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Autologous Skin Grafts, versus Tissue-engineered Skin Constructs: A Systematic Review and Meta-analysis

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Background: For over 100 years, autologous skin grafts have remained the gold standard for the reconstruction of wounds but are limited in availability. Acellular tissue-engineered skin constructs (acellular TCs) and cellular tissue-engineered skin constructs (cellular TCs) may address these limitations. This systematic review and meta-analysis compare outcomes between them.

Methods: A systematic review was conducted using PRISMA guidelines, querying MEDLINE, Embase, Web of Science, and Cochrane to assess graft incorporation, failure, and wound healing. Case reports/series, reviews, in vitro/in vivo work, non-English articles or articles without full text were excluded.

Results: Sixty-six articles encompassing 4076 patients were included. No significant differences were found between graft failure rates (P = 0.07) and mean difference of percent reepithelialization (p = 0.92) when split-thickness skin grafts were applied alone versus co-grafted with acellular TCs. Similar mean Vancouver Scar Scale was found for these two groups (p = 0.09). Twenty-one studies used at least one cellular TC. Weighted averages from pooled results did not reveal statistically significant differences in mean reepithelialization or failure rates for epidermal cellular TCs compared with split-thickness skin grafts (p = 0.55).

Conclusions: This systematic review is the first to illustrate comparable functional and wound healing outcomes between split-thickness skin grafts alone and those co-grafted with acellular TCs. The use of cellular TCs seems promising from preliminary findings. However, these results are limited in clinical applicability due to the heterogeneity of study data, and further level 1 evidence is required to determine the safety and efficacy of these constructs. *(Plast Reconstr Surg Glob Open 2023; 11:e5100; doi: 10.1097/GOX.0000000000005100; Published online 27 June 2023.)*

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INTRODUCTION

Skin loss can result from acute trauma, burns, infection, or surgical intervention. When healing by primary closure or secondary intention is not feasible, skin grafts are utilized. There are several types of skin grafts that have been studied, with the most prominent being autologous skin grafts, which are harvested from one part of the body and transferred to another on the same individual.[1–3] These grafts are considered the standard of care for wound repair and can be full-thickness (FTSG) or split-thickness (STSG).[4–9] Both these grafts require tissue donation from healthy skin, which may be limited in the case of extensive injury and could further predispose

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the patient to infection or blood loss. Other skin grafts include allogeneic and xenogeneic.[4] However, these grafts are temporary and, in general, succumb to host rejection, often warranting subsequent procedures.[4,9–11]

Other types of skin grafts that can be utilized are the tissue-engineered skin constructs: acellular tissue-engineered skin constructs (acellular TCs) and cellular tissue-engineered skin constructs (cellular TCs). Tissue engineering has the potential to generate skin constructs while avoiding donor site morbidity. Acellular TCs can be made from decellularizing skin derived from human or animal tissue, or from engineered scaffolds of structural proteins.[12] These provide structural support, promote revascularization and cell regeneration, and prepare a wound for secondary grafting.[13] They have been explored in combination with autologous skin grafts, as well as on their own for the management of burns, diabetic foot ulcers, and soft tissue reconstruction, but prior systematic reviews have primarily focused on comparing healing times of commercially available acellular TCs (eg, Matriderm, Alloderm, Integra) to standard of care treatment without grafts (ie, dressing changes), rather than comparing grafts/constructs to each other.[13–18] As acellular TCs often lack cells, they are prone to graft failure and poor scar/aesthetic outcomes when compared with autologous skin grafts.[19] On the other hand, cellular TCs can be composed of autologous cells, thus potentiating limited immune rejection.[20] Although significant progress has been made in developing tissue-engineered skin constructs with in vitro and in vivo testing, the use of cellular TCs in medical practice remains limited.[21–27] The aim of this systematic review is to provide a clinical comparison of graft incorporation, healing times, and functional outcomes between three key groups: group 1, autologous skin grafts alone versus acellular TCs alone; group 2, autologous skin grafts alone versus autologous skin grafts co-grafted with acellular TCs (TCs placed in contact with the wound bed with a skin graft placed on top); and group 3, cellular TCs alone versus any graft/construct in groups 1 or 2. This is the first systematic review comparing these grafts and constructs with each other to provide foundational evidence for practice management and potential change.

Takeaways

Question: Is tissue engineering making reliable skin grafts on par with autologous skin grafts?

Findings: A thorough review and literature analysis were conducted to compare skin grafts produced through tissue engineering with autologous skin grafts. Several functional and wound healing outcomes, including re-epithelialization, and graft failure rates, were found to be as good with tissue engineering as those associated with autologous skin grafts.

Meaning: The field of tissue-engineered skin constructs appears promising and, with further research, could lead to widespread usage in the clinical setting.

METHODS

Search Methodology

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines on July 22, 2020.[28] Peer-reviewed, published articles in English, until July 7, 2020, were queried from MEDLINE, Cochrane, Embase, and Web of Science databases (Table 1). Primary outcomes of interest included healing time, graft incorporation rate, graft failure, or functional and aesthetic outcomes, including but not limited to Vancouver Scar Scale (VSS) assessments and range of motion (Table 2).[43]

Selection Criteria

All studies assessing the designated clinical outcomes of any of the graft types in all three groups were included. (**See table, Supplemental Digital Content 1A,** which shows study details, including demographics, grafts utilized, and mechanisms of injury. **http://links.lww.com/PRSGO/C638**.) Other systematic reviews, clinical trial proposals, studies using other grafts such as xenogeneic grafts, in vivo or in vitro work in animals, non-English articles, and full text articles unable to be retrieved were excluded (Table 3). Additionally, billing codes (eg, Current Procedural Terminology codes) were searched for among included articles to standardize categorizations, but no such data were found. Any skin substitute/scaffold lacking cellular components that was modified with the intent of replacing native skin (including decellularized skin grafts) are included as acellular TCs.[2,19,35] Skin substitutes engineered to include cellular components of the epidermal or dermal layers of skin (eg, autologous/allogeneic fibroblasts, keratinocytes, or epithelial cells) are classified as cellular TCs. Four authors, in pairs, independently screened the data using Rayyan software by title and abstract first, and then by full text, and disputes were resolved by mutual agreement.[44]

Data Extraction

Data were extracted from the final 66 articles, and data extraction was performed by all authors independently. The key study characteristics are captured in **Supplemental Digital Content 1A (http://links.lww.com/PRSGO/C638.)** Data were extracted in a standardized manner to allow for meta-analysis.

