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Dermal regenerative matrix use in burn patients: a systematic review

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STRUCTURED ABSTRACT

BACKGROUND: Dermal regenerative matrices (DRMs) have been used for several decades in the treatment of acute and reconstructive burn injury. The objective of this study was to perform a systematic review of the literature to assess the clinical outcomes and safety profile of DRMs in full-thickness burn injury.

METHODS: Comprehensive searches of MEDLINE, EMBASE, CINAHL, and Cochrane Library were performed from 1988–2017. Two independent reviewers completed preliminary and full-text screening of all articles. English-language articles reporting on DRM use in patients with full-thickness burn injury were included.

RESULTS: Literature search generated 914 unique articles. Following screening, 203 articles were assessed for eligibility and 72 met inclusion criteria for analysis. DRM was applied to 1084 patients (74% acute burns, 26% burn reconstruction). Of the twelve studies that described changes in ROM, significant improvement was observed in 95% of reconstructive patients. The most

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CONFLICT OF INTEREST STATEMENT

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frequently treated reconstructive sites were the neck, hand/wrist, lower extremity, and axilla. Vancouver scar scale was used in eight studies and indicated a significant improvement of the scar quality with DRM. The overall complication rate was 13%, most commonly infection, graft loss, hematoma formation, and contracture.

CONCLUSIONS: While variability in functional and cosmetic outcomes was observed, DRM demonstrates improvements in ROM and scar appearance without objective regression. Essential demographic data was lacking in many studies, highlighting the need for future standardization of reporting outcomes in burns following application of dermal substitutes.

Keywords

Burn; burn injury; thermal injury; artificial skin; skin substitute

INTRODUCTION

Burn injuries represent one of the top causes of injury-related death, and its incidence varies worldwide.¹ Significant advancements in burn care made over the past decades have led to improved patient survival and recovery, shifting the primary goal of management of severe burns from mere survival towards improving the “quality” of patient survival.^{2,3} Quality of life largely depends on how patients re-integrate into society, the scar quality and its appearance, and the perception of their own appearance. Autologous split thickness skin graft (STSG) is the current gold standard for the treatment of deep dermal and full thickness burn wounds^{2,4}, however, there are numerous challenges associated with STSGs, including limited donor site availability, donor site morbidity, graft contracture, and an unpredictable or sometimes poor scarring process.^{5,6} In addition to human allograft, epidermal and/or dermal biologic, and synthetic skin substitutes have emerged in the last few decades.⁵ Dermal regenerative matrices (DRMs) are permanent skin substitutes used in the management of skin defect left after excision of burn wounds or release burn wound contractures.

Developed in 1981 by Burke et al.⁷, DRM (Integra, LifeSciences, Plainsboro, NJ, United States) is a bilayer dermal regeneration template composed of distinct dermal- and epidermal-like components. The dermal analog consists of cross-linked bovine collagen and shark chondroitin-6-sulphate, while the epidermal analog is composed of a thin silicone elastomer. After 2–3 weeks, a neodermis is formed, the temporary silicone layer is removed and replaced with a thin epidermal autograft.^{7,8} DRM is approved for use in acute burn surgery and burn reconstruction⁹ and has been shown to produce excellent functional and aesthetic results for both indications.^{6,10–14}

In addition to its many benefits, DRM has also been cited to have several disadvantages, including the need for a two-stage procedure^{15–17}, increased infection risk^{15,17}, and high cost.^{14,17} Although the literature is abundant with studies related to DRM use, the majority lack power of the sample and are mainly case series. The aim of this study was to perform a systematic literature review of DRM use and its outcomes related to functional improvement and scar appearance, when used in acute burn surgery and burn reconstruction for patients with full-thickness burn injury. A review of the safety and efficacy will also be performed.

