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The Effects of Cellular Skin Substitutes on Diabetic Foot Ulcer Healing: A Systematic Review

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Abstract

Introduction: *Diabetic foot ulcer (DFU) is one of the most common lower extremity diabetes-related complications. New therapies have been developed to increase the likelihood of wound healing and reduce complications, including biological and/or synthetic grafts that allow a temporary or permanent occlusion of wounds. Although their efficacy has been demonstrated, novel skin substitutes have been available, and few studies have described the head-to-head comparative effectiveness of those products. Therefore, this mini-review aims to analyze the available randomized clinical trials studying the impact of different cellular skin products on the healing of DFUs.*

Methods: *The databases PubMed, EMBASE, Scopus, Scielo, and Lilacs were assessed from inception to July 30th, 2023, to identify randomized clinical trials on the effects of cellular skin substitutes on ulcer healing in adult patients aged 18 years or older with DFUs restricted to the skin and subcutaneous tissue, compared to standard of care or other skin substitutes.*

Results: *Based on eligibility criteria, 22 articles were selected. These studies showed the efficacy and safety of cell skin substitutes compared to standard treatments, as demonstrated by the reduction in the total area of the ulcer and rates of complete wound healing. We identified a few studies with head-to-head comparisons among those products.*

Discussion: *Cellular skin substitutes have shown promising results in healing DFUs as complementary therapies to the standard of care. Their incorporation into standard-of-care treatments could be discussed. Future studies should focus on head-to-head comparisons, cost-effective analysis, and long-term efficacy and safety.*

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Introduction

Diabetes is a chronic metabolic disease and a global public health issue affecting more than 529 million people in the world. (GBD 2021 Diabetes Collaborators, 2023). Diabetic foot ulcer (DFU) is a common diabetes-related complication occurring due to chronically elevated glucose levels, reduced blood flow,

and nerve damage (Raja et al., 2023). More than 18 million people with diabetes develop a foot ulcer each year, which affects one-third of these individuals during their lifetime (Armstrong et al., 2017; Zhang et al., 2020).

A significant problem with diabetic wounds is that they do not follow the normal process of wound healing, that is, the dynamic process comprising four phases: hemostasis, inflammation, proliferation, and remodeling. In patients with diabetes mellitus (DM), the wound closure processes are affected, starting with a decrease in fibrinolysis, an imbalance of cytokines, and a poor production of the extracellular matrix by fibroblasts, which causes an alteration in wound closure. There is also a decrease in angiogenesis due to hyperglycemia and migration of cells such as keratinocytes and fibroblasts, causing deficient re-epithelialization (Perez-Favila et al., 2019).

The Standard Of Care (SOC) treatment includes wound debridement, infection control, revascularization procedures, ulcer off-loading, and topical interventions (dressings). Still, DFUs are challenging to treat, and healing rates are highly variable. Several studies reported complete healing of approximately 24-31% of DFUs after SOC treatment (Margolis et al., 1999). Skin substitutes have been developed to address this low healing rate, aiming to increase the likelihood of wound healing, reduce the risk of infections, and provide pain relief. Cellular skin substitutes, often made from living cells, provide a structural matrix that promotes skin cell growth, essential growth factors, neovascularization of the wound, anti-inflammatory effect, and a physical barrier from bacteria and trauma. This accelerates wound healing, promoting the formation of healthy tissue. Therefore, they offer a promising therapeutic option for diabetic foot ulcers. (Holl et al., 2021). There are several classification systems for skin substitutes. This review relates to the classification of Davison-Kotler et al., who consider cellularity the most crucial discriminator because the presence of cells increases the rejection risk and manufacturing complexity (Davison-Kotler et al., 2018). Acellular dermal substitutes are made from natural biological materials (Frykberg & Banks, 2015). In contrast, cellular skin substitutes contain cells from human donors like amniotic membrane-derived products, neonatal foreskin, or the patient's skin cells. (Veves et al., 2001). Although previous literature has studied the efficacy of cellular and acellular skin products as a treatment of DFUs (Álvaro-Afonso et al., 2020; Holl et al., 2021), there have been insufficient studies comparing the efficacy of different cellular skin products head-to-head, meaning one skin substitute against the other, nor have they included recent studies on newly developed cellular skin substitutes (Armstrong et al., 2023).

