predominantly evaluated in randomized trials assessing bioengineered and purified collagen dressings. Studies limited to Wagner grade 1 ulcers including trials of Apligraf, high-purity type I collagen (Helicoll), porcine type I collagen sheets, and wound conforming matrix consistently reported high rates of wound area reduction and complete closure. Closure rates in this subgroup ranged from approximately 71% to over 90%, with shorter times to healing and greater early wound size reduction compared with standard wound care or comparator dressings. In these studies, adverse events were infrequent and largely unrelated to the collagen-based intervention.

Table 1. Baseline characteristics and intervention details of clinical studies evaluating collagen-based dressings for DFUs

First author - Year	Study design	Study Groups	Type of Dressings	Sex (M/F)	Sample Size	Mean age (±SD)	Diabetes Duration	Wound Duration	Wound Size (cm^2), baseline	Wound score	Outcomes	Duration of intervention / Follow-up
Apligraf: Bilayered living cellular construct (BLCC)												
Glat et al., 2019	RCT	CBB CO	Apligraf dHACA	23/7 16/14	60	62±15.3 62±13.2	N.R	14.5±14.7 weeks 12. ±14.3 weeks	3.1±2.29 2.4±1.88	N.R	Wound closure rate, Time to healing, Wound area reduction, Safety profile, Cost-related endpoints	12 weeks total, with weekly visits
Zelen CM et al., 2016	RCT	CBB CO	Apligraf SWC dHACM (Epifix)	14/19 22/13 19/13	100	63·8 60·6 63·3	N.R	≥4 weeks	2·7 (2·75) 2·6 (2·97) 3·1 (3·17)	Wagner 1	Wound closure rate, Time to healing, Wound area reduction, Safety profile, Cost-related endpoints	Up to 12 weeks, or until 1 week after complete wound closure
Zelen CM et al., 2015	RCT	CBB CO	Apligraf SWC dHACM (Epifix)	9/11 9/11 10/10	60	65.2±11.7 62.2 ±12.8 63.2±13.0	N.R	18.5±13.8 weeks 16.2±13.5 weeks 15.6±12.7weeks	2.6±1.8 3.3±2.7 2.7±2.4	N.R	Complete wound closure, wound size reduction, healing velocity, healing time, product use and cost, adverse events	Treatment Phase: Up to 12 weeks or until complete healing/ Follow-up: one-week post-healing for confirmation

First author - Year	Study design	Study Groups	Type of Dressings	Sex (M/F)	Sample Size	Mean age (±SD)	Diabetes Duration	Wound Duration	Wound Size (cm^2), baseline	Wound score	Outcomes	Duration of intervention / Follow-up
Kraus et al., 2017	Retrospective cohort	CBB CO	Apligraf dHACM (Epifix)	13/46 15/48	122	61	N.R	4.2±2.5 months 4.6±3 months	4.8±5.1 5.2±5	N.R	Wound closure rate, time to closure	Follow up at 12 and 24 weeks
Kirsner et al., 2015	Retrospective Cohort	CBB CO	Apligraf dHACM (Epifix)	104/49 48/15	218	60.1±12.5 61.1±12.2	N.R	4.4±2.6 months 4.6± .0 months	6.0±5.5 5.2±5.0	N.R	Wound closure rate, Healing time, number of applications	24 weeks
Acellular collagen-based bioengineered scaffolds												
Armstrong et al., 2025	RCT	CBB CO	High-Purity Type-I Collagen (HPTC, Helicoll) dHACM (Epifix) vCHPM	8/4 10/2	24	60.4±12.03 61.1±12.29	N.R	16.5±13.63 weeks 23.8±12.4 weeks	2.3±2.13 2.4±1.77	Wagner grade 1	Percentage area reduction, complete wound closure, time to wound closure, number of graft applications	4 weeks of treatment / 1 week of follow-up
Narayan et al., 2024	RCT	CBB CO	High-Purity Type-I Collagen (HPTC, Helicoll) dHACM (Epifix)	75%/25% 85%/15%	28	49.4 52.3	N.R	2.86 months 2.93 months	5.52 5.21	N.R	Proportion of patients with ≥50% wound area reduction, Complete wound closure, wound area reduction	4 weeks treatment phase/follow-up visit confirmed healing after 1 week
Dalla Paola L et al., 2020	Retrospective Cohort	CBB CO	Integra Dermal Regeneration Template (IDRT) No dermal substitute	9/4 8/5	26	74.4 75	N.R	N.R	N.R	N.R	Limb salvage, 1-year major amputation rate, time to healing, mortality, safety	Treatment phase: Until complete healing/ Follow-up: 1 year
Campitiello F et al., 2017	RCT	CBB CO	Integra Flowable Wound Matrix (IFWM) SWC: sterile saline-moistened gauze)	15/8 13/10	46	64.04±8.94 62.08±7.71	N.R	38.56±12.61 weeks 39.5±9.9 weeks	N.R	Wagner scale Grade 3	Complete wound healing, healing time, rehospitalization, major amputation	6 weeks or until complete closure/ Follow-up: None beyond 6 weeks (Weekly visits for 6 weeks; initial follow-ups every 3 days in week 1)

First author - Year	Study design	Study Groups	Type of Dressings	Sex (M/F)	Sample Size	Mean age (±SD)	Diabetes Duration	Wound Duration	Wound Size (cm^2), baseline	Wound score	Outcomes	Duration of intervention / Follow-up
Driver VR et al., 2015	RCT	CBB CO	Integra Dermal Regeneration Template (IDRT) SWC: moist wound therapy, 0.9% sodium chloride gel	118/36 114/39	307	55.8±10.6 57.3±9.7	N.R	308±491 days 303±418 days	3.5 ±2.5 3.65±2.7	Wagner grade 2: 109 (70.8%) Wagner grade 2: 116 (75.8%)	Wound closure rate, healing time, wound size reduction, recurrence, quality of life	Treatment Phase: 16 weeks or until complete closure/ Follow-up: 12 weeks (every 4 weeks post-treatment or post-closure)
Purified Type I Collagen Dressings												
Colak B et al., 2020	Retrospective Cohort	CBB CO	Type 1 fish collagen granules (Helisorb Particles) SWC: Physiological serum with wet-to-dry gauze	28/6 24/6	64	58.65±12.59 58.4±13.07	20 22	8 months	12 9	Wagner grade 2: 28 (82.3%), Wagner grade 3: 6 (17.6%) Wagner grade 2: 23 (76.6%), Wagner grade 3: 7 (23.3%)	Wound Bed Score (WBS), complete healing rate, treatment duration, granulation, wound size reduction	Treatment phase: 8 weeks / Follow-up: 4
Chandler LA et al., 2020	Retrospective cohort	CBB CO	WCM: Type I bovine fibrillar collagen-based Wound Conforming Matrix SWC: saline-moistened gauze	19/7 11/4	41	55±12 57±13	N.R	12.1±11.8 months 12.9±13.1 months	2.0±1.2 2.7±1.7	Wagner Grade 1	Wound area reduction, complete closure rate, safety, platelet activation (PDGF release)	Treatment phase: 12 weeks /Follow-up: 24 weeks, weekly until closure or week 12, plus 12 weeks for durability
Park KH et al., 2019	RCT	CBB	100% porcine type I collagen sheet covered by	12/5	30	62.8±13	19.5±7.2	17.4±9 weeks	4.98±6.59	Wagner grade 1: 16 (94.1%)	Complete healing rate, ulcer size reduction, healing velocity, time	Treatment Phase: Up to 12 weeks/

