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Burns

# Effectiveness of Dermal Regeneration Templates in Managing Acute Full-thickness and Deep Dermal Burn Injuries: A Comparison with Split-thickness Skin Grafts

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**Background:** The therapeutic challenge of managing acute full-thickness burns is significantly ameliorated with the introduction of dermal regeneration templates (DRTs). However, an updated synthesis of evidence-based data on the efficacy and safety of different DRTs is required.

**Methods:** This systematic review and meta-analysis conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines aims to evaluate the role of various DRTs in comparison with split-thickness skin grafting in managing acute burn injuries after excision and debridement. A total of 28 randomized clinical trials were assessed, encompassing a wide array of DRTs.

**Results:** The study outcomes pointed to the diverse effectiveness of DRTs, with Integra demonstrating peripheral nerve reinnervation potential and TransCyte promoting rapid re-epithelialization. Some DRTs showed scar formation and skin quality comparable to those of autologous skin grafts. In terms of wound infection, certain treatments, including TransCyte, exhibited a significantly low infection rate. The evaluation of scar quality suggested that various interventions produced acceptable or improved outcomes without hypertrophic scarring. Recovery rates after the interventions displayed a range, with certain treatments showing rapid recovery and satisfactory results.

**Conclusions:** The current systematic review points to the potential benefits of DRTs in managing burn wounds. Further research is necessary to shed light on the long-term impacts of these interventions on wound healing, scar quality, and patient recovery.
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## INTRODUCTION

Burns represent one the most common causes of morbidity and mortality worldwide.[1] The treatment of acute full-thickness burns has for decades posed a therapeutic challenge. Although patients with acute burns typically do not have healing impairment, the donor skin available for autologous grafting may be insufficient occasionally, particularly if the total body surface area (TBSA) involved in the burn is large. Historically, the lack of sufficient dermis for transplantation has been a cause for great scarring and contracture before advancements in critical care.[2] Present-day critical care for burn wounds involves artificially engineered "skin substitutes," better known as dermal regeneration templates (DRTs), which can be used in these dire situations.[3] DRTs are defined as synthetic, acellular, bilayer devices, with the first layer comprising a highly porous collagen-glycosaminoglycan

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substructure capable of regenerative activity. This artificial layer resembles normal dermis and allows de novo synthesis of new connective tissue by providing the scaffolding on which dermal regeneration may occur, while it itself is biodegraded.[2] Some examples of DRTs include Integra, Dermagraft, TransCyte, Biobrane, and Apligraf. It is important to note that the name "skin substitutes" is misleading because these synthetic dermal templates do not resemble human skin in color, texture, sensation, or mechanical toughness, nor do they retain the same physiological properties.[2]

DRTs have several advantages. Due to their nature, they can undergo large-scale manufacturing to produce unlimited quantities, can be made available immediately, and provide a more economic alternative for burn patients. Additionally, the artificial skin can be transported, stored, and sterilized with ease. It can also reduce morbidity and mortality of burn wounds.[4] Therefore, grafting with DRTs provides a suitable alternative to split-thickness skin grafting (STSG).

Although there are several systematic reviews assessing the efficacy of dermal substitutes on deep dermal or full-thickness burn injuries,[5–7] these reviews are over 5 years old and do not cover recent advancements in the field. Additionally, most existing literature compares DRTs with techniques involving standard dressing, or addresses only one type of DRT, namely Integra. Therefore, in this systematic review, we aimed to assess published randomized clinical trials (RCTs) for the efficacy of various DRTs in comparison with STSG, in the management of acute burn injuries post excision and debridement, as well as review the current merits and demerits of available interventions and suggest direction for future research. Specifically, we aimed to assess how effective are DRTs in managing acute full-thickness and deep dermal burn injuries after excision and debridement, when compared with STSG, in terms of wound healing, scar quality, and patient recovery.

**Takeaways**

**Question:** Are dermal regeneration templates (DRTs) effective in managing burn wounds?

**Findings:** The study outcomes pointed to the diverse effectiveness of DRTs, with various ones possessing specific benefits over others.

**Meaning:** The current systematic review points to the potential benefits of DRTs in managing burn wounds.

## MATERIAL AND METHODS

This systematic review was performed according to PRISMA guidelines. An electronic search on multiple databases, including PubMed, Cochrane Library, and Google Scholar, was conducted. institutional review board approval is not required because this review only included publicly available data.