METHODS

Literature search and study selection

A systematic search of the literature was completed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (CRD42018080191). Comprehensive searches of MEDLINE, EMBASE, CINAHL, and The Cochrane Library was performed for the period 1988–2017 inclusive. Medical Subject Headings (MeSH) were used where appropriate. The search strategies for all databases are included in Appendix 1. English-language, primary full-text articles describing human subjects with full-thickness burn injury treated with DRM were included for analysis. Following the literature search, duplicate citations were removed and preliminary screening (titles and abstracts) was performed to eliminate studies that did not meet the aforementioned eligibility criteria. Full-text articles were then obtained for all remaining studies, all of which were read in their entirety to identify relevant studies. Only articles that met all inclusion criteria were included for analysis. For the purpose of this systematic review, studies with insufficient information to extract data, review articles or animal studies, and for non-burn related indications were excluded. Two independent reviewers completed preliminary and full-text screening of all articles.

Data extraction and analysis

Extracted data included study characteristics (design, year of publication, authors affiliation), patient factors (demographics, extent of DRM reconstruction (%total body surface area (TBSA)), body regions affected, mechanism of burn injury), surgical factors (acute vs. reconstructive indications, application technique), and clinical outcomes (scar appearance and cosmesis, biomechanics, functional range of motion, complications, mortality). We defined the acute indications when DRM was used to resurface excised burn wounds during the initial admission after the thermal injury. Reconstructive burn surgery addresses functional and/or aesthetic problems (e.g. burn contractures, hypertrophic or keloid scars) that arise after all the burn wounds were treated and healed.⁸

RESULTS

Study selection and characteristics

The systematic literature search generated 2,205 articles, and an additional six were identified through article reference lists (Figure 1). After removal of duplicates, 914 unique articles remained for review. Following preliminary screening, 203 full-text articles were reviewed and 72 met inclusion criteria for data extraction and analysis.^{2–6,8,10–75} Included studies consisted of four randomized controlled trials (Level 1), four comparative studies (Level 2), five cohort studies (Level 3), two case-control studies (Level 3), 24 case series (Level 4), and 33 case reports (Level 5). Most of the studies were from Europe and North America (Table 1).

Patient demographics

DRM was applied to 1084 patients with full-thickness burn injuries, mainly for resurfacing after debridement of acute burns (800 patients, 74%) and 284 for burn reconstruction

(26%). From cumulative data, there was a wide age range (7 months to 93 years), with 333 adult patients (≥ 18 years) and 179 pediatric patients (<18 years). Age was unreported for the majority of patients (53%). Patient gender was available in only 56% of the cases (383 males and 221 females). The mean follow-up period for patients treated for acute burn injury and burn reconstruction was 21.8 and 21.1 months, respectively.

Sites of DRM Use

DRM was applied to a total of 1171 sites, covering a wide variety of body regions (Figure 2). The data lacks accuracy in reporting what body regions were resurfaced, with only 48% of sites specified (215 sites for acute, 346 for burn reconstruction). The most commonly treated body parts for acute burn injury were: face/head (24%), hand/wrist (21%), and lower extremities (21%). For burn reconstruction, the most commonly treated areas were: neck (18%), hand/wrist (15%), lower extremities (14%), and axilla (14%).

It is important to assess how much of the DRM reaches readiness for the skin grafting. The average DRM take for acute and reconstructive burn injuries was 86% (range 0–100%) and 95% (range 0–100%), respectively. STSG was applied over the DRM an average after 24.2 days (range 0–80 days) with an 90% take for acute burns, and 20.2 days (range 7–110 days) with 93% take for burn reconstruction. Cultured epidermal and keratinocyte autografts (CEA) were applied over DRM after 21 days, on average, (range 16–24 days). CEA was used alone for five patients^{31,68,71}, and was combined with a STSG for one patient⁴⁵.

Function and range of movement related outcomes

There was a wide range of reported outcomes related to function and range of motion (ROM). The improvements following DRM application were assessed with objective (four studies) or subjective methods (eight studies).

Objective outcomes related to function and ROM was reported in four studies for 42 patients, all of whom were treated with DRM for burn reconstruction.^{8,11,18,19} Post-operative improvements were seen in 40 of the 42 patients (95%) (Table 2).

Subjective outcomes were reported in 111 patients from eight studies.^{4,20–26} Ten patients were treated for acute burn injury and 101 for burn reconstruction. No improvement or temporary improvement in ROM was reported in 16% of DRM-treated sites.²³ Most patients had partial or significant improvements post-operatively, but minor limitations were still present in some (Table 3).