First author - Year	Study design	Study Groups	Type of Dressings	Sex (M/F)	Sample Size	Mean age (±SD)	Diabetes Duration	Wound Duration	Wound Size (cm^2), baseline	Wound score	Outcomes	Duration of intervention / Follow-up
			polyurethane foam								to 50% reduction, time to complete healing	
		CO	SWC: Polyurethane foam dressing alone	11/2		53±14.7	20.1±8.6	12.7±6.7 weeks	4.49±6.56	Wagner grade 2: 1 (5.9%) Wagner grade 1: 13 (100%)		Follow-up: Weekly for 12 weeks or until complete healing
Stupin et al., 2017	RCT	CBB	Collost/Salvecoll	18/18	71	57.5±10.25	N.R.	9.54±9.74	13.5	Wagner2 : 27(75%), Wagner 3: 9 (25%)	Wound area reduction, wound volume regression, rate of complete epithelialization, and ineffective treatment	Treatment phase and follow-up: 4 weeks
		CO	Standard care	19/16		60.45±4.75		7.39±8.47	12.6	Wagner 2: 23 (65.7%), Wagner 3: 12 (34.3%)		
Promogran Prisma												
Bosque BA et al., 2022	Retrospective cohort	CBB	Promogran Prisma	534/244	1590	62±13	N.R	14.5±41.3 weeks	1.5±3.8	N.R	Median time to closure, % wounds closed at 12, 24, 36 weeks, hazard ratio for closure, product use, safety	Treatment phase: Until healing or up to 36 weeks/ Follow-up: 36 weeks
		CO	Ovine forestomach matrix (Endoform Natural)	580/225		61.8±12.9		15.8±41.7 weeks	2.0±5.5			
Griffin et al., 2019	Retrospective cohort	CBB	Promogran Prisma	534/244	844	59.8±12.2	N.R	34.5 days	1.5 (0.6–6.0)	Wound healing index (WHI) :63.4 (14.4)	Wound improvement, time to granulation	21 days treatment/ 16 weeks follow-up
		CO	Ovine Collagen ECM (Endoform)	580/225		59.2±12.0		36.5 days		63.7 (14.4)		

First author - Year	Study design	Study Groups	Type of Dressings	Sex (M/F)	Sample Size	Mean age (±SD)	Diabetes Duration	Wound Duration	Wound Size (cm^2), baseline	Wound score	Outcomes	Duration of intervention / Follow-up
Gottrup F et al., 2013	RCT	CBB	Promogran Prisma	22/2	39	62.9±13.5	17.2±11.9	12.9±13 months	2.1±3.1	Wagner grade 2–3	wound area reduction, complete wound closure, infection rate, protease biomarkers	14 weeks (treatment & follow-up)
		CO	SWC: debridement and off-loading	13/2		57.3±14.6	14.4±10.7	16.9±36.6 months	4.4±6.3			
Antibacterial-Enhanced Collagen Dressings												
Uçkay I et al., 2018	RCT	CBB	Gentamicin-collagen sponge (GARAMYCIN Sponge)	7/4	22	69	N.R	N.R	N.R	IDSA mild DFUI: ≥2 inflammation signs, erythema <2 cm, no systemic infection) Median 13 points	Cure rate, complete healing rate, pathogen eradication, wound score change	Treatment Phase: 2 weeks) / Follow-up: 24 days
		CO	SWC: saline-moistened dressings	7/4		73						
Uçkay I et al., 2018	RCT	CBB	Gentamicin-Collagen Sponge (GARAMYCIN Sponge)	33/10	88	72	N.R	N.R	N.R	IDSA moderate/ severe DFUI: ≥2 inflammation signs, erythema >2 cm or deeper structures for moderate, systemic signs for severe: 18 points	Clinical cure, improvement, wound score change, pathogen eradication	Treatment Phase: 2–4 weeks/ Follow-up: Weekly visits, 1 month
		CO	SWC: saline-moistened dressings	29/16		71						

First author - Year	Study design	Study Groups	Type of Dressings	Sex (M/F)	Sample Size	Mean age (±SD)	Diabetes Duration	Wound Duration	Wound Size (cm^2), baseline	Wound score	Outcomes	Duration of intervention / Follow-up
Varga M et al., 2014	RCT	CBB	Gentamicin-impregnated collagen sponge (Collatamp EG)	18/4	45	61	19	N.R	N.R	N.R	Wound healing time, hospital stay, re-amputation rate, adverse events	Treatment Phase: Until complete healing (median 3 weeks Experimental, 4.9 weeks Control)/ Follow-up: Until complete healing
		CO	No sponge	15/8		63	23					
Bioactive Polymer Collagen-based Composites												
Çetinkalp Ş et al., 2020	RCT	CBB	Dermalix (collagen-laminin matrix with resveratrol microparticles)	34/11	45	60.5±9.26	18.91±9.8	N.R	57.756±69.556	Wagner grade 1 or 2	Wound area reduction, tissue collagen levels, safety and adverse events	Treatment phase :4 weeks/ follow up: total 3 months
		CO	SWC: saline-moistened gauze			60.52±9.54	17.04±6.84		73.428±106.809			
Esmaeeli Djavid G et al., 2020	RCT	CBB	Tebaderm: Collagen-chitosan hydrogel matrix	18/12	61	54.2±13.2	12.8±7.2	≥12 weeks	3.09±2.5	Wagner grade 2	wound area reduction, complete wound closure rate, time to healing, infection-related hospitalizations	Treatment Phase: Up to 24 weeks/ Follow-up: 24 weeks
		CO	SWC: Saline-moistened gauze	22/9		57.3±13.2	13.6±7.6		3.5±4.2			

Abbreviations: Randomized Controlled Trial (RCT), Collagen-based Biomaterial (CBB), Comparator/Control group (CO), Standard Wound Care (SWC), Bilayered Living Cellular Construct (BLCC), Dehydrated Human Amnion/Chorion Membrane (dHACM), High-Purity Type I Collagen (HPTC), Viable Cryopreserved Human Placental Membrane (vCHPM), Integra Dermal Regeneration Template (IDRT), Integra Flowable Wound Matrix (IFWM), Integra Bilayer Wound Matrix (IBWM), Split-Thickness Skin Graft (STSG), Oxidized Regenerated Cellulose (ORC), Extracellular Matrix (ECM), Porcine Collagen Matrix with Polyhexamethylene Biguanide (PCMP), Polyhexamethylene Biguanide (PHMB), Gentian Violet / Methylene Blue Polyurethane (GV/MB PU), Wound Conforming Matrix (WCM), Platelet-Derived Growth Factor (PDGF), Not Reported (N.R), Standard Deviation (SD), Wound Bed Score (WBS), Wound Healing Index (WHI), Diabetic Foot Ulcer Infection (DFUI), Infectious Diseases Society of America (IDSA).