This review aims to analyze the available randomized controlled trials (RCTs) studying the different cellular skin products (against SOC or each other) on the healing of DFUs in adult patients with DFUs.

Materials and Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines (Page et al., 2021).

Search Strategy

We developed a search strategy (Appendix). We applied the Boolean operators "AND" and "OR," with a combination of descriptors, in the databases PubMed, EMBASE, Scopus, Scielo, and Lilacs from inception to July 30th, 2023. We imported the search results into Rayyan QCRI for screening and data extraction. We included articles published in English, Spanish, and Portuguese.

Inclusion and Exclusion Criteria

Included studies had to meet the following criteria: (1) Population of adult patients ($\geq$18 years) having a DFU with skin damage limited to skin and subcutaneous tissue; (2) Assessing the efficacy and safety of cellular skin substitutes for DFUs; (3) Comparing cellular skin substitutes with SOC or against other skin substitutes; (4) Including data on healing (measured by ulcer size, time to wound closure, wound healing rate, or ulcer-free survival); (5) Only RCT design.

Data Extraction

After removing duplicates, the titles and abstracts of the articles were reviewed for the eligibility criteria. Two independent reviewers blindly performed the analysis. In case of discrepancies, a consensus was achieved among the authors not involved in the first screening analysis. The discrepancies occurred mainly regarding the type of skin substitute and outcomes.

Subsequently, two different reviewers did full-text reviewing, and unsuitable articles were excluded (reasons provided in the flow chart). Again, in case of discrepancy, a consensus achievement was applied after a discussion among other authors not involved in the first screening. After finalizing the selection, two independent persons performed data collection with the extraction of authors, publication year,