Critical Appraisal

Level of evidence classification and study appraisal was performed based on study design as defined below and in accordance with the American Society of Plastic Surgeons rating scale for therapeutic studies (**Supplemental Digital Content 1A, http://links.lww.com/PRSGO/C638**).[45] Nonrandomized studies, including cohort and self-controlled case-control studies, were assessed utilizing the ROBINS-I tool based on seven key criteria, and visualized using robvis.[46,47] Randomized studies were appraised

Table 1. Search Strategies for All Four Databases

Database	Concept 1: Successful Incorporation of Graft to Host Bed	Concept 2: Tissue Engineered Skin	Concept 3: FT/ST Skin Grafts	Concept 4: Dermis and Epidermis Layers	Results	Date Performed
Ovid MEDLINE	exp tissue survival/ OR exp Anastomosis, Surgical/ OR exp Graft Survival/ OR exp Surgical Wound Dehiscence/ OR exp Neovascularization, Physiologic/ OR skin necrosis.mp. OR graft survival.mp OR skin repair.mp.	exp Printing, Three-Dimensional/ OR exp Bioprinting/ OR exp Skin, Artificial/ OR exp Tissue Scaffolds/ OR exp Tissue Engineering OR skin substitute.mp OR artificial skin.mp. OR vascular conduit.mp. OR three dimensional tissue engineering.mp. OR skin construct.mp.	exp Skin Transplantation/ OR exp Acellular Dermis/ OR exp Autografts/ OR vascularized composite.mp. OR autologous skin graft.mp. OR split thickness skin graft.mp. OR full thickness skin graft.mp. OR skin graft.mp.	exp Dermis/ OR exp Epidermis/ OR dermal.mp. OR epidermal.mp.	826	July 22, 2020
Embase	"tissue survival"/exp OR "anastomosis"/exp OR "graft survival"/exp OR "wound dehiscence"/exp OR "angiogenesis"/exp OR "skin necrosis" OR "graft survival" OR "skin repair"	"three dimensional printing"/exp OR "bioprinting"/exp OR "tissue engineering"/exp OR "artificial skin"/exp OR "tissue scaffold"/exp OR "skin substitute" OR "artificial skin" OR "vascular conduit" OR "three dimensional tissue engineering" OR "skin construct"	"skin graft"/exp OR "skin autograft"/exp OR "acellular dermal matrix"/exp OR "skin transplantation"/exp OR "autologous skin graft" OR "split thickness skin graft" OR "full thickness skin graft" OR "skin graft" OR "vascularized composite"	"dermis" OR "epidermis" OR "dermal" OR "epidermal"	1667	7/22/2020
Web of Science	TS=(Tissue Survival OR Surgical Anastomosis OR Graft Survival OR Wound dehiscence OR Angiogenesis OR skin necrosis OR skin repair)	TS=(Three dimensional printing OR Bioprinting OR Artificial skin OR tissue engineering OR tissue scaffold OR skin substitute OR vascular conduit OR three dimensional tissue engineering OR skin construct)	TS=(Skin graft OR skin autograft OR autologous skin graft OR split thickness skin graft OR full thickness skin graft OR vascularized composite OR acellular dermal matrix)	TS=(dermis OR dermal OR epidermis OR epidermal)	3251	7/22/2020
Cochrane	[Tissue Survival]/exp MeSH OR [Anastomosis, Surgical]/exp MeSH OR [Graft Survival]/exp MeSH OR [Surgical wound dehiscence]/exp MeSH OR [Neovascularization, Physiologic]/exp MeSH OR "skin necrosis" OR "graft survival" OR "skin repair"	[Printing, Three-Dimensional]/exp MeSH OR [Bioprinting]/exp MeSH OR [Tissue Engineering]/exp MeSH OR [Skin, Artificial]/exp MeSH OR [Tissue Scaffolds]/exp MeSH OR "skin substitute" OR "artificial skin" OR "vascular conduit" OR "three dimensional tissue engineering" OR ((INSERT TERM FOR SKIN CONSTRUCT HERE – only keywords in other databases, no MeSH found)	[Skin Transplantation]/exp MeSH OR [Acellular Dermis]/exp MeSH OR [Autografts] MeSH OR "vascularized composite" OR "autologous skin graft" OR "split thickness graft" OR "full thickness graft" OR "skin graft"	[Dermis]/exp MeSH OR [Epidermis]/exp MeSH OR "dermal" OR "epidermal"	179	7/22/2020

Search strategies included combinations as follows: (a) "concept 1 terms AND concept 2 terms AND concept 4 terms" and separately conducted; (b)"concept 1 terms AND concept 3 terms AND concept 4 terms." The total results count is a combination of (a) and (b) as listed. Once all four database searches were combined in Endnote, a total of 4217 articles remained after deduplication. Once imported into Rayyan,[29] additional deduplication was performed, and 3921 articles remained for screening

utilizing the RoB2 Cochrane risk of bias tool, which assesses studies against six criteria.[48]

Statistical Analysis

Comparison of graft failure rates, mean percent reepithelialization, and mean VSS were analyzed via odds ratio and mean difference meta-analysis, along with analysis of pooled average failure rates by graft type. Odds ratios were calculated with the Mantel-Haenszel method and depicted in forest plots using Review Manager, version 5.4.[49,50] OpenMeta [Analyst], version 10.2 was used to calculate pooled prevalence through the DerSimonian-Laird method.[51] We applied a random effects model to all calculations due to anticipated heterogeneity. Results of pooled prevalence and risk ratios with 95% confidence intervals are presented in forest plots. *P* values less than 0.05 were considered significant. Power was calculated using Z-tests for correlations of two independent Pearson r values using G power 3.1.9.7 software, and a cutoff of 80% power was deemed significant.[52] For the studies where heterogeneity in study design was too great, statistical analysis was not able to be completed. As