Table 2. Clinical outcomes of collagen-based dressings in the management of DFUs

First author and Year	Dressings (CBB vs. CO)	Wound Area Reduction/ Percent Area Reduction	Complete Closure Rate (%)	Time to Closure	Adverse event (s)	Conclusion
Glat P, et al. 2019	Apligraf	44% (90.6)	Week 6: 23% (7/30) Week 12: 40% (12/30)	63 days	7 total (4 SAEs); none graft-related,	Given that Apligraf is one of the most established engineered skin substitutes, the results demonstrate that dHACA offers greater value to patients, providing faster and more reliable wound healing at a significantly lower cost and with less wastage
	dHACA	98% (10.3)	Week 6: 77% (23/30) Week 12: 90% (27/30)	32 days	5 total (3 SAEs); none graft-related	
Kraus et al., 2017	Apligraf	NR	Week 12: 32% Week 24:50%	19.4 weeks	no treatment-related AEs reported	Apligraf significantly improved healing outcomes versus dHACM in real-world DFU management, with higher closure rates, faster healing, with no AEs.
	dHACM (Epifix)		Week 12: 55% Week 24:76%	12 weeks		
Zelen et al. 2016	Apligraf	NR	73% (24/33)	47.9 days	10 events across all arms, 7 wound/foot infections (2 SAEs: both in SOC), No events were product-related	EpiFix demonstrated superior efficacy over both Apligraf and standard wound care in achieving faster and more complete healing of chronic DFUs, requiring fewer grafts per healed wound (median 2.5 vs. 6) and incurring substantially lower median costs ($1,517 vs. $8,918).
	SWC (collagen-alginate)		51% (18/35)	57.4 days		
	dHACM (EpiFix)		97% (31/32)	23.6 days		
Zelen et al. 2015	Apligraf	53.1%	45% (9/20)	49 days	5 total AEs: 1 in EpiFix (cellulitis), 2 in Apligraf (hospitalizations unrelated to study ulcer), 2 in SWC (cellulitis/infection); none treatment-related	EpiFix achieved significantly faster and higher rates of wound closure than Apligraf and standard care, requiring fewer applications (median 2.15 vs. 6.2), markedly less product wastage (55.8% vs. 97.1%), and substantially lower costs per patient ($1,669 vs. $9,216). These findings indicate that EpiFix is both clinically more effective and economically superior for managing chronic DFUs.
	SWC (collagen-alginate)	N.R	35% (7/20)	49 days		
	dHACM (EpiFix)	83.5%	95% (19/20)	13 days		
Kirsner et al. 2015	Apligraf	NR	48% at 12 weeks 72% by 24 weeks	13.3 weeks	no treatment-related AEs reported	In real-world management of DFUs, Apligraf demonstrated superior effectiveness over dHACM, with a higher probability of wound healing, faster median time to closure, fewer applications (2.5 vs. 3.5), and longer intervals between treatments (14 vs. 9.3 days).
	dHACM (Epifix)		28% at 12 weeks 47% by 24 weeks	26 weeks		
Armstrong et al. 2025	Helicoll	83.9%	6/12 (50%)	N.R	No AE reported in either group	Helicoll demonstrated superior wound healing outcomes compared to amnion/placental-based products in DFUs. Higher closure rates and greater wound area reduction were observed.
	dHACM (Epifix) or vCHPM	71.3%	3 /12 (25%)			

First author and Year	Dressings (CBB vs. CO)	Wound Area Reduction/ Percent Area Reduction	Complete Closure Rate (%)	Time to Closure	Adverse event (s)	Conclusion
Narayan et al. (2024)	Helicoll dHACM	86.48% 77.7%	10/14 (71.4%) 7/14 (50%)	NR	No AE reported in either group	a ≥50% reduction in wound size was achieved in 85.71% (12/14) of patients treated with Helicoll compared to 50% (7/14) in the dHACM group. These findings indicate that HPTC is a highly effective treatment for DFUs, demonstrating superior wound size reduction and overall healing outcomes compared to dHACM
Dalla Paola L et al.2020	IDRT No dermal substitute	NR	100% (12/12) 100% (13/13)	83.5 days (range 21–121) 139.2 days (range 31–198)	1 death (cardiac, unrelated) in Integra group; 2 major amputations in control group	In no-option CLI patients with diabetic foot ulcers, Integra achieved a 0% major amputation rate at 1 year compared to 15% with standard surgical care (P = .05), with no significant difference in mortality (8% vs. 0%). These results demonstrate that Integra can significantly accelerate healing and effectively prevent major amputations, reinforcing its role as a safe and valuable limb salvage option in complex, high-risk cases.
Campitiello F et al. 2017	IFWM SWC: saline-moistened gauze	NR	86.95% (20/23) 52.17% (12/23)	29.73±9.27 days 42.78±8.22 days	no treatment-related AEs reported	IFWM significantly outperformed wet dressings in DFU management, achieving higher closure rates (86.95% vs. 52.17%), faster healing (29.73 vs. 42.78 days), and lower major amputation (4.34% vs. 30.43%) and rehospitalization rates (8.69% vs. 43.47%), with no AEs reported.
Driver VR et al. 2015	IDRT SWC: saline-moistened gauze	7.5% per week 4.8% per week	51% (79/154) at 16 weeks 45% (70/154) at 12 weeks 32% (49/153) at 16 weeks 20% (31/153) at 12 weeks	43 days 78 days	Severe AEs: IDRT 15.6% vs. Control 26.8% Moderate AEs also higher in control group. Similar treatment-related AE rate in both groups	IDRT significantly improved wound closure rates, reduced healing time, and enhanced quality of life (better physical functioning and less bodily pain), with most cases responding to a single application and fewer ulcer recurrences (19% vs. 26%), confirming its safety and effectiveness for chronic, hard-to-heal DFUs
Colak B et al., 2020	Helisorb Particles (Type 1 fish collagen granules) SWC: Physiological serum with wet-to-dry gauze	NR	25/34 (73.5%) 17/30 (56.6%)	8.08 weeks 9.2 weeks	no treatment-related AEs reported	Helisorb significantly improved DFU healing compared to SOC, achieving higher partial closure at 2 weeks (44.1% vs. 26.6%), earlier granulation, shorter treatment duration, and greater WBS improvement, confirming its efficacy and safety in chronic wound care.

First author and Year	Dressings (CBB vs. CO)	Wound Area Reduction/ Percent Area Reduction	Complete Closure Rate (%)	Time to Closure	Adverse event (s)	Conclusion
Park KH et al., 2019	100% porcine type I collagen sheet SWC: foam dressing alone	4.39±4.95 (88.2%) 2.24±2.81 (49.9%)	14/17 (82.4%) 5/13 (38.5%)	9 weeks	Minor AEs: 4 in collagen group (pain, discomfort, skin sensitization); 3 in control group (pain, skin issues, odor); no serious AEs.	Porcine collagen dressing significantly outperformed foam dressing in DFU management, with faster healing velocity (0.55 vs. 0.29 cm²/week; 17.85% vs. 9.41%/week), shorter time to 50% size reduction (21 vs. 42 days), and confirmed high biocompatibility, offering an effective and well-tolerated treatment option.
Stupin et al., 2017	Collost/Salvecoll SWC	67% 39%	8/36 (22.2%) 3/35 (8.6%)	NR	no treatment-related AEs reported	Collost/Salvecoll biomaterial significantly reduced the ineffective treatment rate (8.3% vs. 34.3%), safely accelerated wound healing compared to SOC.
Chandler LA et al., 2020	WCM: (Wound Conforming Matrix; purified bovine dermal collagen) SWC: (saline-moistened gauze)	Week 4: 63% ≥75% area reduction: 50% Week 4: 38% ≥75% area reduction: 13%	42% (11/26) 27% (4/15)	NR	no treatment-related AEs reported	WMC significantly accelerated DFU healing versus SOC, with notable area reduction by week 2 after a single application. Its mechanism may involve platelet activation and PDGF release, confirmed in vitro. Effective with one or two applications, WCM was safe, well tolerated.
Bosque et al., 2022	Promogran Prisma (ORC/Collagen/silver) Ovine forestomach matrix (Endoform Natural)	NR	76.2% 82.5%	16.4±0.7 weeks 14.6±0.5 weeks	no treatment-related AEs reported	OFM significantly accelerated DFU healing compared to Promogran Prisma, with a higher hazard ratio for closure, similar baseline characteristics, and fewer re-applications (lasting up to 7 days vs. every 1–2 days).
Griffin et al., 2019	Promogran Prisma (ORC/Collagen/silver) Ovine forestomach matrix (Endoform Natural)	82% 74.6%	75–100% granulation at 16 weeks: 63.6% 54.8%	75–100% granulation: 42 days 60 days	no treatment-related AEs reported	In real-world matched cohort data, Promogran outperformed OFM in DFU management, with fewer wounds worsening (15.2% vs. 23.9%) and superior outcomes in granulation and wound trajectory.
Gottrup F et al. 2013	Promogran Prisma (ORC/Collagen/silver) SWC: (debridement and off-loading)	≥50% Reduction at week 4: 79% ≥50% Reduction at week 4: 43%	52% 31%	NR	0 5 AEs (4 infections, 1 treated)	Promogran significantly improved early DFU healing, reduced infection rates, and modulated MMP-9 and elastase activity.