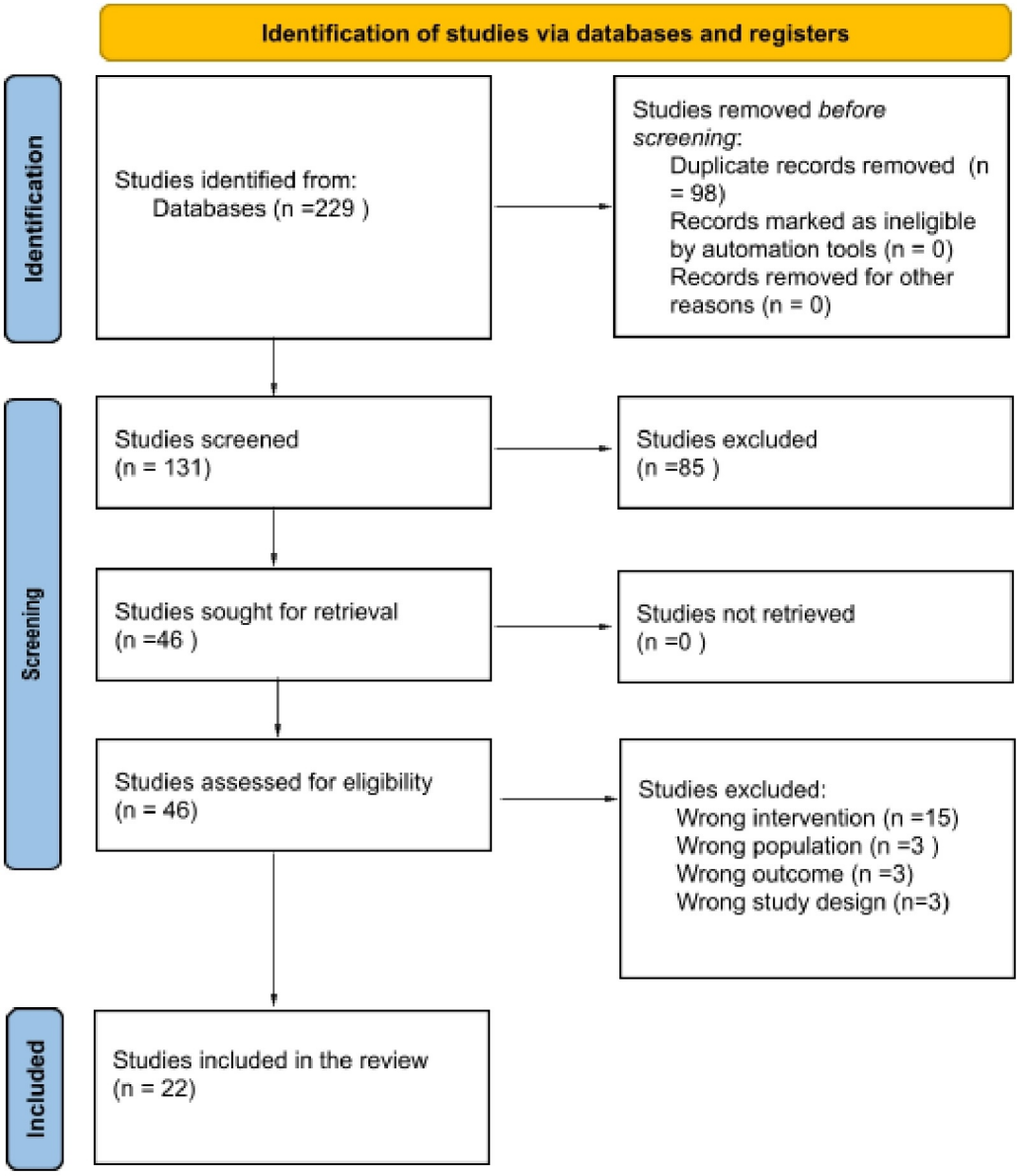

Figure 1: *PRISMA flow diagram.*

sample size, age, sex, type of diabetes, ulcer classification, intervention, control treatment, primary and secondary outcomes (ulcer size, time to wound closure, and wound healing rate) and main results. Reviewer results were compared and, for deviations, discussed among the authors only involved in the first data extraction once agreement was reached.

Risk of Bias

Version 2 of the Cochrane tool for assessing the risk of bias in RCTs (RoB 2) (Sterne et al., 2019) was used to evaluate the methodological quality. The "Robvis" tool generated the traffic light plot (McGuinness & Higgins, 2021).

Results

Study Selection

A total of 229 titles were retrieved after applying the search strategy. Studies were screened for duplicates, and 98 were excluded. After evaluating the titles and abstracts, 46 were selected for full-text analysis based on the eligibility criteria. Therefore, 22 were chosen as the final sample and included for detailed analysis (Figure 1).

1. RCT of cellular skin substitutes vs. SOC

Eighteen RCTs (1665 subjects) were reviewed (Table 1), of which 14 used skin substitutes made entirely from human cells (1335 subjects) (Dermagraft®, Epifast®, Theraskin®, Hyalograft3D, novel autologous heterogenous skin construct (AHSC), Epicord®, Grafix®, Kaloderm®, PMVT) and four combined human cells attached on a bovine type I collagen matrix (330 subjects) (Apligraf®, synonymously Graftskin®).

a) Complete human skin substitutes

With four studies, Dermagraft® (Organogenesis) was the most commonly used substitute (Marston et al., 2003; Hanft & Surprenant, 2002; Gentzkow et al., 1996; Tchanque-Fossuo et al., 2019). Three of them showed significant differences between Dermagraft® and SOC for complete wound closure at 12 weeks: Marston et al. 30% (39/130) vs. 18% (21/115) (p=0.023) and Hanft et al. 71.4% (19/14) vs. 14.3% (2/14) (p=0.003). In the study by Gentzkow et al., the rate of complete wound closure varied with the dose of Dermagraft®. Group A (one piece weekly for eight applications) achieved 50% closure (6/12), Group B (two pieces biweekly for four applications) 21.4% (3/14), Group C (one piece biweekly for four applications) 18.2% (2/11), compared to 7.7% (1/7) in the control group D, which received conventional therapy (p=0.03 between A and D). Whereas Tchanque-Fossuo et al. displayed that wound closure after 12 weeks was achieved in 47.1% (8/17) of the Dermagraft® group, in 73.3% (14/19) of the Oasis (porcine intestinal mucosa) group, and 57.9% (11/19) in SOC group.