Table 2. Definitions

Study Designs
Self-controlled case-control study: Also known as a case-crossover study; the patient is acting as their own control when given a particular intervention (graft type).[30]
Cohort study: Patients are grouped into cohorts based on the intervention received and followed for subsequent outcomes of interest postintervention administration; there may or may not be a comparison group.[30]
Intrapatient controlled: The same number of patients in the experimental and control groups; patients were used as their own controls and experimental groups.[30]
Graft Types
Autograft: A skin graft that is harvested from the patient's body (other names: autologous skin graft). Skin graft details regarding thickness, as presented in **Supplemental Digital Content 4,** have been further defined based on prior guidance and definitions.[31,32]
Allograft: A skin graft harvested from a human, but not from the recipient patient (other names: allogeneic skin graft).[32,33]
Xenograft: A skin graft harvested from a nonhuman animal, such as pigs (other names: xenogeneic skin graft).[32,33]
Cellular-tissue-engineered skin construct (cellular TCs): Any graft that is made via seeding of cells onto a matrix, sprayed cultured cells directly onto a wound, or from three-dimensional printing methods. Examples include cultured epithelial autografts, micrografts, or bioprinted grafts.[34]
Acellular-tissue-engineered skin construct (acellular TC): A skin substitute, scaffold, or matrix that is modified or manipulated with the intent of replacing native skin but lacks cells. Included in this grouping are commercially available products such as Integra (Integra LifeSciences Corp., Plainsboro, N.J.) or Matriderm (Skin and Health Care AG, Billerbeck, Germany), to name a few.[2,19,35]
Outcome Measures
Graft incorporation rate: achievement of 100% reepithelialization of the graft to the wound bed.[36]
Reepithelialization: the resurfacing of a wound with new epithelium via infiltration of keratinocytes into the graft on the wound bed.[37–41]
Graft failure rate: The loss of a graft applied to injured skin, usually in the form of graft necrosis, wound dehiscence, or host immune rejection of the graft.[42]
Healing time: Time to 90%–100% reepithelialization of the graft into the wound bed.

Table 3. Detailed Inclusion and Exclusion Criteria and Outcomes of Interest

Study criteria	Included: clinical studies (n>1) using either FTSG, STSG, or tissue-engineered skin grafts, reporting on graft incorporation into host, dermis and/or epidermis only
	Excluded: in vivo studies in animal models or in vitro studies, grafts including more than dermis and/or epidermis, case reports, no report on graft outcomes related to incorporation into host bed
Intervention	Skin grafting in humans using either FTSG, STSG, allografts, or tissue engineered skin grafts (dermis and/or epidermis only)
Outcomes of interest	1. Graft take rate as measured by percent reepithelialization
	2. Healing time as measured by complete reepithelialization
	3. Graft failure, necrosis, or rejection
	4. Neovascularization of graft
	5. Aesthetic outcomes related to scarring
Study design	Excluded papers in the following categories:
	1. No outcomes data as listed above
	2. Wrong study design: case study, study unrelated to skin grafts, other review articles, not in humans
	3. Not in English
	4. Duplicates
	5. Inaccessible
Publication type	Clinical and scientific peer-reviewed journals
Language	Published or translated to English

such, pooled descriptive analysis of studies utilizing similar grafts was performed, and weighted averages were calculated.

RESULTS

A total of 66 out of 3921 studies met inclusion criteria (Fig. 1—PRISMA diagram). From these 66 studies, 4076 patients were evaluated (58.3% men, 31.5% women, 10.2% undocumented). A summary of the grafts/constructs are listed in Supplemental Digital Content 1B. (**See table, Supplemental Digital Content 1B,** which shows grafts utilized in studies based on category, level, and cell types utilized. **http://links.lww.com/PRSGO/C638**.) Based on definitions listed below, 25 studies were prospective cohorts,[29,37,53–74] 14 were retrospective cohorts,[75–88] eight were intrapatient-controlled nonrandomized studies,[38,89–95] and 19 were randomized prospective trials of variable blinding and control levels.[39,40,96–112]

Critical Appraisal of Included Studies

A total of 47 nonrandomized articles were appraised utilizing the ROBINS-I tool. Only one study (2%) was deemed to be low risk across the seven domains (Fig. 2). (**See figure, Supplemental Digital Content 2,** which features critical appraisal results of each nonrandomized study. **http://links.lww.com/PRSGO/C639**.) Critical appraisal was also performed for the randomized studies utilizing the RoB2 tool, with a total of 19 studies included. In total, seven (36.8%) randomized studies were classified as low risk of bias. Another nine (47.3%) were considered to have some domains of concern for risk of bias, and three (15.8%) studies were high risk of bias (Fig. 3). (**See figure, Supplemental Digital Content 3,** which