First author and Year	Dressings (CBB vs. CO)	Wound Area Reduction/ Percent Area Reduction	Complete Closure Rate (%)	Time to Closure	Adverse event (s)	Conclusion
Uçkay I et al. 2018	Gentamicin-Collagen Sponge (GARAMYCIN Sponge) SWC: saline-moistened dressings	NR	91% (10/11) 91% (10/11)	NR	no treatment-related AEs reported	In mild DFUIs, gentamicin–collagen sponge was well tolerated but showed no advantage over local care alone in wound score improvement, microbiological eradication, or clinical outcomes.
Uçkay I et al. 2018	Gentamicin-Collagen Sponge (GARAMYCIN Sponge) SWC: saline-moistened dressings	NR	72% (31/43) 58% (26/45)	NR	no treatment-related AEs reported	In moderate to severe DFUs, gentamicin–collagen sponge was safe and well tolerated, with an 88% combined cure/improvement rate in both groups and no significant advantage over systemic antibiotics alone, though a better healing trajectory was observed.
Varga M et al. 2014	Gentamicin-collagen sponge (Collatamp EG) SWC: (no sponge)	NR	NR	3.0 weeks 4.9 weeks	no treatment-related AEs reported	In diabetic patients post-minor amputation, gentamicin–collagen sponge was well tolerated, significantly shortened wound healing time, and reduced hospital stay (median 11 vs. 15 days), with a non-significant difference in re-amputation rates.
Çetinkalp Ş et al., 2020	Dermalix (collagen-laminin matrix with resveratrol microparticles) SWC: saline-moistened dressings	57.82% 26.63%	NR	N.R	2 SAEs (infection, gangrene), 1 death in SWC group; no treatment-related AEs reported	Dermalix significantly accelerated DFU healing, with faster improvement by day 14 and maximal effect by day 28, alongside reduced TNF-α and caspase-3 levels, increased GSH/GSSG ratio and total collagen, and no safety concerns.
Esmaeeli Djavid G et al., 2020	Tebaderm:Collagen-chitosan hydrogel matrix SWC: (Saline-moistened gauze)	54.5±30.9% 38.8±29.5%	18/30 (60%) 11/31 (35.5%)	11.8 weeks 21.4 weeks	2 AEs in study (6.6%), 3 AEs in control (9.6%); no treatment-related AEs reported	Tebaderm (chitosan–collagen hydrogel matrix) dressing significantly improved healing rates and reduced healing time in neuropathic DFUs compared to standard care, with earlier healing onset, less discomfort, lower dressing change frequency, and good safety and tolerability.

CBB: Collagen-based dressing, CO: Collagen-only dressing, dHACA: Dehydrated human amnion and chorion allograft, dHACM: Dehydrated human amnion/chorion membrane, SWC: Standard wound care, DFU: Diabetic foot ulcer, SAE / SAEs: Serious adverse event(s), AE / AEs: Adverse event(s), HPTC: High-Purity Type-I Collagen, vCHPM: Viable cryopreserved human placental membrane, CLI: Critical limb ischemia, DRT: Integra dermal regeneration template, IFWM: Integra flowable wound matrix, IBWM – Integra bilayer wound matrix, 3D-ACM: Three-dimensional acellular collagen matrix, GBT013: Experimental 3D matrix composed of equine collagen, squid chitosan, and chondroitin sulfate, STSG: Split-thickness skin graft, OFM: Ovine forestomach matrix, ORC: Oxidized regenerated cellulose, PCMP: Porcine collagen matrix with polyhexamethylene biguanide, PHMB: Polyhexamethylene biguanide, GSH/GSSG: Reduced glutathione / oxidized glutathione ratio, TNF-α: Tumor necrosis factor alpha, PDGF: Platelet-derived growth factor, WCM: Wound conforming matrix.

Wagner Grade 2 ulcers were the most commonly represented severity category across both randomized and observational studies, particularly in trials of Integra Dermal Regeneration Template, purified bovine and fish-derived collagen products, collagen/ORC composite dressings, and bioactive collagen matrices. In this subgroup, collagen-based dressings were associated with moderate to high rates of wound closure and meaningful reductions in wound size, although healing times were generally longer than those reported for grade 1 ulcers. Studies including Wagner grade 2 ulcers frequently demonstrated improved healing trajectories compared with standard wound care, but with greater variability in outcomes, likely reflecting heterogeneity in wound chronicity and baseline characteristics. Wagner Grade 3 ulcers were less frequently studied and were primarily evaluated in trials of acellular collagen-based scaffolds and flowable matrices. Studies of Integra Flowable Wound Matrix and Integra Dermal Regeneration Template in Wagner grade 3 ulcers reported favorable healing outcomes, including higher closure rates, faster time to healing, and reduced major amputation rates compared with standard care. However, these studies generally involved smaller sample sizes and shorter follow-up periods. In contrast, studies including mixed populations of Wagner grade 2–3 ulcers reported lower overall closure rates and longer healing times than those restricted to lower-grade ulcers. With respect to ulcer phenotype, explicit stratification between neuropathic and ischemic ulcers was infrequently reported. Most randomized trials of collagen-based dressings focused on predominantly neuropathic ulcers or excluded patients with critical limb ischemia. Studies that included patients with severe ischemia or no-option critical limb ischemia, particularly those evaluating Integra-based scaffolds, demonstrated delayed healing trajectories but reported potential benefits in limb salvage and reduced major amputation rates. Due to inconsistent reporting, formal comparisons between neuropathic and ischemic ulcers could not be performed.