Two Hyalograft3D (Fidia Advanced Biopolymers) RCTs have not shown significant results for complete wound healing compared to SOC: Caravaggi et al., 2003 65.3% (29/43) vs. 49.6% (18/36) (p=0.191) and Uccioli et al., 2011 24% (19/80) vs. 21% (17/80) (p=0.85) for intervention and control groups respectively. However, Uccioli et al. showed that healing occurred significantly faster in the Hyalograft3D group (mean of 40 days vs. 50 days, p=0.018).

Armstrong et al. described wound healing between TheraSkin® (LifeNet Health) (Armstrong et al., 2022) and AHSC (Armstrong et al., 2023) compared to SOC in two different trials. Statistically significant results in wound healing within 12 weeks with both grafts have been shown: 76% [38/50] vs. 36% [18/50], p=0.00056) for the first and 70% (35/50) vs. 35% (17/50), p=0.00032 for the second.

Epifast® (Bioskinco S.A. De C.V.) was compared to SOC by Martinez-De Jesús et al., 2022, displaying a shorter duration of wound healing than the SOC group (10 ± 5.7 vs. 14.5 ± 8.9 weeks, p<0.05), reaching wound closure at 16 and 30 weeks, respectively. Gould et al., 2022 compared PMVT allograft (mVASC®, MicroVascular Tissues, Inc. [MVT], San Diego, CA) plus SOC versus collagen calcium alginate dressing plus SOC. After 12 weeks, patients in the intervention group had a higher percentage of wound closure (74% [37/50] vs. 38% [19/50], p=0.0003). Lavery et al., 2014 demonstrated that subjects randomized to Grafix® (Osiris Therapeutics, Inc., Columbia, MD) had significantly higher rates of wound closure (62% [31/50] vs. 21% [10/47], p=0.0001) and faster healing rates (42 days vs. 69.5 days, p=0.019) than SOC. Tettelbach et al., 2019 pointed out that 70% (71/100) of the EpiCord® (MiMedx Group, Inc., Marietta, Georgia) showed complete wound closure after 12 weeks compared to 48% (18/36) in the SOC group (p=0.191). You et al., 2012 presented complete wound closure within 12 weeks in 100% (20/20) of the Kaloderm® (Tego Science) group and 69% (18/26) of the SOC group (p<0.05). Bayram et al., 2005 published that the mean reduction of the wound area after 30 days was 92% for the intervention group with cultured keratinocytes attached to microcarriers produced from polyethylene and silica vs. 32% for the control