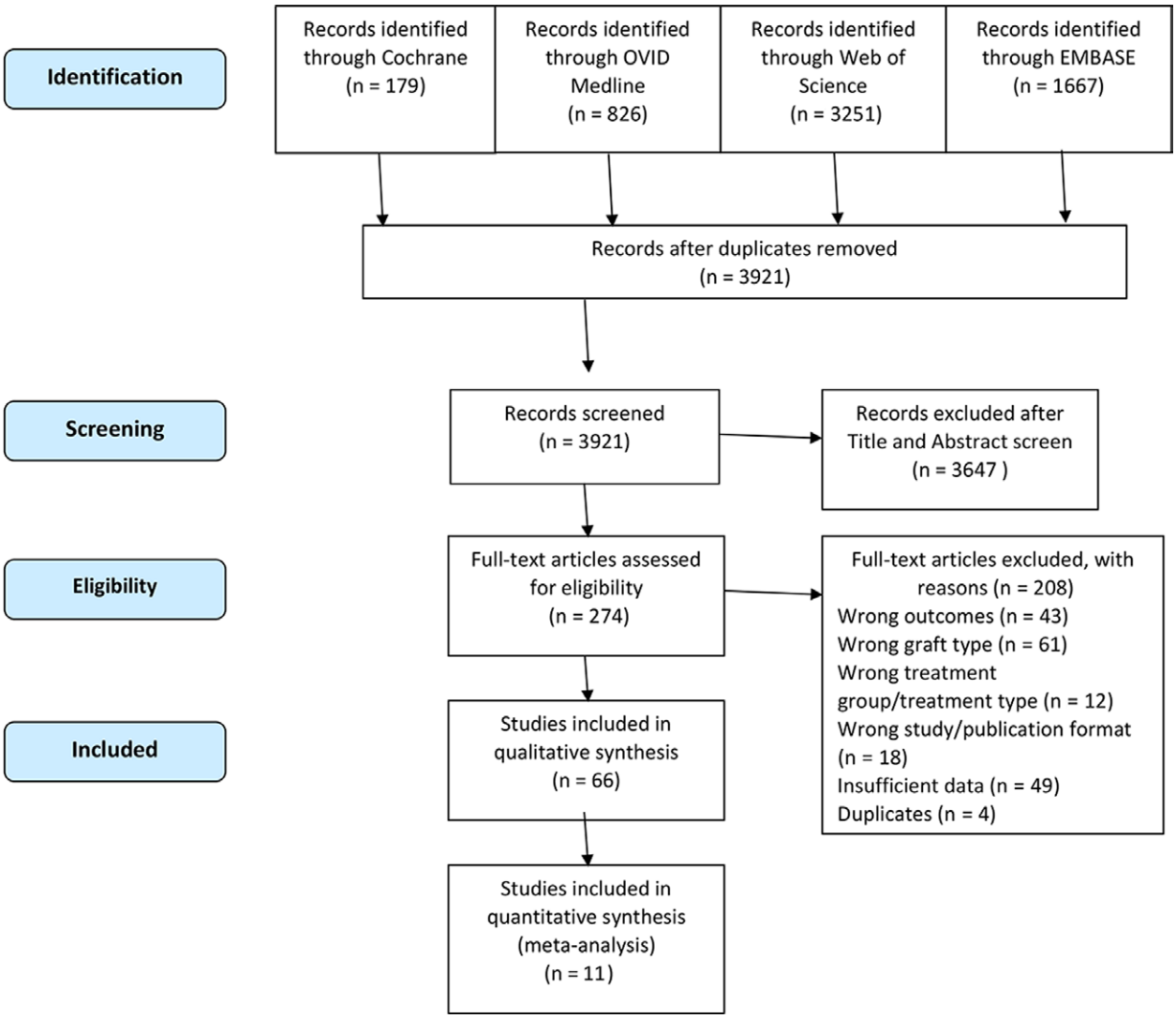

Fig. 1. PRISMA diagram of study selection.[28]

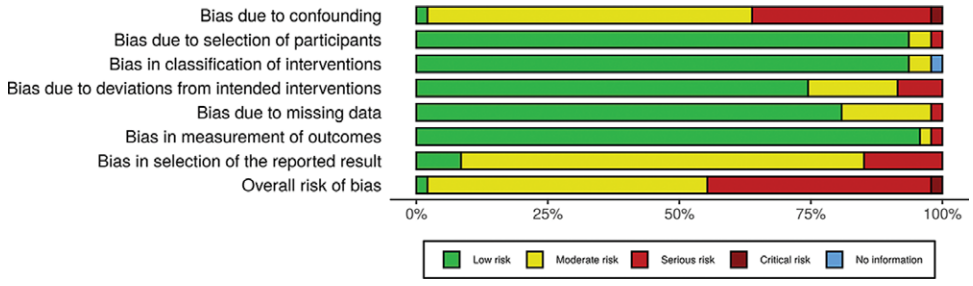

Fig. 2. Risk of bias in nonrandomized studies using the ROBINS-I tool reveals most studies included were moderate or serious risk of bias.[46,47]

features critical appraisal results of each randomized study. **http://links.lww.com/PRSGO/C640**.)

Group 1 Grafts/Constructs: Autologous Skin Grafts versus Acellular TCs

First, we compared failure rates of the common clinically used grafts/constructs in group 1: autologous skin grafts and acellular TCs.[13] Failure of a graft could be due to a number of causes, including but not limited to graft infection, hematoma, dehiscence, necrosis, or need for revision grafting.[113] Due to heterogeneity in study design, odds ratio meta-analysis of failure rates for group 1 grafts/constructs were unable to be calculated. However, via a pooled prevalence analysis, the average failure rate for

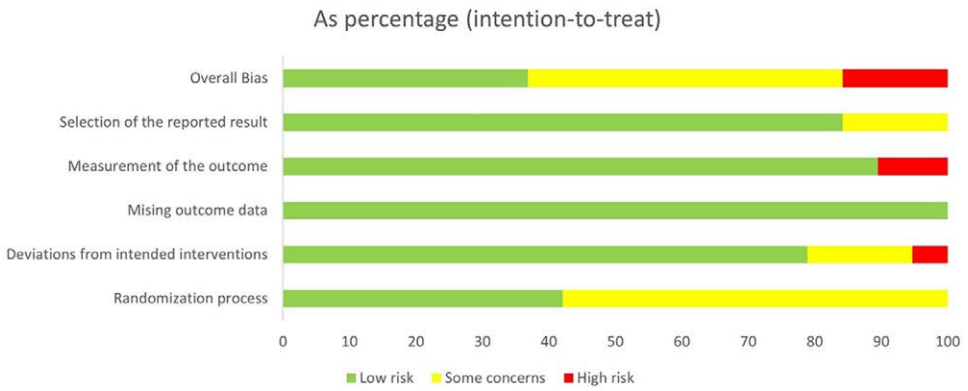

Fig. 3. Risk of bias in randomized studies using the ROB2 tool reveals most studies included were low risk of bias or with some concerns, but a small percentage are noted to be high risk of bias.[48]