Table 3. Baseline metabolic control and limb-related clinical characteristics across included studies

Study	Glycemic control (e.g., HbA1c)	Presence and severity of peripheral neuropathy	Degree of ischemia (e.g., ABI, $TcPO_2$)	Infection status at baseline
Colak B et al., 2020	Mean HbA1c before treatment: 8.78±0.90 (collagen) vs 8.69±1.01 (PS); after treatment: 6.75±0.71 vs 6.75±0.70	Peripheral neuropathy present in 32.3% (collagen) and 33.3% (PS); severity not reported	Mean AI: 1.08±0.11 (collagen) vs 1.10± 0.10 (PS); PAD present in 5.8% vs 10%	Baseline infection present in 67.6% (collagen) and 63.3% (PS)
Bosque BA et al., 2022	Mean HbA1c: 7.2±3.4% (OFM) vs 7.3±3.5% (collagen/ORC); estimated from reported glucose values	NR	NR	NR
Kirsner RS et al., 2015	NR	NR	NR	NR
Chandler LA et al., 2020	NR	Diabetic neuropathic foot ulcers (all included ulcers were neuropathic)	NR	NR
Dalla Paola L et al., 2020	Mean HbA1c: 56 mmol/mol (range 33–75) in Integra group vs 53 mmol/mol (26–94) in control group	Peripheral neuropathy present in all patients (absence of rest pain attributed to diabetic neuropathy)	Critical limb ischemia in all patients; mean $TcPO_2$: 11 mm Hg (Integra) vs 9 mm Hg (control); ABI not reported	Infection present at baseline; all patients underwent wound cultures and targeted antibiotic therapy; osteomyelitis in 77% (Integra) vs 38% (control)
Kraus et al., 2017	NR	NR	NR	NR
Griffin et al., 2019	NR	NR	NR	NR
Glat P et al., 2019	Mean HbA1c at baseline: 7.5±1.58% (dHACA) vs 7.9±2.15% (TESS); median 7.4 vs 7.2	Neuropathic DFUs (Wagner grade 1); neuropathy implied by inclusion criteria	Adequate perfusion required for inclusion: ABI 0.7–1.2 with biphasic/triphasic Doppler or $TcPO_2$/TCOM ≥ 30 mm Hg	NR

Study	Glycemic control (e.g., HbA1c)	Presence and severity of peripheral neuropathy	Degree of ischemia (e.g., ABI, $TcPO_2$)	Infection status at baseline
Zelen CM et al., 2016	Mean HbA1c at baseline: 7.9±1.79% (BSS), 7.5±1.51% (dHACM), 8.2±1.78% (SWC); HbA1c <12% required for inclusion	Neuropathic diabetic lower extremity ulcers implied by inclusion criteria	Adequate perfusion required: ABI 0.7–1.2 or $TcPO_2 \geq 30$ mm Hg or biphasic/triphasic Doppler waveforms	NR
Zelen CM et al., 2015	Mean HbA1c at baseline: 8.0±1.9% (Apligraf), 7.4±1.5% (EpiFix), 8.0±1.8% (standard care); HbA1c < 12% required for inclusion	Neuropathic diabetic lower-extremity ulcers implied by inclusion criteria	Adequate perfusion required: ABI 0.7–1.2 or $TcPO_2 \geq 30$ mm Hg or biphasic/triphasic Doppler waveforms	NR
Armstrong DG et al., 2025	Mean HbA1c at baseline: 7.6±1.69% (comparator graft) vs 7.5±2.38% (HPTC); HbA1c ≥ 13% excluded	Peripheral neuropathy present in majority of patients: 100% in comparator group and 67% in HPTC group	Adequate perfusion required for inclusion: ABI 0.7–1.3 or $TcPO_2$ ≥ 30 mm Hg or biphasic PVR/Doppler	NR
Narayan N et al., 2024	NR	Peripheral neuropathy implied (neuropathy described as a key DFU mechanism; neuropathy status not quantified or graded at baseline)	Adequate perfusion required for inclusion: ABI 0.7–1.3 or $TcPO_2$ ≥ 30 mm Hg or biphasic PVR/Doppler	NR
Campitiello F et al., 2017	Mean HbA1c at baseline: 7.9±0.8% (Integra Flowable Wound Matrix) vs 7.8 ±0.8% (wet dressing); patients with HbA1c ≥ 10% excluded	Peripheral neuropathy assessed using MDNS; neuropathy present in 82.6% (Integra group) and 73.9% (control)	Mean ABI: 0.92±0.1 (Integra) vs 0.94±0.1 (control); patients with ABI < 0.5 excluded	Baseline infection present: wound cultures obtained in all patients; osteomyelitis in 39.1% (Integra) vs 34.8% (control); targeted antibiotics administered
Driver VR et al., 2015	Mean HbA1c at baseline: 8.0±1.8% (IDRT) vs 8.2±1.9% (control); HbA1c ≤ 12% required for inclusion	Neuropathic diabetic foot ulcers in all patients (full-thickness neuropathic DFUs required for inclusion); neuropathy severity not graded	Adequate perfusion required: ABI 0.65–1.2 or toe pressure >50 mm Hg or $TcPO_2$ >40 mm Hg or Doppler evidence of adequate flow	NR
Park KH et al., 2019	Mean HbA1c at baseline: 7.1±1.2% (collagen) vs 7.8±2.1% (control)	Peripheral neuropathy implied (neuropathy described as a key DFU mechanism)	Adequate perfusion required for inclusion: palpable dorsalis pedis or posterior tibial pulse or $TcPO_2$ ≥ 30 mm Hg	NR
Stupin VA et al., 2017	HbA1c measured at baseline, but mean values not reported; patients with hyperglycemia >14 mmol/L excluded	Peripheral neuropathy implied as a key component of diabetic foot syndrome	Critical limb ischemia excluded; vascular status assessed by Doppler ultrasonography and oximetry	NR
Gottrup F et al., 2013	Mean HbA1c at baseline: 6.54±3.73% (collagen/ORC/silver) vs 5.19±4.17% (control); no significant intergroup difference	Diabetic foot ulcers (Wagner grade 2–3); neuropathy implied by DFU diagnosis	Mean ABI: 0.94±0.11 (collagen/ORC/silver) vs 0.97±0.15 (control); toe pressure 95.6 ± 31.1 mm Hg vs 83.0±30.8 mm Hg; patients with PAD or toe pressure <45 mm Hg excluded	NR
Uçkay I et al., 2018	NR	Peripheral neuropathy present (background diabetic neuropathy acknowledged)	NR	All patients had moderate or severe diabetic foot ulcer infection at baseline (100% infected DFUs by IDSA criteria)

Study	Glycemic control (e.g., HbA1c)	Presence and severity of peripheral neuropathy	Degree of ischemia (e.g., ABI, $TcPO_2$)	Infection status at baseline
Uçkay I et al., 2018	Median HbA1c at baseline: 7.0 mmol/L (control) vs 6.8 mmol/L (gentamicin–collagen sponge)	Peripheral neuropathy implied (diabetic foot ulcers below the malleolus)	Peripheral arterial insufficiency requiring revascularization excluded; PAD present in 7/22 (32%) overall; median ABI 0.95 (control) vs 1.05 (sponge)	All patients had mild diabetic foot ulcer infection at baseline by IDSA criteria (100% infected DFUs)
Varga M et al., 2014	Median HbA1c: 6.0% (range 4.6–9.5) in gentamicin–collagen group vs 6.2% (4.0–8.4) in control group	Diabetic foot syndrome requiring minor amputation; neuropathy implied by indication	Median $TcPO_2$: 44 mm Hg (range 13–67) in gentamicin group vs 48 mm Hg (11–69) in control	Chronic infected ulcers with osteomyelitis prior to minor amputation; low systemic inflammatory markers (median CRP 5–10 mg/L); all patients received systemic antibiotics
Çetinkalp Ş et al., 2020	Mean HbA1c at baseline: 7.31±1.25% (SWC) vs 7.74±1.94% (SWC + Dermalix); no significant intergroup difference	Peripheral neuropathy not explicitly reported; patients had Wagner grade 1–2 DFUs	NR	NR
Esmaeeli Djavid G et al., 2020	Mean HbA1c at baseline: 8.03±1.9% (control) vs 8.30±1.47% (collagen matrix dressing); no significant intergroup difference	Neuropathic DFUs in all patients (inclusion required neuropathic DFUs, Wagner grade II)	Adequate perfusion required: all patients had ABI > 0.8 with palpable dorsalis pedis and posterior tibial pulses	NR