Study	Intervention	Control (SOC definition)	Participants	Primary Outcome	Results	p-value
Tchanque-Fossuo et al. (2019)	Group 1 Dermagraft®: culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold + SOC. Group 2: Oasis (acellular pig small intestinal mucosa) + SOC	Group 3 : Non-adherent gauze dressing, Adaptic + Iodosorb gel on a dry gauze	Group 1: n= 17 Group 2: n= 19 Group 3: n= 19	Percentage of wounds achieving complete closure at 12 weeks	Group 1: 8/17 (47.1%) Group 2: 14/19 (73.3%) Group 3: 11/19 (57.9 %)	NS
Marston et al. (2003)	Group 1 Dermagraft®: culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold + SOC	Group 2: Non-adherent interface + saline-moistened gauze + dry gauze + adhesive fixation sheets (Hypafix) + weight off loading	Group 1: n= 130 Group 2: n= 115	Complete wound closure by 12 weeks	Group 1: 39/130 (30%) Group 2: 21/115 (18%)	0.023
Gentzkow et al. (1996)	Group 1 Dermagraft®: culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold (3 groups with different dosages: A, one piece per week; B, two pieces every other week; C, one piece every other week)	Group 2: Conventional wound closure methods (debridement + dressings + pressure relief)	Group 1A: n=12 1B: n=14 1C: n= 11 Group 2: n= 13	Percentage of wounds achieving complete closure at 12 weeks	Group 1A: 6/12 (50%) Group 1B: 3/14 (21.4%) Group 1C: 2/11 (18.2%) Group 2: 1/7 (7.7%) Percentage of patients achieving complete wound closure by week 12 increased with increasing Dermagraft dosage (A > B > C)	0.03
Uccioli L, et al. (2011)	Group 1 Hyalograft 3D + Laserskin: cultured of autologous fibroblast and Keratinocytes grown on scaffolds of benzyl ester of hyaluronic acid	Group 2: non-adherent paraffin gauze + secondary dressing of sterile cotton pads and gauze	Group 1: n= 80 Group 2: n= 80	Complete wound closure by 12 weeks	Group 1: 19/80 (24%) Group 2: 17/80 (21%)	0.85
Hanft, JR, et al. (2002)	Group 1 Dermagraft®: culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold + SOC	Group 2: debridement + saline-moistened Gauze + dry gauze + weight off loading	Group 1: n= 14 Group 2: n= 14	Proportion of patients with ulcers of > 6 weeks' duration that achieved complete wound closure by week 12	Group 1: 10/14 (71.4%) Group 2: 2/14 (14.3%)	0.003
Sams et al. (2002)	Group 1 Apligraf®: cultured from human foreskin-derived neonatal fibroblast and keratinocytes in a bovine type I collagen matrix	Group 2 : Aggressive debridement + saline-moistened woven gauze dressing	Group 1: n= 9 Group 2: n= 8	Complete wound closure by 12 weeks	Group 1: 5/9 (56%) Group 2: 3/8 (38%)	NS
Pham et al. (1999)	Group 1 Apligraf®: cultured from human foreskin-derived neonatal fibroblast and keratinocytes in a bovine type I collagen matrix	Group 2: Saline-moistened gauze dressings + Extensive debridement + weight offloading	Group 1: n= 16 Group 2: n= 17	Percentage of complete wound closure and median time to wound closure at 12 weeks	Group 1: 12/16 (75%) Group 2: 7/17 (41%) Median time: Group 1: 38.5 days vs. group 2: 91 days	<0.05 0.01 log rank test
Edmonds et al. (2009)	Group 1 Apligraf®: cultured from human foreskin-derived neonatal fibroblast and keratinocytes in a bovine type I collagen matrix	Group 2: sharp debridement + saline-moistened dressings + non–weight-bearing Mepitel applied as primary dressing + weight off loading	Group 1: n= 33 Group 2: n= 39	Complete wound closure at 12 weeks	Group 1: 17/33 (51.5%) Group 2: 10/38 (26,3%)	P = 0.049, Fisher exact test
Veves et al. (2001)	Group 1 Apligraf®: cultured from human foreskin-derived neonatal fibroblast and keratinocytes in a bovine type I collagen matrix + SOC	Group 2: Saline moistened gauze + Standard state-of-the-art adjunctive therapy	Group 1: n= 112 Group 2: n= 96	Complete wound closure at 12 weeks	Group 1: 63/112 (56%) Group 2: 36/96 (38%)	0.0042