Scar related outcomes

Three studies investigated the reconstructed tissue quality.^{28,31,72} The average gross elasticity, elastic function, biological elasticity, and viscoelasticity among 21 DRM-treated sites were 0.40, 0.61, 0.82, and 0.69, respectively. No statistical differences in gross elasticity, elastic function, or biological elasticity was found between DRM-treated sites and healthy, unburned skin.^{28,72} One study reported reduced elastic stretch and greater viscous stretch with meshed autograft on DRM, with no difference in total stretch. These differences were not significant when cultured skin substitutes were applied over DRM.³¹

Vancouver scar scale (VSS) is a standardized instrument used to evaluate subjective parameters (burn scars) in an objective way, where a high score correlates with a worse scar (minimum score: 0 – maximum score: 13). The resultant scores are observer-dependent; thus, VSS is most valuable in identifying changes within an individual versus between individuals. Slight alterations in the scoring system exist; for example, additional options in the height and pigmentation categories, generating maximum possible scores of 14 and 15. These scar scales, among several other variations, are termed modified VSS.⁷⁶ Nine studies used scar scales to evaluate scar appearance in a total of 125 patients who had DRM applied for acute (69 patients) or reconstructive indications (56 patients).^{2,6,8,10,18,27–30} The VSS was used in eight studies (original VSS in one, modified VSS in five, unknown for two), and the remaining study used the Hamilton-burn scar score. Post-operative improvements in VSS score was seen in all reconstructive patients,^{8,18,29,30} and ten acute patients (at 12 months vs. 3 months post-operatively).² For the remaining acute burn injury patients, two studies provided only one mean post-operative VSS score (2.08²⁸ and 3.10³⁰) without earlier or later values for comparison. Only one study revealed a non-significant increase of the VSS score for the scars after DRM application, when compared with control sites (6 vs. 4).²⁷ The mean post-operative VSS score was higher in the reconstruction versus acute burn injury group (4.7 vs. 2.3). The mean post-operative VSS score in control patients treated for acute burn injury was 2.9. No control subjects were available for comparison of postoperative VSS scores following burn reconstruction. (Table 4).

Assessment of scar appearance and cosmesis was measured subjectively in thirty-six studies.^{2,4,8,10–13,15,20,21,23–25,29–51} All studies reported good or improved aesthetic outcomes in most patients. Suboptimal cosmetic outcomes were found for a subset of patients, including poor aesthetic result (n=4),^{10,15,37,40} pruritis, dryness, and hyper- or hypo-pigmentation (n=3).^{8,29,42} Less desirable cosmetic results were observed in 4.7% of patients (22 patients)^{2,43} when compared to controls, however these differences were not significant in ten patients. The incidence of “poor aesthetic outcome” was 2.2% (10 patients).^{10,15,37,40} Self-reported patient assessments were largely positive for both acute^{10,12,21,30,33} and reconstructive^{8,23–25,29,30,42,48} burn injuries. In one study of 106 acute burn surgery patients, 26% preferred the appearance of the DRM-treated sites, 64% found no difference, and only 10% preferred the control site (meshed autograft).¹² A Visual Analogue Scale (VAS), where patients were asked to rate their overall satisfaction on a scale of 1–10, was used in two reconstructive studies^{8,29}, with an average VAS score of 8 (range 6–9) reported in one study²⁹. For the other study, the VAS revealed a 59% improvement in appearance compared to pre-operative states.⁸ The colour match of DRM-treated sites was found to be comparable to normal skin for acute burn injury^{2,28,38,43,50}, except for one study which revealed pronounced hypopigmentation and small regions of hyperpigmentation in one patient³¹. For burn reconstruction, two patients developed a sustained colour mismatch.^{40,42} Palao et al.²⁹ reported hyperpigmentation amongst all patients; however this improved in all patients at long-term follow-up (12–18 months). All other studies revealed comparable pigmentation between DRM-treated sites and healthy skin.^{8,24,40,42} Additionally, the majority of DRM-treated sites (>280) showed good or excellent texture match to autograft-treated sites, with the final skin being soft, supple, and pliable.^{4,8,11–13,20,23,24,29,31,33,39–42,46,50} A subset of 22 acute burn patients developed thicker skin on DRM-treated hands compared to healthy, non-

burned hands (1.6 mm vs 1.18 mm), however this was not a statistically significant difference.²⁸ Loss et al.⁴⁵ reported subjectively thicker skin for one patient treated for acute burn injury (compared to non-burned skin). Two other studies reported inferior post-operative tissue quality at DRM- versus autograft-treated sites^{2,43}, with one article reporting no statistical difference².