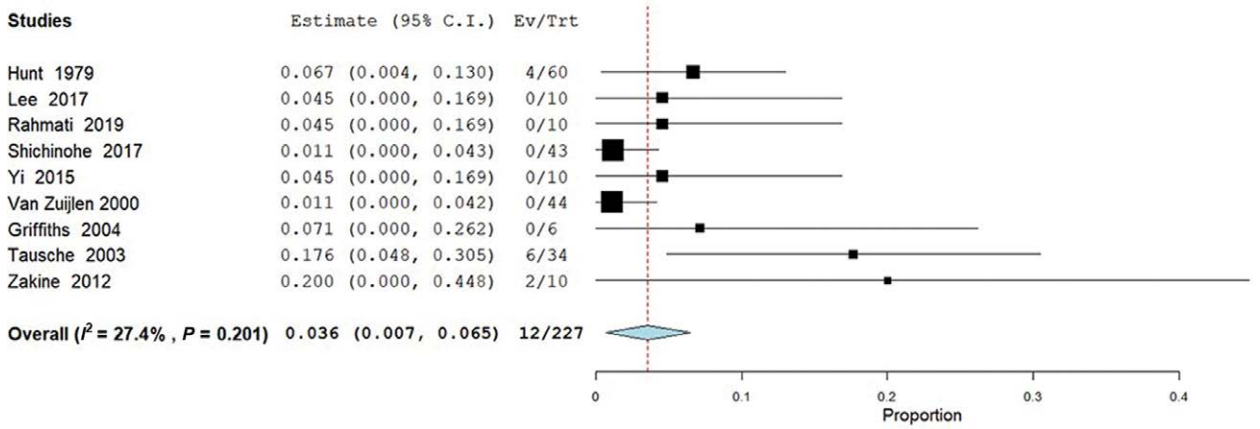

Fig. 4. Weighted average graft failure rates reported among studies utilizing STSGs alone revealed 3.6% average failure rate among nine studies included. Individual study data are represented in each row, with the event rate representing graft failure among the total number of grafted sites. There was moderate heterogeneity with I^2 of 27.4%. This result was nonsignificant with P = 0.201.

STSGs among nine studies included was estimated at 3.6% (P = 0.201; Fig. 4). A similar analysis for acellular TCs alone was not able to be computed due to limited homogeneity in study data.

Group 2 Grafts/Constructs: Co-grafts of Acellular TCs with Autografts versus Autografts Alone

Given the limitations for meta-analysis due to heterogeneity of the studies involved, we assessed the failure rates of group 2 grafts/constructs: co-grafts of acellular TCs with autologous skin grafts compared with autologous skin grafts alone. The technique of combining two types of grafts (with acellular TCs in contact with the wound bed and autografts on top) has become prominent, especially for deep wounds, to help achieve more aesthetically pleasing and functional outcomes.[114] In an odds ratio meta-analysis of four studies, the number of graft failures in co-grafting compared with STSGs alone was not significant.[40,69,107,112] The power of this analysis was 97.8% [OR 5.34; 95% CI, 0.85–33.59; P = 0.07] (Fig. 5). In 11 studies focused only on co-grafts of STSGs and acellular TCs, the average graft failure rate was estimated to be 6.1% (Fig. 6).[29,40,56,60,61,66,69,70,107,112] The average graft failure rates of full thickness skin grafts co-grafted with acellular TCs was 5.7% in two separate studies (Fig. 7).[74,88,99]

Measurement of percent reepithelization of a wound bed is important for assessing graft success and wound healing. Reepithelialization was characterized in these studies as migration of the host keratinocytes into the graft/construct placed over the wound bed.[37,38,40,92] Overall, reepithelialization and graft take was determined to be similar between STSG alone when compared with the acellular TC co-grafted with a STSG in three of the four included studies.[37,38,92] This demonstrates that addition of dermal substitutes between the skin graft and the wound bed do not necessarily result in any impedance to the diffusion of blood and vascular ingrowth. When analyzing the results of percent reepithelialization via a mean difference meta-analysis of these four studies, it was determined that no difference in reepithelialization was observed overall between acellular TCs with STSGs versus STSGs alone. The power of this calculation was 98%. [mean difference 0.09; 95% CI, – 1.69 to 1.88; P = 0.92] (Fig. 8).[37,38,40,92]

Functional outcomes of healing were also analyzed, the most common of which was the VSS.[115] Among three studies, the mean difference meta-analysis revealed no

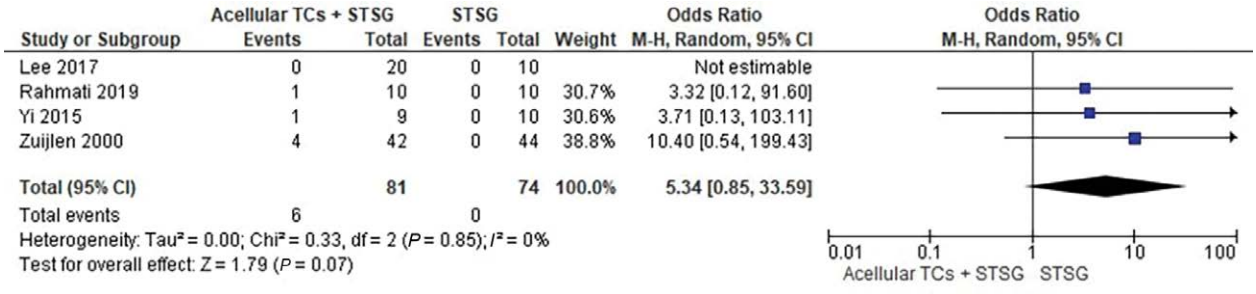

Fig. 5. Odds ratio meta-analysis for reported graft failures among co-grafts of acellular TCs and STSGs compared with STSGs alone in four total studies revealed a nonsignificant difference [OR 5.34; 95% CI, 0.85–33.59; $P = 0.07$]. Heterogeneity was 0%. Power was calculated at 97.8%. Data for each study are represented by the rows, with the final row representing overall effect.