Table 1: *Studies of cellular skin substitutes vs. standard of care.*

You et al. (2012)	Group 1 Kaloderm®: allogeneic cultured keratinocytes from foreskin of a circumcised infant	Group 2: Vaseline gauze	Group 1: n= 20 Group 2: n= 26	Complete wound closure by 12 weeks	Group 1: 20/20 (100%) Group 2: 18/26 (69%)	<0.05
Bayram et al. (2005)	Group 1: cultured keratinocyte attached onto microcarriers (made from polyethylene and silica) + SOC: debridement and petroleum jelly gauze)	Group 2 (SOC + Placebo): microcarriers (made from polyethylene and silica, without keratinocyte) + SOC: debridement and petroleum jelly gauze)	Group 1: n= 20 Group 2: n= 20	Mean reduction of wound area at 30 days	Group 1: 92% Group 2: 32%	<0.01
Armstrong et al. (2022)	Group 1: TheraSkin®: cryopreserved human split-thickness skin allograft	Group 2: collagen alginate dressing	Group 1: n=50 Group 2: n= 50	Complete wound closure at 12 weeks	Group 1: 38/50 (76%) Group 2: 18/50 (36%)	0.00056
Armstrong et al. (2023)	Group 1 Autologous heterogeneous skin construct (AHSC): autologous harvest of the patient's full-thickness + SOC	Group 2: weight offloading + debridement + dressing with collagen alginate + multilayer compression bandaging system	Group 1: n= 50 Group 2: n= 50	Complete wound closure at 12 weeks	Group 1: 35/50 (70%) Group 2: 17/50 (34%)	0.00032
Caravaggi et al. (2003)	Group 1 Hyalograft 3D + Laserskin: cultured of autologous fibroblast and Keratinocytes grown on scaffolds of benzyl ester of hyaluronic acid + SOC	Group 2: non-adherent paraffin gauze	Group 1: n= 43 Group 2: n= 36	Complete wound closure at 11 weeks	Group 1: 29/43 (65.3%) Group 2: 18/36 (49.6%)	0.191
Gould et al. (2022)	Group 1 mVASC ®: processed microvascular tissue harvest from the subcutaneous tissue of cadaveric human donors + SOC	Group 2: Debridement + primary collagen calcium alginate dressing + secondary three-layer dressing + weight offloading	Group 1: n= 50 Group 2: n= 50	Complete wound closure at 12 weeks	Group 1: 37/ 50 (74%) Group 2: 19/50 (38%)	0.00029
Tettelbach et al. (2019)	Group 1 Epicord®: dehydrated human umbilical cord allograft + moist dressings + off loading	Group 2: alginate wound dressing, non-adherent silicone dressing, absorbent non-adhesive hydropolymer secondary dressing + gauze bandage roll + off loading	Group 1: n= 101 Group 2: n= 54	Complete wound closure at 12 weeks	Group 1: 71/101 (70%) Group 2: 26/54 (48%)	0.0089
Lavery et al. ((2014)	Group 1 Grafix®: a human viable wound matrix (cryopreserved product of components of the human placental membrane) + SOC	Group 2: surgical debridement + off-loading + non-adherent dressings	Group 1: n= 50 Group 2: n= 47	Complete wound closure at 12 weeks	Group 1: 31/50 (62%) Group 2: 10/47 (21.3 %)	0.0001

SOC: Standard of Care

Table 1: *Studies of cellular skin substitutes vs. standard of care.*

Study	Publication year	Intervention	Comparison	Participants	Primary Outcome	Results	p-value
Zelen et al.	2015	Group 1: Dehydrated human amnion/chorion membrane allograf EpiFix®) weekly application	Group 2: Apligraf, cultured from human foreskin-derived neonatal fibroblast and keratinocytes in a bovine type I collagen matrix: weekly application. Group 3: SOC* weekly debridement, collagen - alginate and gauze dressing, off loading	Group 1: n= 20 Group 2: n= 20 Group 3: n= 20	Percentage change in complete wound healing after 4 and 6 weeks	At 4 weeks Group 1: 17/20 (85%) Group 2: 7/20 (35%) Group 3: 6/20 (30%). At 6 weeks Group 1: 19/20 (95%) Group 2: 9/20 (45%) Group 3: 7/20 (35%)	≤ 0·003
Ananian et al. Non Inferiority	2018	Group 1: Cryopreserved human placental membrane (Grafix Prime®) weekly application	Group 2: Dermagraft®, culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold: weekly application	Group 1: n= 31 Group 2: n= 31	Percentage change in complete wound healing after 9 weeks (8 weekly applications)	Group 1: 15/31 (48.4%) Group 2: 12/31 (38.7%)	Grafix Prime® is non-inferior to Dermagraf® (estimated difference 9.68%, 90%CI −10.67- 28.94)
Frykberg et al. Non Inferiority	2016	Group 1: Matri Stem Wound Matrix® (porcine-derived extracellular matrix, in sheet form) + MatriStem Micro Matrix® (porcine-derived extracelluar matrix, in particle form) up to eight weekly device applications	Group 2: Dermagraft®, culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold: up to eight weekly device applications	Group 1: n= 27 Group 2: n= 29	Complete wound closure by 8 weeks with weekly device application	Group 1: 5/27 (18.5%) Group 2: 2/29 (6.9%)	0.244
Sanders et al.	2014	Group 1: Dermagraf®, culture of neonatal dermal fibroblasts onto a bioabsorbable polyglactin mesh scaffold: weekly applications	Group 2: TheraSkin®: cryopreserved human split-thickness skin allograft, applications every other weeks	Group 1: n=12 Group 2: n=11	Complete wound closure by 12 weeks	Group 1: 4/12 (33%) Group 2: 7/11 (63.3%)	0.0498