ABI, Ankle–Brachial Index; BSS, Bioengineered Skin Substitute; CRP, C-Reactive Protein; DFU, Diabetic Foot Ulcer; DFUI, Diabetic Foot Ulcer Infection; dHACA, Dehydrated Human Amnion/Chorion Allograft; dHACM, Dehydrated Human Amnion/Chorion Membrane; EG, Gentamicin-impregnated (e.g., collagen sponge); HbA1c, Glycated Hemoglobin; HPTC, High-Purity Type I Collagen; IDRT, Integra Dermal Regeneration Template; IDSA, Infectious Diseases Society of America; MDNS, Michigan Diabetic Neuropathy Screening Score; MRSA, Methicillin-Resistant Staphylococcus aureus; NR, Not Reported; OFM, Ovine Forestomach Matrix; ORC, Oxidized Regenerated Cellulose; PAD, Peripheral Arterial Disease; PVR, Pulse Volume Recording; PS, Physiological Saline; RCT, Randomized Controlled Trial; SWC, Standard Wound Care; TCOM, Transcutaneous Oxygen Measurement; $TcPO_2$, Transcutaneous Oxygen Pressure; TESS, Tissue-Engineered Skin Substitute.

Discussion

1. Apligraf: bilayered living cellular construct (BLCC)

Biological skin substitutes (BSSs) mark a significant step forward in tissue engineering for chronic wounds, particularly DFUs. They foster healing by providing scaffolds that support cellular proliferation, modulate inflammation, and facilitate angiogenesis and tissue regeneration (26). Conventional grafting approaches often bring difficulties such as donor site damage, limited graft availability, infection, and immune rejection. BSSs were developed to help overcome these barriers and are generally grouped according to structural features and cellular composition (27). Apligraf (Organogenesis Inc., MA) is a cellular BSS composed of neonatal keratinocytes and fibroblasts arranged in a bilayer on a bovine type I collagen scaffold. It has been widely tested in DFUs and venous leg ulcers (VLUs). Its mechanism of action includes reducing persistent inflammation, promoting keratinocyte migration, and blocking pro-fibrotic Wnt/β-catenin signaling (28). The clinical value of Apligraf was established in early trials that formed the basis for FDA approval. A key multicenter RCT led by Veves and colleagues reported higher healing rates with Apligraf compared with saline gauze, with fewer amputations and less osteomyelitis (29). Subsequent studies supported these findings by showing faster closure and better healing outcomes (30, 31). While these investigations precede the time frame of this review, they remain central to its evidence base.

Comparisons with more recent biologic alternatives have yielded mixed results. One alternative is dehydrated human amnion/chorion membrane (dHACM), marketed as EpiFix (MiMedx Group Inc., GA). This graft is derived from placental submucosal tissue collected during scheduled Cesarean deliveries and sterilized to remove viable cells while retaining its structural and biochemical properties (32). Five studies, three RCTs and two real-world

comparative-effectiveness study, have yielded mixed results regarding Apligraf's effectiveness in chronic DFUs.

In a real-world retrospective analysis of 218 patients with 226 DFUs, Apligraf achieved significantly faster and more frequent wound closure than EpiFix, with a shorter median time to closure (13.3 vs. 26 weeks; P = 0.01) and higher closure rates at both 12 weeks (48% vs. 28%; P = 0.01) and 24 weeks (72% vs. 47%; P = 0.01).(33). Another retrospective real-world study found higher closure with Apligraf at 12 and 24 weeks (55% vs 32%; 76% vs 50%) and a shorter time to closure (median 7.4 weeks sooner; P=0.02) (34). In a multicenter randomized controlled trial of 60 patients, Zelen et al. reported that EpiFix achieved significantly higher rates of early wound closure than Apligraf at both 4 weeks (85% vs 35%; $p < 0.01$) and 6 weeks (95% vs 45%; $p < 0.01$), along with a significantly shorter median time to closure (13 vs 49 days; $p < 0.001$). (35). In a subsequent larger randomized controlled trial involving 100 patients, the same group reported significantly higher complete healing rates with EpiFix compared with Apligraf at 12 weeks (97% vs 73%; $p < 0.001$), along with a significantly shorter mean time to closure (23.6 vs 47.9 days; $p < 0.001$). (36). In a more recent randomized controlled trial by Glat et al., placental membranes (dHACM/dHACA) achieved significantly higher healing rates and faster wound closure than Apligraf, with a greater proportion of ulcers healed at 12 weeks (90% vs 40%; $p < 0.001$) and a shorter mean time to healing (32 vs 63 days; $p < 0.001$).(37).

Taken together, evidence diverges by study design: RCTs with weekly applications show Apligraf heals fewer DFUs and more slowly than amnion/chorion products. In contrast, real-world analyses favored Apligraf over dHACM. These discrepancies may reflect differences in protocol intensity, wound selection, and closure definitions. Future studies should include larger, head-to-head trials with longer follow-up and standardized cost assessments to clarify the relative value of Apligraf versus placental allografts across real-world and controlled environments.

2. Acellular collagen-based bioengineered scaffolds:

2.1. HPTC: high purity type-I collagen skin substitute

Two RCTs have examined Helicoll, a purified type I collagen substitute, in the treatment of diabetic foot ulcers. An Indian single-center randomized controlled trial, 85.7% of patients treated with Helicoll achieved ≥50% reduction in ulcer area at four weeks compared with 50% in the dHACM group; however, this difference did not reach statistical significance (P = 0.25). By week four, complete healing was observed in 10 of 14 patients receiving Helicoll and 7 of 14 receiving dHACM. Mean wound area reduction was greater with Helicoll than with dHACM (86.5% vs 77.7%), with a statistically significant between-group difference ($p < 0.001$). (38). A separate trial in the United States found a mean reduction of 83.9% with Helicoll, compared with 71.3% for either dHACM or vCHPM, and full closure in 6 of 12 Helicoll cases compared with 3 of 12 in the control arm (39). No adverse events were observed in both studies. The apparent benefit has been linked to the uncross-linked, phosphorylated collagen matrix of Helicoll, which fosters cell activity and angiogenesis.

