South American Publishing

SAP Podiatry. 2026;3:267
doi: 10.62486/pod2026267

REVIEW

Cellular and tissue-based skin substitutes for diabetic foot ulcers

Sustitutos cutáneos celulares y basados en tejidos para las úlceras del pie diabético

Yenny Elers Mastrapa[1]
Fabian Quiroz Zendejas[2]

[1] Universidad del Deporte. La Habana, Cuba.
[2] Instituto Mexicano del Seguro Social. México.

Submitted: 05-03-2026 | Revised: 30-04-2026 | Accepted: 09-08-2026 | Published: 13-08-2026

ABSTRACT

Introduction: Diabetic foot ulcers heal slowly and precede most diabetes-related lower limb amputations. Cellular and tissue-based skin substitutes are used when standard care fails, but their effect on complete healing remains uncertain. Methods: This systematic review followed PRISMA 2020. Scopus, PubMed, OpenAlex and Crossref were searched from 2018 to 2026 for randomized controlled trials and comparative studies comparing a cellular or tissue-based skin substitute with standard care, placebo or another substitute in adults with diabetic foot ulcers. Results: Of 414 records identified, 307 were screened and 11 randomized controlled trials were included. Of five trials with a standard-care comparator, intact fish skin graft achieved healing in 44% versus 26% at 16 weeks, ovine forestomach matrix in 46% versus 24% at 12 weeks, and dehydrated amnion-chorion in 50% versus 17%; one large cryopreserved amniotic trial found no significant difference (66.1% versus 59.8%). Conclusions: Cellular and tissue-based skin substitutes increased complete healing of diabetic foot ulcers in most included trials, although the evidence is limited by small samples, open designs and clinical heterogeneity.

Keywords: diabetic foot ulcer; skin substitutes; bioengineered skin; wound healing; systematic review.

RESUMEN

Introducción: Las úlceras del pie diabético cicatrizan con lentitud y preceden a la mayoría de las amputaciones de miembros inferiores relacionadas con la diabetes. Los sustitutos cutáneos celulares y basados en tejidos se emplean cuando fracasa la atención estándar, pero su efecto sobre la cicatrización completa sigue siendo incierto. Métodos: Esta revisión sistemática siguió PRISMA 2020. Se buscó en Scopus, PubMed, OpenAlex y Crossref de 2018 a 2026 ensayos clínicos aleatorizados y estudios comparativos que compararan un sustituto cutáneo celular o basado en tejidos con la atención estándar, un placebo u otro sustituto en adultos con úlceras del pie diabético. Resultados: De 414 registros identificados, se cribaron 307 y se incluyeron 11 ensayos clínicos aleatorizados. De cinco ensayos con comparador de atención estándar, el injerto intacto de piel de pescado logró cicatrización en el 44% frente al 26% a las 16 semanas, la matriz de preestómago ovino en el 46% frente al 24% a las 12 semanas y la membrana deshidratada de amnios-corion en el 50% frente al 17%; un ensayo grande de membrana amniótica criopreservada no halló diferencias significativas (66,1% frente a 59,8%). Conclusiones: Los sustitutos cutáneos celulares y basados en tejidos aumentaron la cicatrización completa de las úlceras del pie diabético en la mayoría de los ensayos incluidos, aunque la evidencia está limitada por muestras pequeñas, diseños abiertos y heterogeneidad clínica.

Palabras clave: úlcera del pie diabético; sustitutos cutáneos; piel de bioingeniería; cicatrización de heridas; revisión sistemática.

© 2026; The Authors. This Open access article is distributed under CC BY 4.0 licence.

INTRODUCTION

Diabetic foot ulcers are among the most disabling and costly complications of diabetes, and they precede more than 80% of nontraumatic lower limb amputations worldwide.(1)The lifetime risk of developing a foot ulcer approaches 34% in people with diabetes, and the five-year mortality after a first ulcer is comparable to that of several solid cancers.(1,2) A recent systematic review of the global epidemiology of the diabetic foot estimated that the pooled lifetime prevalence of ulceration approaches one in five adults with diabetes, with substantial variation across regions and income levels, and it confirmed that low-income settings carry a disproportionate share of amputation and death.(3)The five-year mortality after a diabetic foot ulcer approaches 30% in high-income cohorts and is higher still after major amputation, which places the wound and its closure at the center of any limb-salvage strategy.(1) The pathophysiology is well characterized: sensory neuropathy removes protective sensation, motor neuropathy alters foot architecture and increases plantar pressure, and autonomic neuropathy dries the skin, while peripheral artery disease and impaired angiogenesis delay tissue repair.(4)The resulting wound is trapped in a chronic inflammatory state in which matrix metalloproteinases degrade the extracellular matrix faster than it can be replaced, and fibroblasts and keratinocytes fail to migrate and proliferate normally.(5)The economic burden follows the clinical burden, because the direct cost of diabetic foot ulcer care reaches tens of billions of dollars each year in the United States alone and rises sharply when a wound becomes chronic and requires advanced therapy.(5)Healing is the defining clinical event: a closed ulcer is the strongest protection against infection, hospitalization and amputation, and recurrence is common even after successful closure, which keeps the cumulative risk high over time.(1)

Standard care addresses these mechanisms through sharp debridement, infection control, revascularization when indicated and pressure offloading, as recommended by the International Working Group on the Diabetic Foot.(6)The 2023 evidence review of that group confirmed that these components remain the foundation of treatment, but it also documented that many ulcers fail to heal within twelve weeks and that adjunctive therapies are frequently required.(7)The quality of offloading in trials is itself variable, as a meta-research audit of the trials supporting the 2023 recommendations demonstrated.(8)Cellular and tissue-based skin substitutes were developed to supply the missing biological components of healing, either by delivering living cells such as fibroblasts and keratinocytes or by providing a tissue-derived matrix that restores the structural scaffold and releases growth factors and cytokines.(9,10) They include bilayered living cellular constructs, human fibroblast-derived dermal substitutes, keratinocyte grafts, amniotic and chorionic membranes, placental matrices, fish skin grafts and ovine forestomach matrix, and they are usually applied weekly as adjuncts to standard care.(5)These products are conventionally grouped as cellular, acellular and matrix-like products, a taxonomy that reflects whether living cells are present and whether the scaffold is derived from human or animal tissue, and the regulatory and reimbursement framework treats the categories differently.(9)