### Study Selection

Two reviewers individually searched from the database's published date until October 2022. The aim was to search for terms relevant to the efficacy of dermal substitute on burns, including burns [MESH] "AND" skin substitute "OR" dermal regeneration template "OR" dermal matrix "OR" 'dermal substitute "OR" artificial skin "OR" bioengineered skin "OR" Integra. The articles were screened, and duplicates were resolved using Rayyan Software. The articles were screened by title, then abstract, and the included articles were reviewed extensively by full text. For a detailed search strategy, please refer to the PRISMA flow chart in Figure 1.[8]

### Selection Criteria

The inclusion criteria of the studies selected for this systematic review were (1) RCTs; (2) only human studies involving burn wound treated with dermal substitute; (3) only studies that had comparative controls such as autograft, allograft, or standard burn dressings; (4) pediatric and adult population; and (5) deep dermal to full-thickness burn wounds requiring excision and grafting. As for the exclusion criteria, the excluded studies were (1) case reports; (2) systematic reviews; (3) meta-analysis; (4) studies without original data; (5) abstracts without accompanying publication; and (6) dermal substitute used on other wound etiology such as scar reconstruction, traumatic wounds, vascular/diabetic ulcers or malignancy reconstruction. Other studies were excluded if they presented with insufficient data that could be extracted and analyzed or if accessibility to the full text was limited.

In our study, we adopted a two-phase reference selection process, initially screening potential articles by title and abstract, followed by a thorough full-text review of shortlisted studies. This approach ensured a focused and relevant inclusion of literature. Any selection conflicts were resolved by the supervising author (B. N. S.). For data management, we used Rayyan and Microsoft Excel.

### Data Extraction and Risk of Bias Assessment

The articles that met the previously defined criteria from the systematic search were extracted by the team members and further checked by a senior author. The following data fields were extracted for the purpose of this systematic review: sample size, dropout rate, type of patient, mean TBSA percentage or range, intervention, follow-up time, main outcome, secondary outcome, graft take, wound infection, scar quality, donor site morbidity, recovery of the patient, and the need for regraft. The quality of the included studies was assessed using the JBI critical appraisal tool; the risk of bias can be seen in Supplemental Digital Content 1, showing that a majority of the studies having a low risk of bias, with some variation. (**See table, Supplemental Digital Content 1,** which displays the table comprising the enrolled studies and corresponding details. **http://links.lww.com/PRSGO/D49**.)