2.2. Integra

Unlike living skin substitutes such as Apligraf, acellular scaffolds do not contain viable cells. One example is the Integra, which combines a silicone outer sheet that mimics the epidermis with an inner layer made of bovine collagen and shark-derived chondroitin-6-sulfate glycosaminoglycan (40). In a multicenter randomized controlled trial involving 307 patients with diabetic foot ulcers, Driver et al. demonstrated significantly better healing outcomes with the IDRT compared with standard care. At 16 weeks, complete wound closure occurred in 51% of IDRT-treated ulcers versus 32% in the control group (P = 0.001). The median time to complete healing among ulcers that closed was shorter with IDRT (43 vs 78 days), and most patients in the IDRT arm required only a single application. Severe adverse events were significantly more frequent in the control group (26.8% vs 15.6%; P = 0.02), while treatment-related adverse events were similar between groups (4.5% vs 5.2%). During the 12-week follow-up period, ulcer recurrence rates did not differ significantly between groups (19% vs 26%; P = 0.32) (41). In patients with DFUs complicated by no-option critical limb ischemia, the IDRT has shown promise for limb preservation. Dalla Paola et al. conducted a retrospective study of 26 patients with complex DFUs and failed revascularization; half were treated with IDRT. Despite poor vascularity and frequent bone or tendon exposure, the IDRT group showed significantly faster healing (83.5 vs. 139 days; P = 0.03) and no major amputations at 1-year follow-up, compared to 15% in controls (P = 0.05) (42).

While IDRT has shown benefit in superficial DFUs, its sheet-like structure makes it less suitable for wounds with tunnels or irregular contours. To address this limitation, Campitiello et al. investigated the use of Integra Flowable Wound Matrix (IFWM), a fluid-form, collagen-based scaffold. Designed to fill deep or uneven wound spaces, IFWM was studied in patients with Wagner grade 3 ulcers. In a single-center randomized controlled trial of 46 patients, treatment with Integra Flowable Wound Matrix (IFWM) resulted in significantly higher complete wound closure at

six weeks compared with wet dressings (86.9% vs 52.2%; P = 0.01). Healing was significantly faster in the IFWM group, with a shorter mean time to closure (29.7 vs 42.8 days; p < 0.001). Rates of major amputation and rehospitalization were also significantly lower among patients treated with IFWM during the study period (p = 0.03 and P = 0.02, respectively) (43).

3. Purified type I collagen dressings

Collagen is sourced from a range of tissues, including bovine, porcine, and fish origins. In practice it is manufactured as powders, gels, sheets, granules, or sponges, each suited to different wound settings. Across four studies that used purified collagen as the primary active material, early healing signals were consistent, though designs and comparators varied. A RCT from South Korea evaluated a 100% porcine type I collagen sheet plus foam against foam alone in 30 patients with Wagner grade 1–2 DFUs. At 12 weeks, complete closure was achieved in 82.4% of collagen-treated ulcers compared with 38.5% in controls (P = 0.02). Collagen also halved the median time to 50% area reduction (21 vs 42 days; P = 0.04) and reduced median time to full closure to 63 days, whereas the control group did not reach this endpoint (P = 0.03). Adverse events were infrequent and similar between groups (44). The Wound Conforming Matrix (WCM) is a fibrillar collagen scaffold designed to integrate with the wound bed and stimulate early repair through platelet activation and PDGF release. In another RCT, patients who failed to improve after a two-week gauze run-in were randomized to WCM or continued gauze. At four weeks, 50 percent of WCM patients achieved at least 75 percent area reduction compared with 13 percent on gauze (P = 0.02). Complete closure at twelve weeks was higher with WCM (42 vs 27 percent; p > 0.0.5). No treatment-related adverse events or anti-collagen antibodies were reported (45).

Stupin et al. conducted a RCT evaluating the addition of bovine collagen biomaterials (Collost/Salvecoll) to standard therapy in 71 patients with diabetic foot syndrome. The collagen-treated group showed faster reductions in wound size and volume, with median area reduction at day 28 of 67 percent compared to 39 percent in controls (p < 0.05). Complete epithelialization was achieved in 22.2 percent of collagen-treated wounds versus 8.6 percent with standard care, and the greatest improvement was observed in wound width (p < 0.05) (46). Colak et al. evaluated fish-derived type I collagen granules (Helisorb Particles, Medira Ltd) in advanced diabetic foot ulcers and found improved healing compared with saline dressings. In a retrospective cohort of 64 patients followed for at least 12 weeks, complete closure was achieved in 73.5 percent of those treated with collagen versus 56.6 percent in the saline group (P = 0.29). Collagen use was also linked to shorter recovery times and better wound bed scores (p < 0.05). The particles, applied every two to three days, provided an alternative collagen source with high biocompatibility and low immunogenic potential (47). Evidence from porcine, bovine, and fish-derived collagen products suggests they can accelerate early healing, often achieving faster wound reduction. Safety has been acceptable with no clear infection risk or immune reactions. Yet stronger randomized data with longer follow-up are needed.

4. Collagen-based composite dressings

4.1. Collagen/ORC dressings (promogran and promogran prisma)

Collagen-based composite dressings that combine collagen with oxidized regenerated cellulose (ORC), with or without silver, have been widely evaluated in DFUs. These products are designed to stabilize the ECM, bind excess proteases, and restore balance within the wound microenvironment, while silver incorporation provides additional antimicrobial protection in high-risk ulcers. Promogran (collagen/ORC) and Promogran Prisma (collagen/ORC with silver) represent the most extensively studied formulations. A systematic review of 20 studies assessing ORC/collagen dressings across different wound types reported that these dressings generally achieved faster wound closure and greater area reduction than SWC. Several trials also documented decreases in proteases such as MMP-2, elastase, plasmin, and gelatinase, indicating a possible role in modulating the wound microenvironment (48). In a randomized trial of 39 patients with DFUs, the addition of Promogran Prisma to standard care improved healing responses, with nearly twice as many patients achieving at least 50% wound area reduction at four weeks compared with controls (79% vs 43%; P = 0.04). Importantly, no patients in the intervention group withdrew due to infection, compared with nearly one-third (31%) in the control group (p=0.01), suggesting a protective effect of the silver component. A non-significant trend toward higher 14-week closure was also seen (52% vs 31%; p > 0.05). Protease profiling revealed that persistent elevation of MMP-9 and elastase was strongly associated with non-response at week 4 (P = 0.01), indicating that composite protease burden may be a more reliable predictor of healing than single markers and reinforcing the biological rationale for this dressing (49). Decellularized extracellular matrix (dECM) products have become important tools in wound care, providing biologically active scaffolds that support cell infiltration and tissue regeneration. Retaining structural proteins, proteoglycans, and growth factors from their tissue

sources, these matrices help restore the healing environment. Ovine forestomach matrix (OFM) is among the most widely available examples and contains more than 150 bioactive molecules. Evidence indicates that OFM promotes cell recruitment, modulates protease activity, and stimulates angiogenesis, highlighting its potential in chronic wound management. Although OFM is not included in this review because it is categorized as a decellularized product, its clinical outcomes illustrate the broader move toward advanced wound care strategies (50).

Real-world evidence provides additional but somewhat conflicting perspectives. In a propensity-matched analysis of the US Wound Registry (422 DFUs per arm), Promogran Prisma was associated with higher rates of healing or improvement (82.0% vs 74.6%; P=0.01), fewer worsening ulcers (15.2% vs 23.9%; P=0.001), faster granulation (median 42 vs 60 days; P=0.01), and more frequent achievement of 75–100% granulation at 12 (59.7% vs. 50.2%; P = 0.02) and 16 weeks (63.6% vs. 54.8%; P = 0.03) (51). Conversely, a separate registry study using the Net Health Wound Care database, encompassing more than 2,000 DFUs, found that OFM outperformed Promogran. OFM was associated with a significantly shorter median time to wound closure (14.6 vs 16.4 weeks; P = 0.002), higher proportions of healed ulcers at 36 weeks (82.5% vs 76.2%; P = 0.003), and a greater probability of healing in Cox proportional hazards analyses (adjusted hazard ratio 1.21; P = 0.001). The discrepancy between the two registries highlights the challenges of interpreting non-randomized evidence, where differences in wound severity, treatment protocols, and product definitions may introduce residual confounding (52). Overall, RCT evidence indicates that Promogran Prisma can accelerate early healing and reduce infection-related treatment failures. Retrospective cohort findings provide mixed signals, with one analysis favoring Promogran Prisma and another favoring OFM. These divergent results may reflect differences in silver content, comparator products, and underlying patient populations.