Several systematic reviews have examined portions of this literature, but their scope has been narrower than the present review and their conclusions have been discordant. A Cochrane review of skin grafting and tissue replacement concluded that the evidence was of low certainty and that no product could be recommended over another.(11)Meta-analyses restricted to human amniotic membrane reported benefit for healing diabetic foot ulcers,(12,13) and a meta-analysis of placenta-derived biomaterials reached a similar conclusion against standard care.(14)A scoping review of bioengineered skin found promising but heterogeneous results,(15)and network meta-analyses of topical and adjunctive therapies suggest benefit for several products, although the ranking depends on the comparator set and the geometry of the network.(16,17) A meta-analysis of fish skin grafts against standard care reported higher healing with fish skin.(18)These reviews were published at different times, included different product classes and rarely isolated the specific comparison that guides clinical decisions, namely complete healing against standard care within the most recent bibliographic window. An updated synthesis restricted to randomized comparisons is therefore warranted to inform product selection in diabetic foot practice. The objective of this systematic review was therefore to synthesize the evidence published between 2018 and 2026 on the effectiveness of cellular and tissue-based skin substitutes for achieving complete healing of diabetic foot ulcers. The review question was formulated in the PICO format: in adults with diabetic foot ulcers, do cellular and tissue-based skin substitutes increase complete ulcer healing compared with standard care, placebo or another substitute?

METHODS

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were eligible if they enrolled adults with a diabetic foot ulcer of any University of Texas or Wagner grade and compared a cellular or tissue-based skin substitute with standard care, placebo or another skin substitute.

Cellular substitutes were defined as products containing living or previously living human cells, including bilayered living cellular constructs, human fibroblast-derived dermal substitutes and keratinocyte grafts. Tissue-based substitutes were defined as products derived from human or animal tissue applied as a wound covering or matrix, including amniotic, chorionic and placental membranes, umbilical cord tissue, decellularized dermal matrices, fish skin grafts and ovine forestomach matrix. Injectable cell suspensions and intramuscular cell therapies were excluded because they are not applied as a skin replacement, even when they contain cells of placental origin. The primary outcome was complete wound healing, defined as full epithelialization with no drainage. Secondary outcomes were time to complete healing and adverse events. Randomized controlled trials and comparative observational studies were eligible; case reports, case series, preclinical studies, reviews and editorials were excluded. Studies published in English, Spanish or Portuguese between 2018 and 2026 were considered, consistent with the bibliographic window of the journal volume, and no restriction was applied by wound severity, follow-up length or sample size. Studies that compared two application frequencies or two preservation methods of the same product were retained because they inform the practical use of the products, and they were analyzed separately from the comparisons against standard care. Wound severity was recorded with the University of Texas or Wagner classification when the authors reported one, and trials that enrolled diabetic foot ulcers without a formal grade were included and described by the ulcer characteristics reported by the authors.

Information sources and search strategy

Databases: Scopus, PubMed, OpenAlex and Crossref

Search strategy:

TITLE-ABS-KEY(“diabetic foot ulcer” AND (“skin substitute” OR “skin substitutes” OR “tissue substitute” OR “bioengineered skin” OR “cellular dermal substitute” OR “living skin equivalent” OR “bilayered cellular construct”)) AND PUBYEAR > 2017 AND PUBYEAR < 2027.

TITLE-ABS-KEY(“diabetic foot” AND (“amniotic membrane” OR “placental membrane” OR “dehydrated human amnion” OR “chorion membrane” OR “allograft” OR “xenograft”) AND (“ulcer” OR “wound”)).

For each included study the following items were extracted into a structured table: first author and year, country, design, sample size, population and wound severity, intervention and comparator, complete healing rates with their point estimates and, where reported, confidence intervals or P values, time to healing, and adverse events. The risk of bias assessment was extracted alongside. Data were taken from the abstract and results sections of each retrieved report, and no missing field was completed by assumption; fields that were not reported were recorded as not reported. Extraction was performed by a single reviewer directly from the retrieved full texts, and the product names, sample sizes and healing proportions were checked against the abstract of each report to reduce transcription error.

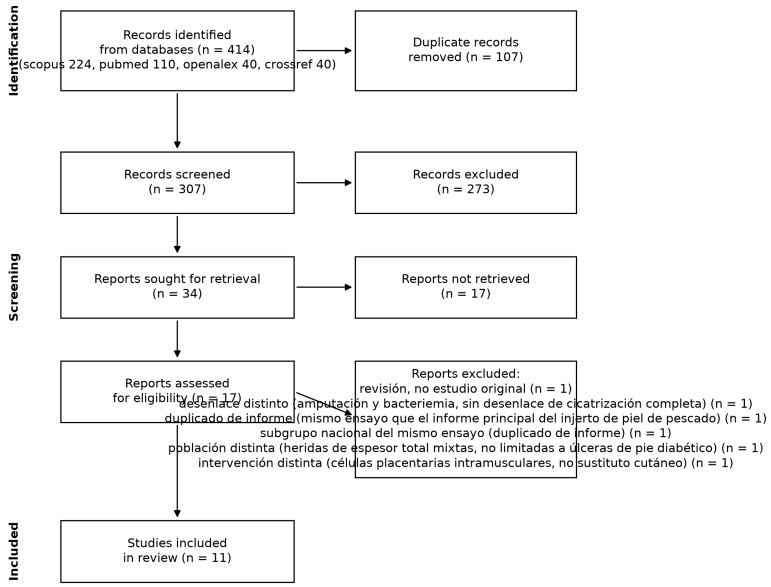
Results were synthesized narratively and organized by comparison type, separating trials with a standard-care or placebo comparator from head-to-head comparisons between two substitutes or two application regimens. The five trials with a standard-care or placebo comparator were considered the primary evidence for the review question, and the six head-to-head trials were summarized separately as secondary evidence on relative effectiveness. For each synthesis claim the number of supporting studies was stated explicitly, in accordance with the analytical style of the review. Heterogeneity was described in terms of product class, wound severity, comparator, follow-up length and effect size, and a meta-analysis was not performed because these dimensions were not comparable across the eleven trials. The evidence was also organized into a study-by-study matrix that links each finding to the study that produced it, so that every synthesis claim can be traced to its source, and a separate table reports the risk of bias by domain.