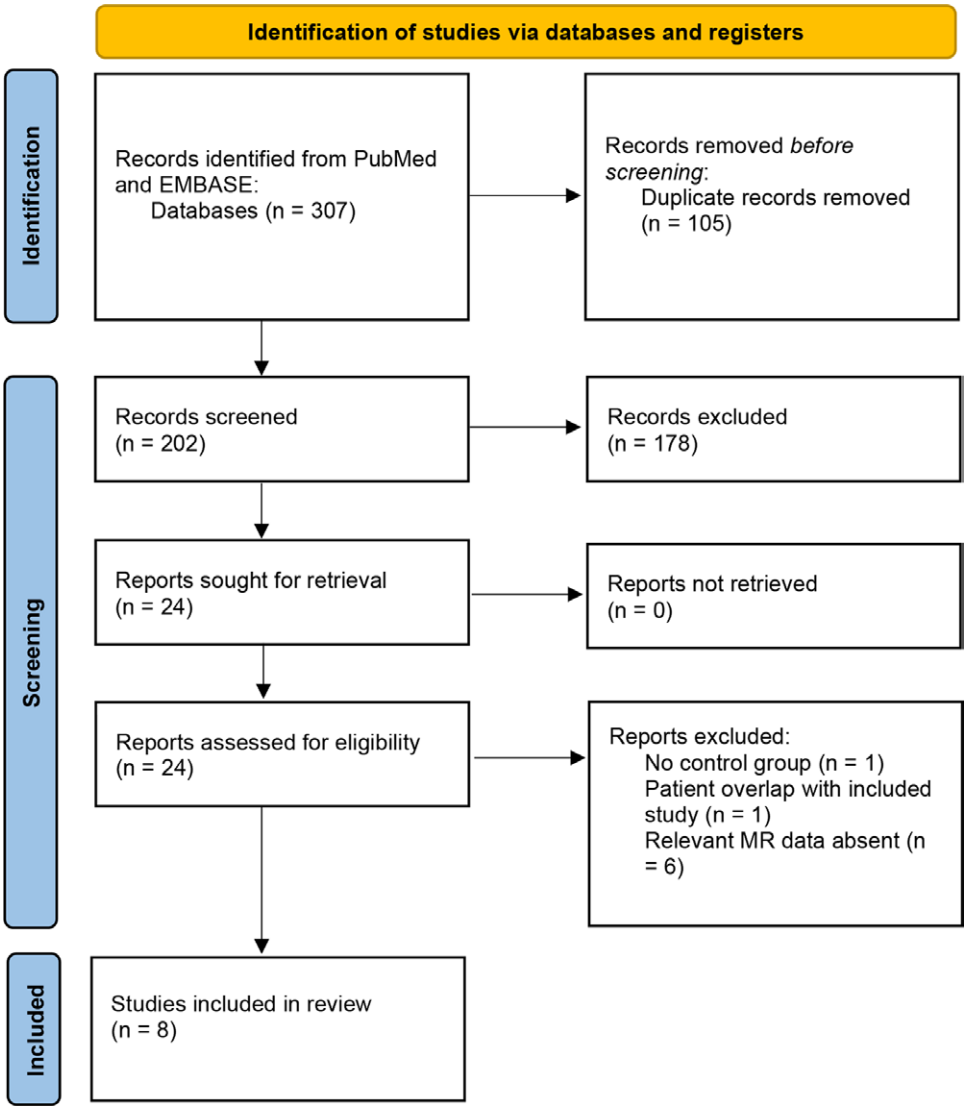


**Fig. 1.** PRISMA flowchart.

## RESULTS

### Study Characteristics

A comprehensive literature search yielded a total of 1180 abstracts, of which 1173 full-text articles were selected for detailed review. Ultimately, 28 studies met the inclusion criteria and were included in the final analysis. The study selection process is visually represented using a PRISMA flow chart, which can be observed in Figure 1.

The 28 studies comprised a collective sample size of 1073 patients and were all conducted as RCTs. Their primary focus was to assess the efficacy of various dermal substitutes in the treatment of different types of burns. During the full article review, the most common reason for exclusion was the studies were not relevant to our objective, indicating a rigorous selection process. Geographically, the included studies were distributed as follows: 13 studies were from the United States, with a sample size of 441; eight studies were from Europe, with a sample size of 334; two studies were from Australia, with a sample size of 36; three studies were from China, with a sample size of 180; one study was from Iran, with a sample size of 10; and one study was from Brazil, with a sample size of 62.

Across all 28 studies, the inclusion criteria predominantly required a specific percentage of TBSA affected by burns. The eligible TBSA percentage varied widely, ranging from 5% to 95%, with an average around 40%–50%. Additionally, some trials specified further criteria, such as second-degree burns or partial-thickness burns. The clinical trials used a diverse range of interventions to measure primary and secondary outcomes. These interventions may be found in Supplemental Digital Content 1 (**http://links.lww.com/PRSGO/D49**). Regarding the follow-up periods postintervention, they varied considerably, ranging from a few months to over a year, allowing for an assessment of both short-term and long-term treatment outcomes. The primary outcomes of all the trials may also be found in Supplemental Digital Content 1 (**http://links.lww.com/PRSGO/D49**),

with an expanded version found in Supplemental Digital Content 2. **(See table, Supplemental Digital Content 2,** which displays an expansion of supplemental table 1, showing further details and costs of the substitutes. **http://links.lww.com/PRSGO/D50**.)

**Effectiveness of Interventions**

The analyzed studies' primary outcomes encompassed a diverse array of dermal substitutes used for treating burns and skin injuries. Notably, Integra, (Integra LifeSciences Corporation, United States), demonstrated the potential for peripheral nerve reinnervation, and TransCyte (Smith & Nephew, United States) stood out for its ability to promote rapid re-epithelialization. Additionally, several dermal substitutes displayed comparable scar formation and skin quality when compared with autologous skin grafts. Glyaderm (Euro Skin Bank, Netherlands) exhibited promising take rates, especially when combined with STSG. Tilapia skin treatment proved advantageous with faster re-epithelialization, reduced pain, and minimized dressing changes. Autologous dermal substitutes with STSG (AD-STSG) treatment presented accelerated healing and improved survival rates for severely burned patients. Furthermore, certain substitutes exhibited enhanced wound healing rates, better hand function recovery, and improved quality of life at 6 months postoperation. Notably, acellular dermal matrix showcased an anticontraction effect and superior aesthetic outcomes compared with STSG. However, Integra's long-term scar maturation and persistence of fibers required consideration.