SOC: Standard of Care

Table 2: *Studies of cellular skin substitutes vs. another intervention different from standard of care.*

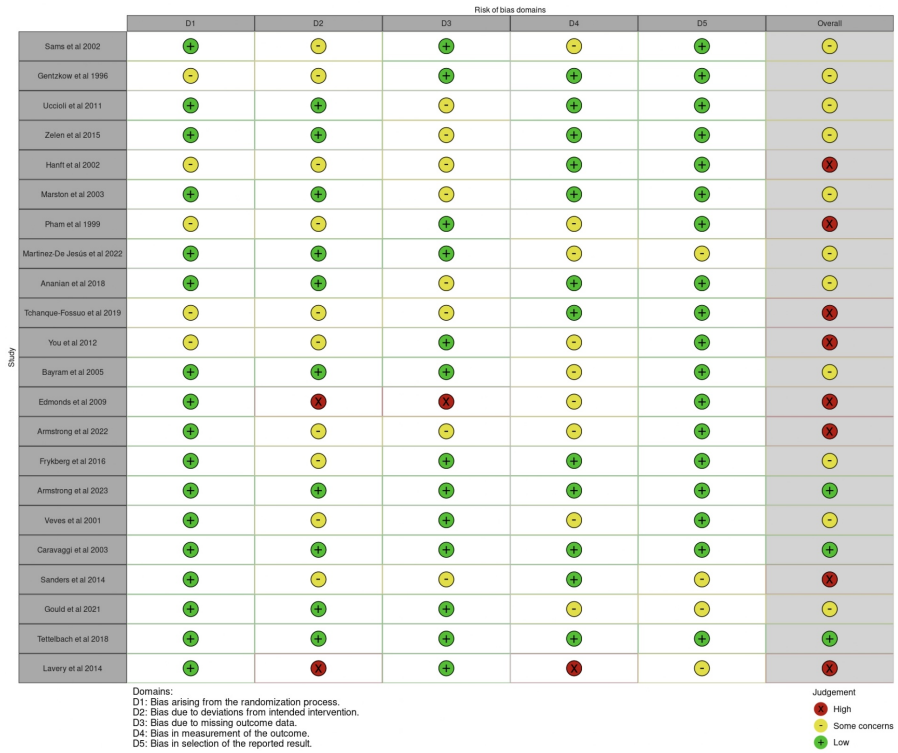

Figure 2: *Risk of bias evaluated by version 2 of the Risk of Bias of Randomized Controlled Trials (RoB 2) tool based on the Cochrane Handbook for Systematic Reviews of Interventions.*

group (p<0.01).

b) Human and animal skin substitutes

Despite different sample sizes, Pham et al., 1999 and Veves et al., 2001 published significant differences in the treatment with Apligraf vs. SOC regarding complete wound closure at 12 weeks: respectively 75% (12/16) vs. 41% (7/17) (p<0.01), and 56% (63/112) vs. 38% (36/96) (p=0.00042). Sams et al., 2002 showed a 56% (5/9) vs. 38% (3/8) success rate with no reported p-value.

Although Edmonds, 2009, focused on 52 weeks (13 months) to show complete healing, Kaplan-Meier analysis indicated a non-significant (p=0.059) trend to shorter time to complete wound healing in the Apligraf® group than in the control group during the 12-week treatment. By 12 weeks, 51.5% (17/33) of the subjects treated with Apligraf® achieved complete wound closure compared to 26.3% (10/38) of subjects treated with SOC (p= 0.049).