RESULTS

Study selection

The searches identified 414 records, of which 107 duplicates were removed before screening (Figure 1). Of the 307 records screened at the title and abstract stage, 273 were excluded and 34 reports were sought for retrieval. Seventeen reports could not be retrieved because a full text was not available in open access, and 17 reports were assessed for eligibility. Of these, six were excluded at full text: one was a review, one assessed a mixed population of full-thickness wounds rather than diabetic foot ulcers, one evaluated intramuscular placental cells rather than a skin substitute, one reported amputation and bacteremia without a healing outcome, and two were duplicate or subgroup reports of the same fish skin trial. Eleven randomized controlled trials were included in the review.

Figure 1. PRISMA 2020 flow diagram of study selection.



Note: SOC = standard care. Source: Elaborated from the search and screening records.

Characteristics of included studies

The eleven trials randomized a total of 955 participants, with sample sizes ranging from 24 to 255 (Table 1). Five trials compared a substitute with standard care or placebo, and six compared two substitutes or two application regimens. The primary endpoint was complete healing or the proportion of wounds closed in seven trials, percentage wound area reduction in three trials, and wound grade and healing duration in one, and the follow-up windows ranged from four weeks to fifty weeks. The products evaluated were intact fish skin graft, ovine forestomach matrix with hyaluronic acid, dehydrated human amnion and chorion membrane, cryopreserved and lyopreserved umbilical cord tissue, cryopreserved ultra-thick amniotic membrane, high-purity type I collagen-based skin substitute, a tissue-engineered skin substitute and an amniotic fluid gel. The trials were conducted in the United States, India, Iran and Italy, and one was a multinational European trial, and all were published between 2019 and 2026, which places every included study inside the 2018 to 2026 bibliographic window. Wound severity ranged from superficial Wagner grade 1 or University of Texas grade 1A ulcers to deep grade 2 and 3 wounds with exposed bone, tendon or joint capsule. Four trials enrolled superficial ulcers of Wagner grade 1 or University of Texas grade 1A, three enrolled deep wounds with exposed bone, tendon or joint capsule, and the remaining trials enrolled full-thickness or non-healing wounds of mixed depth. Of the eleven trials, six randomized fewer than 60 participants, and the two largest trials together accounted for half of the total sample.

Table 1. Characteristics and main results of the eleven included randomized controlled trials.

Study	Country	Design	Sample	Intervention versus comparator	Complete healing result
Dardari 2024	Multinational	Open RCT	255	Intact fish skin graft versus SOC	44% versus 26% at 16 weeks
Armstrong 2026	United States	RCT	143	Ovine forestomach matrix plus SOC versus SOC	46% versus 24% at 12 weeks
Caporusso 2025	Italy	RCT	220	Cryopreserved amniotic membrane plus SOC versus SOC	66.1% versus 59.8% at 26 weeks
Hall 2025	United States	Two RCTs	53	Amnion-chorion allograft plus SOC versus SOC	50% versus 17%
Niami 2022	Iran	Triple-blind RCT	92	Amniotic fluid gel versus placebo gauze	Improved grade and healing duration
Narayan 2025	India	Multicentre RCT	120	HPTC versus dHACM	83.3% versus 51.7%
Narayan 2024	India	RCT	28	HPTC versus dHACM	71.4% versus 50%
Armstrong 2025	United States	RCT	24	HPTC versus dHACM or placental membrane	50% versus 25% at 4 weeks
Glat 2019	United States	RCT	60	Amnion-chorion allograft versus tissue-engineered skin	24 versus 39 days to heal
Lavery 2026 (umbilical cord)	United States	RCT	40	Cryopreserved versus lyopreserved umbilical cord	36.8% versus 19.0%
Lavery 2026 (AmnioExcel)	United States	RCT	40	Amniotic allograft weekly versus biweekly	30.0% versus 50.0%

Note: UT = University of Texas; SOC = standard care; dHACM = dehydrated human amnion/chorion membrane; HPTC = high-purity type I collagen-based skin substitute. Source: Elaborated from the included reports.

Risk of bias

Table 2. Risk of bias of the included trials assessed with the Cochrane RoB 2 tool.

Study	D1	D2	D3	D4	D5	Overall
Dardari 2024	Low	Some concerns	Low	Low	Low	Some concerns
Armstrong 2026	Low	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Caporusso 2025	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Hall 2025	Some concerns	Some concerns	Some concerns	Some concerns	High	High
Niami 2022	Low	Low	Some concerns	Low	Some concerns	Some concerns
Narayan 2025	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Narayan 2024	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Armstrong 2025	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Glat 2019	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Lavery 2026 (umbilical cord)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Lavery 2026 (AmnioExcel)	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns

Note: D1 = randomization process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result. Source: Elaborated from the included reports.

The overall risk of bias was rated as some concerns in ten trials and as high in one (Table 2). The randomization process was adequately described and judged at low risk in six trials, while four trials provided insufficient detail to rule out allocation problems. Blinding of participants and care providers was generally not possible because the products differ visually from standard dressings, and most trials were therefore judged to carry some concerns in the domain of deviations from the intended interventions. Several trials mitigated this limitation with blinded adjudication of healing or with three-dimensional planimetric measurement, and the fish skin trial was rated at low risk for outcome measurement because a blinded adjudication committee confirmed healing at two consecutive time points.