**Wound Infection**

The analysis of wound infection and its associated interventions revealed noteworthy findings across various treatments. Notably, TransCyte exhibited a remarkably low infection rate, with only one of the 20 treated wounds requiring infection treatment. In contrast, certain interventions, such as the application of a Polyacetide-based temporary skin substitute versus STSG, demonstrated no statistically significant difference in infection rates between the two groups. Similarly, the combination of Glyaderm with STSG versus STSG alone showed no infections in either group. Notably, the use of Suprathel (PolyMedics Innovations GmbH, Germany) with paraffin gauze demonstrated a decreased likelihood of infection when there was a potential for dermal regeneration. In contrast, there were instances of infection in cases where only Suprathel was used without the possibility of dermal regeneration. Moreover, specific treatments, including Matriderm (MedSkin Solutions Dr. Suwelack AG, Germany) with STSG versus STSG alone, amniotic membrane seeded with fetal fibroblasts versus amniotic membrane versus Vaseline gauze, and autologous cell harvesting (ACH) interventions, showed no infections in any patients. Overall, the data suggest that certain interventions may contribute to a reduced risk of wound infection, warranting further investigation into their potential benefits in managing infections in wound healing scenarios. However, it is noteworthy to mention that many of the trials did not report wound infections at all.

**Scar Quality**

The evaluation of scar quality after different interventions yielded valuable insights. For some treatments, such as Integra + cultured epithelial autograft + STSG, there were no significant differences in scar quality compared with conventional methods. However, TransCyte demonstrated superior outcomes in adults, promoting faster healing and reduced scarring in partial-thickness burns when compared with conventional wound care. Glyaderm treatment resulted in good scar quality, as observed through lower Vancouver Scar Scale and Patient and Observer Scar Assessment Scale scores. Similarly, interventions like AD-STSG showed lower Vancouver Scar Scale scores in donor or recipient areas compared with intermediate-thickness skin graft groups at multiple time points. Notably, certain interventions showed acceptable or improved scar quality without hypertrophic scarring, suggesting favorable outcomes for patients. Others, like Matriderm + STSG, demonstrated good scar quality, and ACH-treated wounds exhibited higher scar satisfaction rates compared with conventional treatments. StrataGraft (Stratatech, a Mallinckrodt company, United States) tissue donor sites exhibited better cosmesis and lower pain scores compared with autograft donor sites. Overall, the studies reported positive effects on scar quality for specific interventions, indicating their potential benefits in enhancing aesthetic outcomes and patient satisfaction. Further investigations may elucidate the long-term effects of these treatments on scar formation and quality because the follow-up periods were not too long, relatively.

**Recovery**

The recovery of patients after various interventions displayed notable variations. Unfortunately, limited assessment of the effects on reinnervation and sensory function recovery after burn injury was available for artificial dermal scaffolds like Integra. TransCyte demonstrated the fastest time to re-epithelialization (7.5 days), followed by Biobrane (9.5 days), and Silvazine (11.2 days). In contrast, interventions like Polyacetide-based temporary skin substitute versus STSG were not specifically mentioned regarding patient recovery. Nile tilapia (*Oreochromis niloticus*) skin treatment resulted in a significant reduction in re-epithelialization time compared with silver sulfadiazine treatment. AD-STSG group patients experienced significantly shortened healing time and better functional activity recovery rates compared with intermediate-thickness skin graft alone. Suprathel demonstrated optimal recovery outcomes, with eventless recoveries noted for all treatments. Similarly, StrataGraft treatments exhibited comparable re-epithelialization rates to autograft sites by day 28. Conversely, the recovery period was not mentioned for interventions like ACH and artificial dermis composed of a porous collagen-chondroitin 6-sulfate fibrillar mat covered with a thin sheet of silastic. Data were collected postoperatively at 1 month, 6 months, and 12 months. This was considered adequate, as it was the most commonly reported follow-up time for patients receiving DRTs in these studies. Overall, certain treatments

demonstrated rapid recovery, improved healing rates, and satisfactory results, whereas others showed no significant differences or provided limited data on patient recovery. Further research is essential to better understand the recovery outcomes associated with different interventions for burn patients.

## DISCUSSION

The main objective of this systematic review was to assess the effectiveness of various DRTs in managing acute burn injuries post excision and debridement, compared with STSG. We investigated several pertinent facets of DRT usage, including wound healing, wound infection, scar quality, and patient recovery. The findings from this review not only provide insights into the efficacy of DRTs but also illuminate areas for future research.