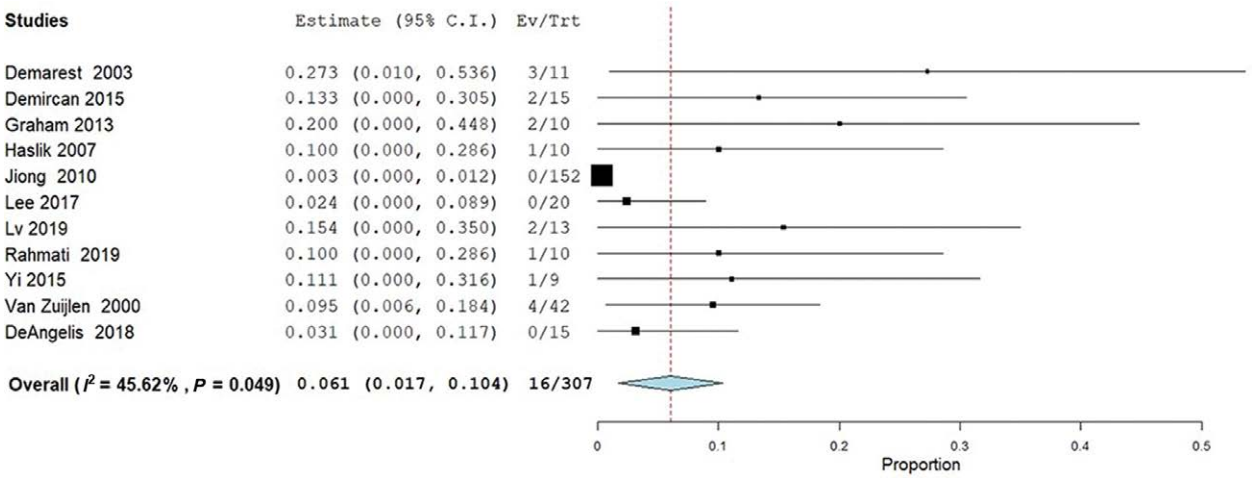

Fig. 6. Weighted average graft failure rates reported among studies utilizing co-grafts of acellular TCs with STSGs revealed 6.1% average failure rate among the eleven studies included. Individual study data are represented in each row with the event rate representing graft failure among the total number of grafted sites. There was heterogeneity in this analysis with I^2 of 45.62%.

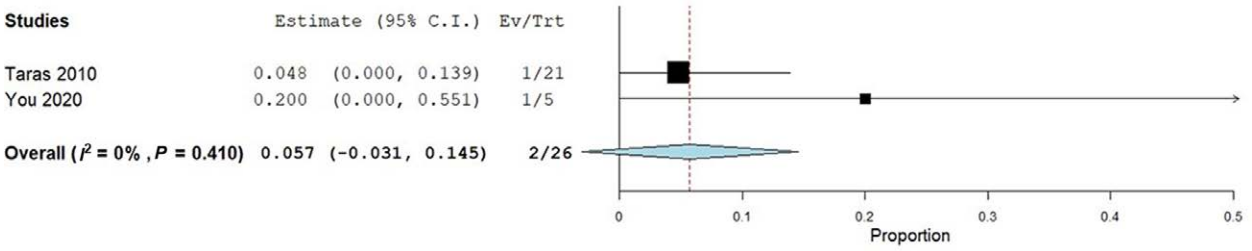

Fig. 7. Weighted average graft failure rate among studies utilizing co-grafts of FTSGs with acellular TCs revealed a 5.7% average failure rate among the two studies included. Individual study data are represented in each row, with the event rate representing graft failure among the total number of grafted sites. There was no heterogeneity observed ($I^2 = 0\%$). This result was nonsignificant with $P = 0.653$.

statistically significant difference in VSS improvement for co-grafts compared with STSGs alone, with a power of 79.7% [mean difference: – 2.6, 95% CI, – 5.58 to 0.38; $P = 0.09$] (Fig. 9).[69,98,112] Moreover, two studies utilizing co-grafts compared with STSGs alone employed another standardized measurement of wound healing and scarring, the Manchester Scar scale (MSS).[116] When interpreting the MSS, the final score may range from 4 to 14, with a lower score representing a more optimal healing and scar outcome. One study compared 26 diabetic foot ulcer wounds treated with co-grafts to 26 similar ulcer wounds treated with STSGs and reported statistically significant and improved median MSS of 9 for the co-grafts and 11 for STSGs alone ($P = 0.006$).[104] In another study, 10 wounds were created as a result of scalp skin cancer excision to the skull bone were treated with co-grafts, whereas 10 were treated with STSGs. The mean MSS of 7.2 (0.833 SD) was found for the co-grafts versus 10 (1.33 SD) for the

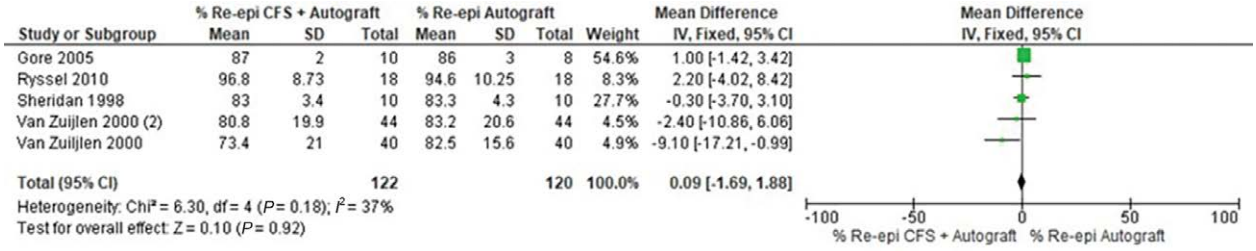

Fig. 8. Mean difference meta-analysis revealed a nonsignificant difference with almost equivalent graft incorporation, as measured by percent reepithelialization, of wounds co-grafted with acellular TCs and STSGs compared with STSGs alone in four included studies [mean difference: 0.09; 95% CI, − 1.69 to 1.88; $P = 0.92$]. There was observed heterogeneity ($I^2 = 37\%$), and power was 98%.