The interim analysis of two randomized trials was rated at high overall risk because one of the contributing studies had been terminated early and the pooled analysis was not fully prespecified. In the domain of missing outcome data, ten trials reported complete or nearly complete follow-up and were judged at low risk, while the ovine forestomach matrix trial was rated as some concerns because of post-randomization exclusions and differential withdrawal between arms. In the domain of selective reporting, the interim analysis was the only trial rated at high risk, and the remaining trials reported their prespecified primary outcome.

Synthesis by outcome domain

Complete healing versus standard care

Of the five trials that compared a substitute with standard care or placebo, four reported a higher proportion of complete healing in the substitute arm and one reported no significant difference. The largest trial randomized 255 participants with deep University of Texas grade 2 and 3 ulcers across fifteen European centres, and intact fish skin graft achieved healing at 16 weeks in 44% of participants compared with 26% in the standard care group (P < 0.001), with healing at 20 weeks of 46% versus 32% and at 24 weeks of 55% versus 38%.(19)The trial was open label and stratified randomization by wound type and ankle-brachial index, and a blinded adjudication committee confirmed healing at two consecutive time points; the study was funded by the European Commission and the manufacturer of the graft.(19)In a trial of 143 participants with full-thickness foot wounds in diabetes, ovine forestomach matrix with hyaluronic acid healed 46% (31 of 68) at 12 weeks versus 24% (17 of 72) with standard care (P = 0.008), and the Kaplan-Meier comparison favored the substitute (log-rank P = 0.023).(20)In that trial 197 participants were screened and 143 were randomized, and the modified intention-to-treat analysis excluded three ulcers after randomization, which the authors acknowledged as a source of uncertainty together with differential withdrawal.(20)In the interim analysis of two randomized trials that enrolled 53 participants with non-healing ulcers, dehydrated human amnion-intermediate layer-chorion membrane healed 50% (14 of 28) versus 17% (4 of 23) (P = 0.019), with a wound area reduction of 71% versus 46% (P = 0.0517).(21)A triple-blind trial of 92 participants found that an amniotic fluid gel improved wound grade, wound color, the condition of surrounding tissue and the duration of healing compared with placebo gauze at eight weeks (P < 0.05).(22)That trial assigned participants to three amniotic fluid gel arms and one placebo arm, and the comparison reported here corresponds to the contrast between the combined gel arms and placebo.(22)By contrast, a multicentre trial of 220 participants with complex ulcers and controlled osteomyelitis found no significant difference between cryopreserved ultra-thick amniotic membrane and standard care, with complete healing of 66.1% versus 59.8% at 26 weeks (P = 0.40) and 77.1% versus 71.6% at 50 weeks (P = 0.29).(23)The product was applied at baseline and at intervals of at least four weeks when healing stalled, with a mean of 1.67 applications, and adverse events were comparable between arms.(23)

Head-to-head comparisons

Of the six trials that compared two substitutes or two application regimens, four favored one product and two found no significant difference. In the largest head-to-head trial, which randomized 120 participants across four Indian centres, high-purity type I collagen-based skin substitute achieved complete closure in 83.3% (50 of 60) versus 51.7% (31 of 60) with dehydrated human amnion/chorion membrane (P < 0.001), with a mean wound area reduction of 81.5% versus 64.2% and a mean time to closure of 22.2 versus 28.8 days.(24)The proportion achieving a wound area reduction of at least 50% was 88.3% versus 55% in the same trial.(24)The same trial reported greater histological vascular infiltration and capillary density in the collagen arm on day five biopsy.(24)The single-centre precursor trial randomized 28 participants and reported complete closure in 10 of 14 versus 7 of 14 participants over four weeks, with a reduction in wound area of at least 50% in 85.7% versus 50%.(25)A third trial randomized 24 participants with Wagner grade 1 ulcers and reported healing of 6 of 12 versus 3 of 12 at four weeks and a mean area reduction of 83.9% versus 71.3%, with no adverse events in either arm.(26)Dehydrated human amnion/chorion allograft produced faster healing than a tissue-engineered skin substitute in a trial of 60 participants with Wagner grade 1 ulcers, with a mean time to heal of 24 versus 39 days and a hazard ratio of 5.76 (95% CI 2.35 to 14.12).(27)

In a pilot trial of 40 participants with complex postoperative wounds and a mean baseline area of approximately 12 cm2, cryopreserved and lyopreserved umbilical cord tissue showed no significant difference in closure (36.8% versus 19.0%, P = 0.21), infection (10.5% versus 4.8%, P = 0.60) or wound area reduction (75.9% versus 65.5%, P = 0.41), and the study had no standard-care arm.(28)Likewise, weekly versus biweekly application of an amniotic allograft in 40 participants showed no significant difference in healing (30.0% versus 50.0%, P = 0.20).(29)

Time to healing and adverse events

Time to healing was reported in four trials and favored the substitute in three of them. Intact fish skin graft was associated with a mean time to healing of 17.3 weeks versus 19.4 weeks and a hazard ratio for faster healing of 1.59 (95% CI 1.07 to 2.36).(19)The collagen-based substitute closed ulcers in a mean of 22.2 versus 28.8 days,(24)and the amnion-chorion allograft healed in 24 versus 39 days.(27)Adverse events were reported consistently in only two trials. Primary wound infections occurred in 30.2% of the fish skin group and 29.3% of the standard care group,(19)and adverse events affected 89.8% and 87.3% of participants in the cryopreserved amniotic membrane trial, with no difference between arms.(23)The remaining trials reported adverse events only sporadically or described them narratively, which limits any formal safety comparison across products. No trial reported an excess of serious adverse events attributed to the substitute, and the three small head-to-head trials of the collagen substitute reported no adverse events.(25,26)

DISCUSSION

The main finding of this review is that cellular and tissue-based skin substitutes increased complete healing of diabetic foot ulcers in most of the included trials, and that the direction of the effect was consistent across product classes. Of the five trials with a standard-care comparator, four reported higher healing in the substitute arm, with absolute differences ranging from 6.3 to 33 percentage points, while the largest amniotic membrane trial found no significant difference. When restricted to the two standard-care trials at lower risk of bias, namely the fish skin and ovine forestomach matrix trials, the benefit remained statistically significant, which supports a moderate level of evidence for these two products and a lower level of evidence for the remaining products. The overall certainty is limited because most trials were small, open label and partly industry funded, and because one large trial showed no effect.