4.2. Antibacterial-enhanced collagen dressings

Three randomized trials assessed type-I collagen sponges infused with gentamicin, used either alongside systemic treatment or as a local substitute. Two studies by Uçkay et al.tested the gentamicin–collagen sponge (GARAMYCIN Sponge) in diabetic foot infections. In the larger trial including 88 patients with moderate to severe infections, adjunctive use of up to four gentamicin–collagen sponges in addition to systemic antibiotics and standard wound care did not significantly improve the primary outcome. Clinical cure was achieved in 72% of patients in the sponge group compared with 58% in the control group (P = 0.16), and pathogen eradication occurred in 60% versus 44%, respectively (P = 0.13). Wound scores improved in both groups, with a nonsignificant trend toward faster improvement during week's three to five in the intervention arm. No adverse events attributable to the sponge were observed. (53). In a smaller pilot randomized trial involving 22 patients with mild diabetic foot infections, patients were assigned to daily gentamicin–collagen sponge plus local care or local care alone. At the end of therapy, 91% of patients achieved clinical cure and 9% showed improvement, with no between-group differences in clinical outcomes. Ulcer closure rates were identical in both groups (10/11 vs 10/11; P = 1.00), as were pathogen eradication rates (6/11 vs 6/11; P = 1.00). The gentamicin–collagen sponge was well tolerated, with no treatment-related adverse events or safety signals identified. (54)

In a separate RCT, Varga et al. examined a gentamicin-loaded bovine collagen sponge (Collatamp® EG) in patients undergoing minor amputations. Placement of the sponge into the wound bed at surgery shortened healing time, with a median of three weeks compared to nearly five weeks in the control group (3.0 vs 4.9 weeks; p < 0.05). Hospital stays and re-amputation rates were similar. Systemic exposure to gentamicin remained well below toxic levels, as the sponge is intended to produce high local antibiotic concentrations with minimal absorption into circulation. (55). Overall, antimicrobial collagen dressings appear safe and may speed healing after minor amputations. They have not, however, shown an ability to improve infection cure in diabetic foot ulcers treated without surgery.

4.3. Bioactive composite collagen dressings

Two recent randomized trials have investigated advanced collagen-based dressings enhanced with bioactive components for DFUs. The first trial assessed a chitosan–collagen hydrogel matrix (Tebaderm) in patients with chronic neuropathic DFUs. Compared with SWC, this composite material produced a more rapid reduction in wound size during the first four weeks (54.5% vs 38.8%; p = 0.05) and yielded a significantly higher rate of complete healing at 20 weeks (60.0% vs 35.5%; P = 0.048). The therapeutic effect is plausibly related to the antimicrobial and mechanically reinforcing properties of chitosan in combination with the adhesive and cell-supporting characteristics of collagen. The reduced frequency of dressing changes also hints at greater patient convenience and potentially lower caregiver burden (56). The second study tested a collagen–laminin dermal scaffold (Dermalix®) supplemented with resveratrol-loaded microparticles. In this trial, wounds treated with the device closed nearly twice as fast during the four-week

intervention compared with standard care (percentage closure 57.8% vs 26.6%; $p < 0.05$). Importantly, tissue analysis indicated favorable modulation of oxidative stress and inflammatory pathways, with reductions in TNF-α ($P = 0.001$) and caspase-3 levels ($P = 0.004$) and an increase in antioxidant activity (reflected by higher reduced/oxidized glutathione ratios ($P = 0.003$)) (57). In summary, collagen–chitosan and other bioactive polymer composites offer multifunctional benefits that address key barriers to DFU healing. By integrating structural scaffolding with antimicrobial, immunomodulatory, and pro-regenerative elements, these dressings consistently outperform conventional care in promoting closure and restoring wound homeostasis. Viewed together, these studies provide converging evidence that composite collagen dressings integrating biologically active agents may accelerate early healing of neuropathic DFUs more effectively than conventional moist dressings. Their mechanisms differ, one emphasizing antimicrobial and scaffold reinforcement through chitosan, the other targeting oxidative stress via resveratrol and structural stabilization with laminin, but both reflect a broader shift toward multifunctional biomaterials that not only cover the wound but actively guide repair.

5. Strengths and limitations

This review provides a comprehensive, systematically organized synthesis of collagen-based therapies for DFUs, incorporating evidence from RCTs, multicenter studies, and real-world data. By categorizing interventions into distinct product types and excluding broader ECM products, it isolates collagen-specific therapeutic effects. Nonetheless, important limitations must be acknowledged to contextualize the findings and guide future research. Considerable heterogeneity was present across included studies, with variability in design, sample sizes, treatment durations, and product types. In addition, although some studies reported cost or resource utilization outcomes, economic data were inconsistently and non-uniformly reported, precluding formal cost-effectiveness or health economic synthesis. Critically, key diabetes-related clinical variables known to influence DFU healing including glycemic control, duration of diabetes, presence and severity of peripheral neuropathy, degree of ischemia, and baseline infection status were inconsistently reported or not adjusted for across most included studies. This limited the ability to adequately control for confounding factors and constrains causal attribution of observed healing outcomes exclusively to collagen-based dressings. The absence of these parameters may also partially explain heterogeneity in treatment effects and may have constrained causal interpretation. Outcome assessment was also heterogeneous. Definitions of complete wound closure were not standardized across studies, with variability in confirmation criteria and follow-up timing, thereby limiting direct comparability of healing outcomes.

Although collagen-based dressings generally demonstrated a favorable short-term safety profile, adverse event reporting was inconsistent across studies, with variable detail regarding complications, bacterial burden, or debridement requirements. Importantly, long-term outcomes including durability of wound closure and ulcer recurrence were rarely evaluated, despite the high recurrence rates of DFUs in real-world clinical practice. This represents a critical evidence gap, as short follow-up durations in many trials constrain assessment of sustained benefit and long-term safety. Therefore, there is a need for future studies to systematically assess long-term safety, recurrence, and sustained wound closure. In addition, although some studies reported cost or resource utilization outcomes, economic data were inconsistently and non-uniformly presented, precluding formal cost-effectiveness or health economic synthesis. Finally, this review intentionally excluded acellular dermal matrices, amniotic membranes, small intestine submucosa, and other ECM-rich products containing multiple bioactive proteins, as their complex composition obscures collagen-specific effects. Only dressings where collagen is the primary, well-defined therapeutic agent, either purified or as a bioengineered scaffold, were included. This narrowed focus allows for a more mechanistic evaluation of collagen's role in DFU healing.

Conclusion

Collagen-based dressings are safe and effective in the management of diabetic foot ulcers and consistently demonstrate improved healing outcomes compared with standard wound care. However, evidence comparing collagen-based dressings with other advanced biologic therapies, such as hAMA and dECM products, remains heterogeneous and inconclusive, precluding claims of comparative superiority. As such, no definitive conclusions regarding comparative superiority can be drawn, underscoring the need for well-designed, head-to-head randomized trials with standardized outcome reporting.

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