DRTs have revolutionized the management of acute full-thickness burns and deep dermal injuries, where autologous skin grafts may be insufficient. The analysis revealed a diverse range of DRTs used in burn management, each with its unique advantages and challenges. The most frequently evaluated DRT, Integra, not only showed potential for peripheral nerve reinnervation but also indicated a potential for a longer initial healing time, aligning with previous studies highlighting its efficacy in reducing scar formation and wound contracture.[9,10] TransCyte displayed impressive rates of re-epithelialization and was found suitable for acute partial-thickness burns. Moreover, its low infection rate substantiates its antimicrobial properties and aligns with prior research.[11,12] Glyaderm, when combined with STSG, exhibited promising take rates and enhanced scar quality, echoing previous findings.[13]

The use of unconventional materials like tilapia skin introduced an innovative approach to burn treatment. Studies reported reduced pain, faster re-epithelialization, and minimized dressing changes with tilapia skin. This aligns with recent studies indicating that tilapia skin, because of its high collagen content and tensile strength, stands out as a potential biological dressing for burn wounds.[14–16]

Of significant note were the studies focusing on AD-STSG. They reported enhanced healing and survival rates for severely burned patients. The presence of the autologous component in AD-STSG reduces the risk of immune rejection, thus accelerating healing and bolstering survival rates. These findings reaffirm the versatility and potential of DRTs in burn management and emphasize the necessity of continuous research and development.

When it comes to scar quality post-treatment, it is clear that certain interventions, like TransCyte and Glyaderm, yield superior results. ACH-treated wounds also showcased higher satisfaction rates, suggesting their prospective benefits in improving aesthetic outcomes and patient contentment. This aligns with earlier indications that some DRTs can emulate the skin's extracellular matrix, promoting tissue regeneration with minimal scar formation.[17]

In terms of recovery, interventions such as TransCyte and AD-STSG fast-tracked healing and the restoration of functional activity. This highlights the potential of DRTs to not only heal the wound but also reinstate functionality. Future research delving into the recovery phase, encompassing sensory function and quality of life metrics, can offer a more comprehensive view of patient outcomes following the intervention.

However, this review has some limitations. Our review's inherent heterogeneity is accentuated by the inclusion of both pediatric and adult burn patients. It is well recognized that, barring complicating factors like malnutrition or comorbidities, pediatric patients often exhibit greater healing potential than their adult counterparts when faced with similar acute burn injuries. This variation in patient demographics can introduce substantial variability in the outcomes and responses to DRTs. In addition, diverse country-specific regulations on stem cell usage may restrict the uniform availability and applicability of certain DRTs across different regions.

Furthermore, our study's methodology raises potential concerns. The decision to include Integra explicitly in our search terms while not mentioning other specific DRTs might induce selection bias. By potentially favoring studies focusing on Integra, we risk overlooking or underrepresenting research on less commonly cited DRTs. This selective search approach is an acknowledged limitation that could shape our findings and interpretations.

Coupled with the aforementioned factors, the previously noted inconsistencies in study designs, outcome measures, and reporting styles further challenge the generalizability of our conclusions. We also acknowledge the potential biases, such as publication bias, and the varied quality of the studies included, which might impact our interpretations. The emphasis on certain DRTs might overshadow the potential of less-studied alternatives, suggesting an avenue for future research.

Looking ahead, we anticipate further advancements in the design of DRTs to address current challenges. Greater emphasis should be placed on sensory recovery, an aspect often overlooked yet crucial for the quality of life post-treatment. Also, future research should focus on developing DRTs that more closely mimic the native dermis, both in structure and function.

Moreover, as our understanding of wound healing and tissue regeneration evolves, the development of DRTs could benefit from integrating bioactive components, such as growth factors or antimicrobial agents, to enhance wound healing, control infection, and reduce scarring. Further well-designed RCTs with larger sample sizes and longer follow-up periods are needed to validate the effectiveness of these novel DRTs.

## CONCLUSIONS

In conclusion, this systematic review corroborates the efficacy of DRTs in managing acute burn injuries. It underscores their potential benefits in wound healing, scar quality improvement, patient recovery, and infection control. The emerging DRTs, from conventional synthetic substitutes to bioengineered tissues and unconventional materials like fish skin, illuminate the exciting landscape of burn wound management. As we stand on

the brink of these advancements, the future of burn care seems promising.

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## DISCLOSURE

*The authors have no financial interest to declare in relation to the content of this article.*

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