The results agree with several prior meta-analyses of placental and amniotic products. A meta-analysis of placenta-derived biomaterials versus standard care reported higher healing with placental products overall,(14)and meta-analyses restricted to human amniotic membrane reached similar conclusions.(12,13,30)A 12-week trial meta-analysis of placental products likewise found a benefit,(31)a meta-analysis of cellular and acellular tissue-based products reported improved healing despite advanced age and larger wound size,(32) and a systematic review with an indirect treatment comparison between cellular, acellular and amniotic products found differences in favor of active treatment.(33)The pooled estimates in these reviews consistently favored the active products, although the magnitude varied by product class and follow-up, and the trials contributing to the pooled estimates overlapped only partially with the present set. The fish skin findings are consistent with a meta-analysis that compared fish skin grafts with standard care(18)and with systematic reviews of acellular fish skin.(34,35) In contrast, the null result of the cryopreserved amniotic membrane trial is discrepant with these pooled estimates, and the discrepancy has a plausible explanation: that trial enrolled complex wounds with exposed bone, tendon or joint capsule and controlled osteomyelitis, a population that heals more slowly than the superficial ulcers included in most other trials and one in which the standard care arm itself achieved a healing rate above 59%.(23)The Cochrane review of skin grafting and tissue replacement, which predates most of the included trials, judged the evidence of low certainty,(11)and the present synthesis extends that evidence base with eleven randomized comparisons published after 2018.

The head-to-head comparisons provide product-specific information that the standard-care trials cannot offer. The consistent advantage of the high-purity type I collagen-based substitute over dehydrated amnion/chorion membrane across three independent trials, including one multicentre trial of 120 participants, was the most reproducible finding of the review.(24-26)The amnion-chorion allograft also healed faster than a tissue-engineered skin substitute in one trial.(27)However, these head-to-head trials enrolled mostly superficial ulcers, measured area reduction at four to five weeks, and several were sponsored by the manufacturer of the favored product, which limits the strength of the comparisons. The two trials that found no difference compared preservation

methods or application frequency of the same product rather than different products, and both were pilot studies without statistical power.(28,29) These null results do not undermine the class effect, but they do caution against treating every product as interchangeable. The advantage of the collagen-based substitute over amnion-chorion in the head-to-head trials was attributed by the authors to its composition, which enhances cellular attachment and accelerates tissue regeneration, although these histological explanations come from the same trials and require independent confirmation.(24)

Heterogeneity across the eleven trials was substantial and has several identifiable sources. The products differ in mechanism, from living bilayered constructs to acellular matrices, and they were applied at different frequencies and for different durations. Wound severity ranged from grade 1A to deep grade 3 ulcers, and the standard-care comparator was not uniform, although most trials adhered to International Working Group recommendations for debridement and offloading.(6) Follow-up ranged from four to fifty weeks, and the definition of healing, although always epithelialization, was confirmed by different methods. The quality of offloading across the underlying trials is itself variable, as the meta-research audit of the 2023 recommendations showed.(8)These sources of heterogeneity justify the decision not to pool the estimates and explain why the absolute healing rates in the standard-care arms ranged from 17% to 59.8%. The generalizability of the findings is also constrained by the populations enrolled. The trials recruited predominantly people with type 2 diabetes and adequate arterial perfusion, and most excluded active osteomyelitis, severe ischemia and end-stage renal disease, which are common among patients who ultimately undergo amputation.(6)The head-to-head collagen trials were conducted in India and the amniotic fluid trial in Iran, while the fish skin and placental trials were conducted in Europe and the United States, and wound care practices, product availability and offloading adherence differ across these settings.(22,24) The benefit observed under trial conditions, with protocolized debridement and offloading, may therefore be smaller in routine care where adherence to offloading is lower.

The biological plausibility of the observed benefit is supported by the composition of the products. Amniotic and placental membranes contain extracellular matrix components, growth factors and cytokines that modulate inflammation and promote angiogenesis, and fish skin provides an omega-3-rich scaffold that supports granulation tissue, while collagen matrices restore a substrate for cellular attachment and migration.(9,10) These mechanisms are consistent with the larger effects observed in deep wounds, where the missing scaffold and the inflammatory blockade are most pronounced, and they explain why the products perform best as adjuncts to debridement and offloading rather than as replacements for them.(5)The healing rates observed in the control arms of the included trials frame the absolute gains in the substitute arms. The fish skin trial noted that a review of 26 randomized controlled trials found that only about 30% of ulcers assigned to standard care healed by 12 weeks and about 45% healed at any time, which makes the 44% versus 26% difference at 16 weeks a meaningful clinical gain in a deep-wound population.(19) In the present review the standard-care healing rates ranged from 17% at twelve weeks in the interim amnion-chorion analysis to 59.8% at 26 weeks in the complex-wound amniotic trial, and this spread reflects the variation in wound depth and follow-up length rather than differences in the quality of care.(21,23) The measurement of healing itself deserves attention. Several trials defined healing as complete epithelialization confirmed at a second visit, while others relied on a single clinical assessment or on percentage area reduction as a surrogate, and this difference affects the comparability of the estimates.(6)Area reduction at four to twelve weeks was the primary endpoint in several head-to-head trials, and although it correlates with eventual closure it is not equivalent to it, so the head-to-head results should be read as surrogate evidence rather than as definitive healing.(24)