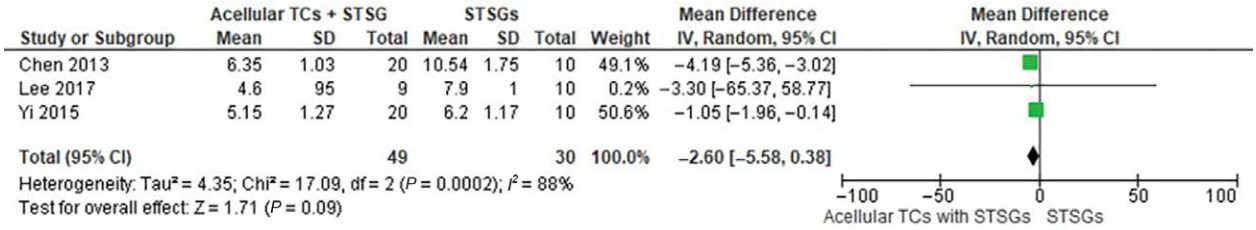

Fig. 9. Mean difference meta-analysis revealed a nonsignificant difference in wound healing based on VSS reporting, in co-grafts of acellular TCs with STSGs compared with STSGs alone among three included studies. VSS scoring is on a scale from 0 to 13, with a lower score representing improved healing results. [mean difference: − 2.6; 95% CI, − 5.58 to 0.38; $P = 0.09$]. There was high heterogeneity observed in this analysis with an I^2 of 88%. Power was 79.7%.

STSGs alone. Also, improved mobility scores ($P = 0.0198$) and surgeon satisfaction ($P < 0.0001$) were reported for the co-grafted wounds.[107] Although these studies cannot be pooled for meta-analysis, their individually reported data show promise of improved scar and functional healing outcomes for co-grafts owing to greater elasticity and pliability[92]. (**See table, Supplemental Digital Content 4A**, which lists reported study outcomes for studies used in meta-analysis only. **http://links.lww.com/PRSGO/C641**.)

The impact of the thickness of the STSGs on wound healing and functional outcomes was also analyzed. Four studies utilized the same STSGs thickness in their co-grafts and STSGs alone (with a thickness ranging from 0.008 to 0.024-in). In all four studies, the authors reported improved scar scale outcomes or functionality of the wounded site for the co-grafts.[40,69,104,107] Additionally, six studies reported thinner STSGs used in their co-grafts compared with the STSG alone (thickness of co-graft STSGs ranging from 0.004 to 0.010 inches; the STSG alone ranging from 0.010 to 0.016-in).[37,38,76,94,106,112] In three of these six studies focused on burns, no difference was found in functional improvement or healing times between the co-graft and the STSG site alone,[38,94,106] whereas improvement in functional outcomes was reported in the remaining three studies for the co-grafted sites.[37,76,112]

Group 3 Grafts/Constructs: Cellular TCs versus other Grafts/Constructs

Twenty studies described the use of one or more cellular TC: 11 used the epidermal layer only,[54,55,64,71,79,80,86,89,103,109,110] four employed the dermal layer,[83,93,96,100] four utilized both dermal and epidermal layers,[62,64,90,101] two utilized the Rigenera (Human Brain Wave LLC, Turin, Italy) micrograft protocol,[72,111] one utilized an alternate micrografting protocol,[93] and one utilized a cryopreserved placental membrane graft containing epithelial cells, fibroblasts, and mesenchymal stem cells.[96] Regarding type of cells employed, eight studies used autologous cells. However, the remaining 12 studies use allogeneic cells/grafts (Table 2). Two studies (Harding et al, 2005[93] and Ananian et al, 2018[86]) did not report any findings on the immunity reaction. Aubock et al[41] reported rejection of allogeneic cultured epidermis within 10–22 days after grafting. In another study, Sun et al[83] said graft rejection took place after 2 weeks when microskin autografts were overlaid with cadaver skin allografts to repair deep burn wounds. In comparison, the use of Apligraf survived for up to 6 weeks and mainly acted as a temporary biological dressing.

Meta-analysis was limited due to heterogeneity, but no significant difference was found in failure rates comparing epidermal only cellular TCs against STSGs in two studies focused on the treatment of recalcitrant vascular leg ulcers and deep dermal wounds [OR 8.74; 95% CI, 0.01–11053.59; $P = 0.55$] (Fig. 10).[64,109] This analysis had a computed power of 91.3%. Utilizing the definition of graft failure as no reduction or an increase in ulcer size during the study, there were three reported graft failures for the cellular TC with keratinocytes compared with six total failures in the STSG group for one study.[109] The other study reported no graft failures (based on their definition of graft adherence and vascularization) for the deep dermal wounds treated with the cellular TCs with

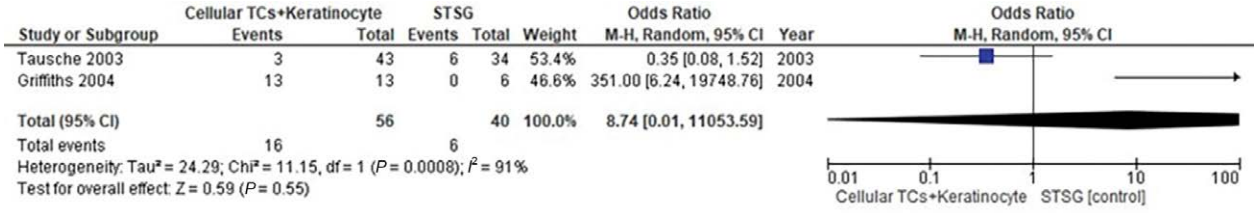

Fig. 10. Odds ratio meta-analysis revealed an odds ratio of graft failure for two studies utilizing cellular TCs with keratinocytes compared with STSGs alone [OR 8.74; 95% CI, 0.01–11053.59; $P = 0.55$]. There were high levels of heterogeneity ($I^2 = 99\%$) likely due to one of the two studies representing outlier results. The power of this result was low at 91.3%.

keratinocytes versus two graft failures for those treated with STSGs.[64] No clear attributions were made in these studies to explain graft failures. Additionally, three studies reported on the average healing time for dermal only cellular TCs, yielding a weighted average of 25.3 days,[90,96,100] and three studies reported an average healing time for epidermal cellular TCs, yielding a weighted average of 28.9 days.[64,89,110] Comparatively, meta-analyses of STSGs in prior studies demonstrated anywhere from 2 to 6 weeks of average healing time, varying based on the type of wound being treated.[10,117]