2. RCT of cellular skin substitutes vs. other skin substitutes

Four RCTs (178 subjects) have been published comparing cellular skin substitutes with treatments other than SOC (Table 2).

Zelen et al., 2015 compared Apligraf®, Dehydrated Human Amnion Chorion Membrane (EpiFix®), and SOC. The study showed that at six weeks, the EpiFix® group had the highest rate of complete healing (95% for EpiFix® vs. 45% for Apligraf® vs. 35% for SOC, p<0.001). Time-to-heal was less in the EpiFix® group (median = 13 days) compared to other arms (median = 49 days, in both).

Ananian et al., 2018 compared complete epithelialization after eight weeks between Grafix Prime® and Dermagraft® (48.39% vs. 38.71%). A cost analysis showed that Dermagraft® was more expensive than Grafix Prime®.

Sanders et al., 2014 directly compared Dermagraft® vs. TheraSkin® for wound closure at 12 weeks (63.6% vs. 33.3%, p=0.0498) and at 20 weeks (90.91%, vs. 66.67%, p=0.4282).

However, Frykberg et al., 2016 failed to show any significant difference between the treatment with MatriStem® (ACell, Inc., Columbia, MD) and Dermagraft® regarding complete wound closure after eight weeks (18.5% (5/27) vs. 6.9% (2/29) p=0.244) and recurrence rate (1/27 in the MatriStem® group and 2/29 in the Dermagraft® group).

Risk of Bias

For the risk of bias assessment, we found three stud-

ies with an overall risk of bias identified as "low," 11 had "some concerns," and 8 had a "high" risk of bias (Figure 2).

Discussion

This mini-review found that cellular skin substitutes are a promising therapy when treating DFUs, either as an adjunct or alternative to standard treatment. Products such as EpiFix®, TheraSkin®, PMVT, Epicord®, AHSC, and Grafix® showed approximately 60% to 70% of complete wound closure at 12 weeks, showing superiority to other treatments or SOC.

Previous evidence has shown that cellular substitutes in conjunction with SOC can improve the healing rate of DFU (Alfonso, 2020). However, they are not recommended as standard therapy according to the IWGDF guidelines (Chen et al., 2023). This review may help revise these guidelines if future studies confirm the positive trends. One of the strengths of this mini-review is the description of studies of cellular skin substitutes versus another intervention different from SOC.

Controversy exists because the included studies have different designs, with varying comparator groups and endpoints. Nevertheless, the most relevant limitation is the small sample size of some studies with less than 20 subjects per group (Gentzkow et al., 1996; Hanft & Surprenant, 2002; Pham et al., 1999; Sams et al., 2002; Tchanque-Fossuo et al., 2019). Differences in follow-up times are another challenge to assessing and comparing skin substitutes.

In general, there is a risk of publication bias. Studies conducted with manufacturers might not have been published if the results were negative.

The highlighted results of various practical and promising treatments must be confirmed in further studies with high quality and sample size to improve the care of patients with refractory DFUs and for skin substitutes to be considered in future guidelines. More studies on head-to-head comparisons are needed, and future studies could also focus on the cost-effectiveness of skin substitute products compared to standard therapy, such as comparing the cost of prolonged hospitalization and complications associated with failure of wound healing versus the increased cost of skin substitute therapy. Furthermore, long-term studies are needed to assess their long-term safety and efficacy.

Conclusion

In conclusion, we showed the promising effects of cellular skin substitutes on the healing of DFUs. The discussed benefits, such as quicker healing, may help to make cellular skin substitutes part of the SOC for DFUs. However, further trials with larger samples and more standardized outcomes are needed to assess their comparative effectiveness, cost-effectiveness, long-term safety, and efficacy.

Author Contributions

In this systematic review, all authors conceived the initial idea, designed the study, selected and reviewed the articles, and extracted the data. All authors drafted the manuscript article. All authors reviewed and approved the final version of the paper.

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Conflicts of Interest

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