Several network meta-analyses have compared topical and adjunctive therapies and generally rank skin substitutes among the more effective options, although the ranking depends on the comparator set and the geometry of the network.(16,17,36-39)A narrative synthesis of the certainty of evidence for diabetic foot ulcer therapies concluded that most interventions rest on low certainty evidence,(40)and the present review is consistent with that assessment. The meta-analysis conducted for the Italian guidelines and a scoping review of bioengineered skin similarly emphasize the need for larger and better blinded trials before product-specific recommendations can be made.(15,41) The pharmacotherapy review of diabetic foot ulcer management reaches the same conclusion about the evidence base for advanced products.(5)Cost-effectiveness studies of these products are fewer than efficacy trials, and the published analyses suggest that a higher acquisition cost can be offset by fewer applications and avoided amputations, although the estimates depend on the assumed healing benefit.(5)

Taken together, the certainty of the evidence for a class effect is moderate at best. The body

of evidence is downgraded by the risk of bias from open designs and industry sponsorship, by inconsistency between the significant and null trials, by imprecision in the small studies, and by the possibility of retrieval bias, while it is supported by the consistency of direction across product classes and by one large trial with blinded adjudication. The net assessment is that a benefit is probable for fish skin and ovine forestomach matrix, possible for amnion-chorion products, and uncertain for cryopreserved amniotic membrane in complex wounds.

This review has strengths and limitations. Its strengths are the prospective PRISMA protocol, the restriction to randomized evidence for the primary question, the use of four bibliographic sources with Scopus as the first, the separation of standard-care from head-to-head evidence, and the explicit quantification of the number of studies supporting each claim. Its limitations are described below.

Limitations

The studies included in this review had limitations concerning size, design and sponsorship. Six of the eleven trials randomized fewer than 60 participants, and the two largest trials together account for half of the total sample. Most trials were open label because the physical appearance of the products precludes masking of care providers, and although some used blinded adjudication of healing, measurement bias cannot be excluded. Several trials were funded by the manufacturer of the tested product, and one analysis was interim with a terminated contributing study. These features recommend cautious interpretation of the effect sizes and support replication in independent trials.

The evidence itself is limited by precision and consistency. The absolute healing differences were large in some trials but imprecise in the smaller ones, and confidence intervals were not reported for several estimates. The null result of the largest amniotic trial indicates that the benefit is not uniform across products and wound severities, and the absence of head-to-head trials against active comparators for most products leaves the relative effectiveness largely unknown. The evidence therefore supports a class effect for some substitutes but not a reliable ranking of products.

For clinical practice, the findings suggest that intact fish skin graft, ovine forestomach matrix and amnion-chorion products are reasonable adjuncts to standard care for diabetic foot ulcers, particularly deep ulcers that have not responded to conventional treatment, whereas cryopreserved amniotic membrane offers no clear advantage in complex wounds despite being safe. Clinicians should weigh the acquisition cost of each product against the magnitude and certainty of the expected benefit, and should document complete healing with a standardized definition. Access and reimbursement are additional considerations, because these products are expensive and their coverage varies across health systems, and the decision to use a substitute should be reserved for wounds that have not responded to a defined period of high-quality standard care.(7)

For research, future trials should enroll deep and ischemic ulcers, use blinded adjudication of healing, report time-to-event outcomes with hazard ratios and confidence intervals, and include standard care arms rather than only head-to-head comparisons, because the standard-care comparator is the one that answers the clinical question of whether a substitute adds value.(7)Trial reports should also state the funding source, the number of product applications and the completeness of offloading, since these variables explain part of the observed heterogeneity and are inconsistently reported at present. Prevention remains the least expensive strategy, and structured programs that combine risk stratification, education and offloading reduce ulceration and amputation, which is why the substitute evidence should be interpreted within a broader limb-salvage pathway rather than in isolation.(42)

CONCLUSIONS

The eleven included trials were heterogeneous in product class, wound severity and comparator, and their overall risk of bias was some concerns or high. Intact fish skin graft, ovine forestomach matrix and amnion-chorion membranes increased complete healing compared with standard care in four of five comparative trials, while one large amniotic membrane trial found no significant difference. High-purity type I collagen-based skin substitute healed more ulcers than dehydrated amnion/chorion membrane across three head-to-head trials. The evidence supports the use of selected cellular and tissue-based skin substitutes as adjuncts to standard care, but larger independent trials with blinded healing adjudication are required before product-specific recommendations can be made.