Among all studies reporting on cellular TCs, only three reported on measures of functional change or scar outcomes for wounds.[62,72,93] In a study reporting on the use of a dermal cellular TC, the authors noted that, at the 12-month follow-up period, 93.4% of the wounds had some form of wound contracture, with most being graded as mild and 16.4% rated as severe.[62] Furthermore, two studies utilized micrograft cellular TCs; one study reported a statistically significant improvement in mean VSS at 12 months for the cellular TC group (2.03; range: 0–4; $P < 0.05$),[72] and the other noted no functional impairment in the cellular TC group compared with the control ($P > 0.05$).[93] Furthermore, weighted averages of outcomes were calculated for the remaining cellular TCs, and the extracted data can be found in Supplemental Digital Content 4B. (**See table, Supplemental Digital Content 4B,** which shows mean reepithelialization, graft failure rates, and average healing time reported for individual studies incorporating cellular TCs. **http://links.lww.com/PRSGO/C641**.)

DISCUSSION

To our knowledge, this study represents the first comprehensive synthesis of clinical wound healing outcomes for autografts, autografts co-grafted with acellular TCs, and cellular TCs. The focus of this review was on reported outcomes related to the healing of wounds treated with these various grafts, namely graft failure rate, percent reepithelialization of the wound bed, average healing time, and the functional and aesthetic outcomes of the grafts related to scar assessment. It provides a foundation for further development and optimization of cellular and acellular tissue-engineered skin constructs for increased incorporation and adoption into clinical practice. However, this review also illustrates the paucity of homogenous large randomized controlled clinical trials comparing new skin construct outcomes against the gold standard graft: the autologous skin graft.

Although there was no statistically significant difference ($P = 0.09$) in the percentage of reepithelialization of wounds treated with co-grafts of acellular TCs with STSGs compared with STSGs alone, this result implies no difference in wound closure rates between the two groups. Furthermore, meta-analysis revealed a nonsignificant difference ($P = 0.07$) for STSGs over co-grafts based on graft failure rates. Our results illustrate that, although graft failure may be more prevalent in individually reported study data utilizing co-grafts, overall, there was no significant difference in failure rates identified. Furthermore, wound functionality as measured by the VSS also showed a nonsignificant difference ($P = 0.09$) in the co-grafts compared with STSGs alone.

Cellular TCs represent a promising avenue for tissue-engineered grafts to be explored in large-scale clinical studies. Given the variability among these reported wound healing outcomes and graft failure rates, it is imperative that further randomized controlled trials be conducted comparing tissue-engineered skin constructs with autologous skin grafts, along with their co-grafting, to determine the most favorable grafting configuration.

LIMITATIONS

There are several limitations to this review, some of which have already been discussed. Firstly, there was no standard nomenclature among constructs that lacked cells but acted as a dermal matrix/scaffold for skin regeneration. Therefore, all substitutes lacking cells were grouped and defined as acellular TCs, per prior definitions.[2,19,35] Additionally, the critical appraisal of these studies highlights various levels of risk of bias in the data reported, which limits the generalizability and application of results in clinical practice. Next, the lack of homogeneity in study design limited our ability to comprehensively analyze clinical outcomes for the various grafts. Additionally, not all studies represented in the meta-analyses included the same acellular TCs for comparison. Further work needs to be done to independently analyze if different acellular TCs each have their own significant difference in wound healing outcomes. Finally, although there was a lack of statistically significant improvements in wound healing for

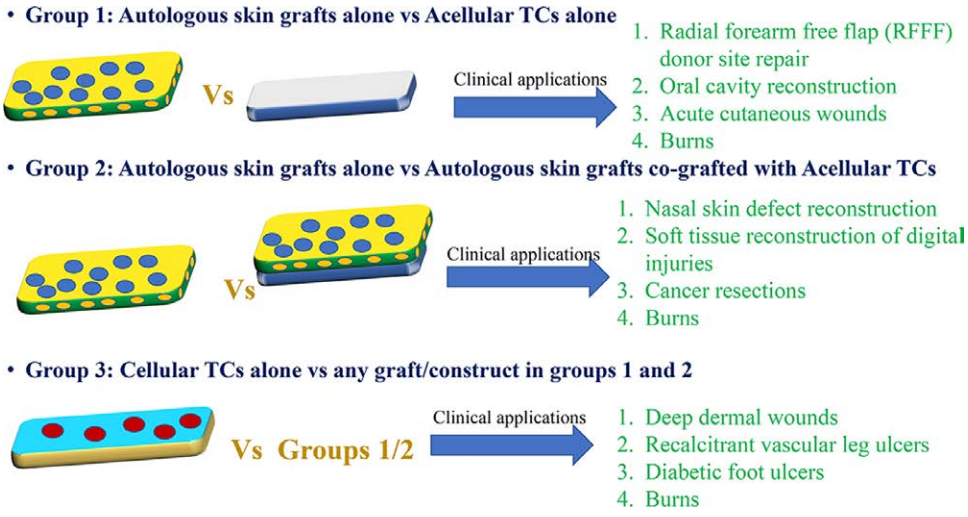

Fig. 11. Different skin graft/construct groups and their clinical applications.

cellular TCs (composed of keratinocytes) compared with STSGs, the number of studies included in these analyses was a small sample of all included studies, and more level 1 clinical evidence is needed to draw any conclusions as to the efficacy of these new skin constructs in healing time and reepithelization of a wound bed compared with STSGs.

CONCLUSIONS

This systematic review shows promising results in wound healing outcomes for newer cellular tissue-engineered skin constructs and presents an opportunity for expanding research to analyze their efficacy and safety compared with existing grafting methods: autologous skin grafts and acellular engineered skin constructs (Fig. 11). However, although initial data in *in vitro* and *in vivo* animal studies are promising, there are still restricted applications in the clinical setting, likely due to poor postgrafting survival times, limited shelf life, relatively long development times, and storage/handling difficulty.[118–123] Higher-power clinical evaluation is still required to support their approval and use of next-generation cellular tissue-engineered skin constructs for grafting procedures.

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