REFERENCES

1. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence. N Engl J Med. 2017;376(24):2367-2375. doi: 10.1056/nejmra1615439
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Annals of Medicine. 2017;49(2):106-116. doi: 10.1080/07853890.2016.1231932
3. Carollo M, Ingrasciotta Y, Crisafulli S, Maccarrone F, Pellegrino D, Francescon A, et al. Global Epidemiology of Diabetic Foot: A Systematic Review and Meta-Analysis. Diabetes Metabolism Res. 2026;42(6):e70223. doi: 10.1002/dmrr.70223
4. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. Annals of the New York Academy of Sciences. 2018;1411(1):153-165. doi: 10.1111/nyas.13569
5. Dixon D, Edmonds M. Managing Diabetic Foot Ulcers: Pharmacotherapy for Wound Healing. Drugs. 2021;81(1):29-56. doi: 10.1007/s40265-020-01415-8
6. Schaper NC, van Netten JJ, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA, et al. Practical Guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metabolism Res. 2020;36(S1):e3266. doi: 10.1002/dmrr.3266
7. Chen P, Vilorio NC, Dhatariya K, Jeffcoate W, Lobmann R, McIntosh C, et al. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: A systematic review. Diabetes Metabolism Res. 2024;40(3):e3786. doi: 10.1002/dmrr.3786
8. Bandeira MA, Alvarez YG, López Moral M, Flores Escobar S, Lázaro Martinez JL, Santos VLCDG. Offloading Matters: A Meta-Research Audit of Mechanical Validity in Trials Supporting the 2023 IWGDF Recommendations on Interventions to Enhance Healing of Foot Ulcers in People with DM. The International Journal of Lower Extremity Wounds. 2026:15347346261493802. doi: 10.1177/15347346261493802
9. Vecin NM, Kirsner RS. Skin substitutes as treatment for chronic wounds: current and future directions. Front Med. 2023;10:1154567. doi: 10.3389/fmed.2023.1154567
10. Álvaro-Afonso FJ, García-Álvarez Y, Lázaro-Martínez JL, Kakagia D, Papanas N. Advances in Dermoepidermal Skin Substitutes for Diabetic Foot Ulcers. CVP. 2020;18(2):182-192. doi: 10.2174/1570161117666190408170144
11. Santema TB, Poyck PP, Ubbink DT. Skin grafting and tissue replacement for treating foot ulcers in people with diabetes. Cochrane Database of Systematic Reviews. 2016;2017(3). doi: 10.1002/14651858.cd011255.pub2
12. Mohammed YA, Farouk HK, Gbreel MI, Ali AM, Salah AA, Nourelden AZ, et al. Human amniotic membrane products for patients with diabetic foot ulcers. do they help? a systematic review and meta-analysis. Journal of Foot and Ankle Research. 2022;15(1):71. doi: 10.1186/s13047-022-00575-y
13. Zheng C, Tang W, Ran X. Efficacy and Safety of Human Amniotic Membrane for Chronic Wounds: A Systematic Review and Meta-Analysis of Clinical Trials. Advances in Wound Care. 2026:21621918251411808. doi: 10.1177/21621918251411808
14. Ruiz-Muñoz M, Martinez-Barrios FJ, Lopezosa-Reca E. Placenta-derived biomaterials vs. standard care in chronic diabetic foot ulcer healing: A systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2025;19(1):103170. doi: 10.1016/j.dsx.2024.103170
15. Primous NR, Elvin PT, Carter KV, Andrade HL, La Fontaine J, Shibuya N, et al. Bioengineered Skin for Diabetic Foot Ulcers: A Scoping Review. JCM. 2024;13(5):1221. doi: 10.3390/jcm13051221
16. Chen L, Chen JC, Lin T, Shi F, Chen D, Wang C, et al. Topical therapies for diabetic foot ulcers: a systematic review and network meta-analysis. BMJ Open Diab Res Care. 2026;14(3):e006026. doi: 10.1136/bmjdrc-2026-006026
17. Luo W, Sun Y, Weng Y, Huang K, Gan Y. Adjunctive therapies added to standard of care for diabetic foot ulcers: a systematic review and network meta-analysis with pairwise comparisons. Front Endocrinol. 2026;17:1891173. doi: 10.3389/fendo.2026.1891173
18. Ruiz-Muñoz M, Martinez-Barrios FJ, Cervera-Garvi P, Lopezosa-Reca E, Marchena-Rodriguez AJ. Fish skin grafts versus standard of care on wound healing of chronic diabetic foot ulcers: A systematic review and meta-analysis. Primary Care Diabetes. 2024;18(3):291-298. doi: 10.1016/j.pcd.2024.03.008
19. Dardari D, Piaggesi A, Potier L, Sultan A, Diener H, Francois M, et al. Intact Fish Skin Graft to Treat Deep Diabetic Foot Ulcers. NEJM Evidence. 2024;3(12):EVIDoa2400171. doi: 10.1056/evidoa2400171
20. Armstrong DG, Orgill DP, Galiano RD, Lantis JC, Glat P, Reyzelman AM, et al. A Composite Ovine Forestomach Matrix and Hyaluronic Acid CAMP for the Treatment of Full Thickness Wounds of the Foot in People With Diabetes: A Randomized Controlled Trial. International Wound Journal. 2026;23(10):e71056. doi: 10.1111/iwj.71056
21. Hall HJ, Keenan A, Massey K, D'Costa WF, Moyer P. Bridging the Wound Gap: Interim Results From Randomized Trials Evaluating Dehydrated Human Amnion-Intermediate Layer-Chorion Membrane for the Treatment of Non-healing Diabetic Foot Ulcers. Cureus. 2025;17(11):e97875. doi: 10.7759/cureus.97875
22. Niami F, Molavynejad S, Hemmati AA, Bijan Nejad D, Yazdanpanah L, Maram NS, et al. Evaluation of the effect of a gel made with amniotic fluid formulation on the healing of diabetic foot ulcers: A triple-blind clinical trial. Front Public Health. 2022;10:1025391. doi: 10.3389/fpubh.2022.1025391
23. Caporusso J, Motley T, Lantis JC, Heisler S, Hicks A, Wu SC, et al. A Multi-Centre, Randomised, Controlled Clinical Trial Assessing Cryopreserved Ultra-Thick Human Amniotic Membrane in the Treatment of Complex Diabetic Foot Ulcers. Wound Repair Regeneration. 2025;33(6):e70110. doi: 10.1111/wrr.70110
24. Narayan N, Shivaiah R, Kumar V, Kumar KM, Chethan S, Gowda S. Comparative Efficacy of High Purity Type I Collagen-Based Skin Substitute and Dehydrated Human Amnion/Chorion Membrane in Diabetic Foot Ulcers: A Multicentre Randomized Controlled Trial. Cureus. 2025;17(10):e94952. doi: 10.7759/cureus.94952

25. Narayan N, Gowda S, Shivannaiah C. A Randomized Controlled Clinical Trial Comparing the Use of High Purity Type-I Collagen-Based Skin Substitute vs. Dehydrated Human Amnion/Chorion Membrane in the Treatment of Diabetic Foot Ulcers. Cureus. 2024;16(12):e75182. doi: 10.7759/cureus.75182
26. Armstrong DG, Hanft J, Surprenant M, Isaac A, Carter M, Zelen C, et al. Comparing the Efficacy of a Unique Advanced Bioengineered Type-I Collagen-Based Skin Substitute Versus an Amnion Graft With Standard of Care in the Treatment of Non-healing Diabetic Foot Ulcers: A Randomized Clinical Trial. Cureus. 2025;17(1):e78021. doi: 10.7759/cureus.78021
27. Glat P, Orgill DP, Galiano R, Armstrong D, Serena T, DiDomenico LA, et al. Placental Membrane Provides Improved Healing Efficacy and Lower Cost Versus a Tissue-Engineered Human Skin in the Treatment of Diabetic Foot Ulcerations. Plastic and Reconstructive Surgery - Global Open. 2019;7(8):e2371. doi: 10.1097/gox.0000000000002371
28. Lavery LA, Suludere MA, Johnson MJ, Killeen AL, Raspovic KM, Crisologo PA, et al. Randomized Clinical Trial to Compare Cryopreserved and Lyopreserved Umbilical Cord Tissue to Treat Complex Diabetic Foot Wounds. The International Journal of Lower Extremity Wounds. 2026;25(3):852-860. doi: 10.1177/15347346241273282
29. Lavery LA, Suludere MA, Raspovic K, Crisologo PA, Johnson MJ, Tarricone AN. Randomized Controlled Trial to Compare AmnioExcel Human Amniotic Allograft in Weekly Versus Biweekly Treatment of Diabetic Foot Ulcers. The International Journal of Lower Extremity Wounds. 2026;25(3):891-898. doi: 10.1177/15347346241276697
30. Alomairi AA, Alhatlani RA, Alharbi SM, Alqurain ZJ, Alanazi IZ, Alanazi SA, et al. Assessing the Application and Effectiveness of Human Amniotic Membrane in the Management of Venous and Diabetic Ulcers: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Cureus. 2024;16(3):e56659. doi: 10.7759/cureus.56659
31. Theodorakopoulos G, Armstrong DG. Cellular, Acellular, and Matrix-Like Placental Products for Diabetic Foot Ulcers: A 12-Week Randomised-Trial Meta-Analysis. International Wound Journal. 2026;23(10):e71058. doi: 10.1111/iwj.71058
32. Lu W, Hu M, Zhang Z, Slaughter J, Hingorani A, Oropallo A. Meta-analysis of cellular and acellular tissue-based products demonstrates improvement of diabetic foot ulcer healing despite age and wound size. JVS-Vascular Insights. 2025;3:100215. doi: 10.1016/j.jvsvi.2025.100215
33. Banerjee J, Lasiter A, Nherera L. Systematic Review of Cellular, Acellular, and Matrix-like Products and Indirect Treatment Comparison Between Cellular/Acellular and Amniotic/Nonamniotic Grafts in the Management of Diabetic Foot Ulcers. Advances in Wound Care. 2024;13(12):639-651. doi: 10.1089/wound.2023.0075
34. Gao J, Ge LX, Gao QY, Zhang AM, Hu LJ. Efficacy of acellular fish skin graft in the management of chronic ulcer: a systematic review and meta-analysis. Langenbecks Arch Surg. 2024;409(1):64. doi: 10.1007/s00423-024-03230-1
35. Khan MA, Karhana S. Omega-3 Acellular Fish Skin Grafts for Chronic and Complicated Wounds: A Systematic Review of Efficacy and Safety. Dermatology Practical & Conceptual. 2025;15(2):4945. doi: 10.5826/dpc.1502a4945
36. Guan X, Zhu G, Jiang H, Wang B, Cheng J. Comparative efficacy of advanced therapeutic modalities for diabetic foot ulcers: a systematic review and meta-analysis including NPWT, stem cells, ESWT, and bioengineered treatments. Front Bioeng Biotechnol. 2026;14:1792670. doi: 10.3389/fbioe.2026.1792670
37. Chen ACY, Lu Y, Hsieh CY, Chen YS, Chang KC, Chang DH. Advanced Biomaterials and Topical Medications for Treating Diabetic Foot Ulcers: A Systematic Review and Network Meta-Analysis. Advances in Wound Care. 2024;13(2):97-113. doi: 10.1089/wound.2023.0024
38. Zhang J, Zhao Y, Hu Z, Qi Q, Jia M, Ren Z, et al. Efficacy and Safety of Biomaterials and Antimicrobial Dressings in the Treatment of Diabetic Foot Ulcers: A Systematic Review and Network Meta-Analysis. Journal of Diabetes Research. 2025;2025(1):1548984. doi: 10.1155/jdr/1548984
39. OuYang H, Yang J, Wan H, Huang J, Yin Y. Effects of different treatment measures on the efficacy of diabetic foot ulcers: a network meta-analysis. Front Endocrinol. 2024;15:1452192. doi: 10.3389/fendo.2024.1452192
40. Mueller SM, Shi HD, Kaveti A, Du A, Clegg DJ, Wagner R, et al. Comparative Certainty of Evidence for Diabetic Foot Ulcer Therapies: A Narrative Synthesis. Diabetology. 2026;7(7):131. doi: 10.3390/diabetology7070131
41. Monami M, Scatena A, Ragghianti B, Miranda C, Monge L, Silverii A, et al. Effectiveness of most common adjuvant wound treatments (skin substitutes, negative pressure wound therapy, hyperbaric oxygen therapy, platelet-rich plasma/fibrin, and growth factors) for the management of hard-to-heal diabetic foot ulcers: a meta-analysis of randomized controlled trials for the development of the Italian Guidelines for the Treatment of Diabetic Foot Syndrome. Acta Diabetol. 2024;62(7):1081-1095. doi: 10.1007/s00592-024-02426-7
42. Chávez Moya MO, Cabrera LH, Ramírez LM, González González MA, Pazos AA, Fernández Feitó LB, et al. From ulcer to remission: podiatric and technological strategies to prevent ulceration and amputation in the diabetic foot. SAP Podiatry. 2026;3:160. doi: 10.62486/pod2026160

FUNDING

No financing

CONFLICT OF INTEREST

None

AUTHORSHIP CONTRIBUTIONS

Drafting – original draft: Yenny Elers Mastrapa, Fabian Quiroz Zendejas.
Writing–review and editing: Yenny Elers Mastrapa, Fabian Quiroz Zendejas.