Complications

Complications associated with DRM were reported in 56% of studies (n=40) for 144 patients out of the total 1084 patients (13%). The most frequent complication was infection (n=27), reported in fifty patients (4.6%) – 32 for acute burn injury, 17 for burn reconstruction, one unknown. Five of the twenty-seven studies did not report an exact number of patients that developed an infection; however, infection rates were reported in three of these studies, at 10%,²⁸ 17%,⁵² and 20%²³. The remaining two studies had either an unknown number,⁵³ or a maximum of two patients develop infection⁵⁴. On average, infection was reported to occur on post-burn day 22.4 (range 7–42). The organisms responsible were most commonly *Staphylococcus aureus* (including MRSA, ORSA) and *Pseudomonas aeruginosa*, and less frequently *Staphylococcus epidermidis*, *Enterococcus*, *Aspergillus*, *Candida*, *Acinetobacter*, *Bacillus coliforms*, *Enterobacter*, *Klebsiella pneumoniae*, and *Serratia marcescens*. Partial or total DRM, CEA, and STSG loss occurred in 22, one, and 11 cases, respectively. Other complications observed included: hematoma formation (n=11), contracture or re-contracture (n=10), seroma formation (n=5), and hypertrophic scar (n=5). Ninety-two patients developed a complication other than infection (8.5%), but the information was scarce and insufficient for reporting.

Ten studies reported mortality data,^{3,5,6,12,52,54–58} however only nine provided the specific number of deaths for DRM-treated patients. Death occurred for 89 patients treated for acute burn injury and one patient treated for burn reconstruction. The overall mean mortality rate seen amongst the nine studies was 30% (range 3.4%–100%). The cause of death was revealed for a subset of patients (15 patients) and included etiologies related to the severity of burn injury, such as multiresistant infection and sepsis^{5,6,56,58} (13 patients), inhalational injury⁵ (one patient), and multiple organ failure⁵⁵ (one patient). Toxic shock syndrome was the cause of death for one patient.⁵⁸

Safety of DRM Use

Forty-nine studies commented on safety of DRM. The majority of authors agreed that DRM is safe to use on full-thickness burn injuries where insufficient donor skin is available, both in the acute and reconstructive settings.

4,6,8,10,12,14,15,17,18,21,24,29–32,34–38,42–44,47,48,51,52,59,60 Authors also frequently commented that in acute burn surgery, DRM with autograft is capable of achieving functionally and aesthetically similar results to that of autograft alone^{12,31} or unburned skin^{2,4}. Three studies preferred DRM versus traditional options due to improved functional and cosmetic outcomes.^{10,13,14} These statements were applicable to a variety of body sites^{10,21–23,28–30,32,36,43,44,48,51,61} and age groups^{3,6,14,23,37,42,47,62}.

For acute burn injury, two of the articles presented instances where application of DRM may be not be indicated, such as patients with multiple comorbidities where anesthesia places them at higher risk for a two-stage procedure,¹⁶ and eyelid burns⁴³. When DRM is used for burn reconstruction, compliance with the treatment and adherence to frequent follow-ups is mandatory in order to achieve good results^{11,15}. Additionally, several studies indicated that surgeon experience plays a role in the successful application of DRM.^{5,6,23,33}

DRM Application – Tips & Tricks

Thirty-five percent of articles (n=25) made recommendations surrounding DRM application for improved effectiveness. There was variability in surgeon preference with respect to the use of meshed^{13,25,26,40,42,43} vs. un-meshed DRM³⁷. Several studies reinforced the importance of adequate immobilization of DRM on the recipient wound bed to ensure successful take.^{15,30,35,40,47,51–53,62} Methods recommended include: tie-over dressings (especially when applied over joints)¹⁵, extensive hemostasis³⁰, VAC dressings,^{25,26,35,47,52,53,62} an outer Biobrane dressing,⁵¹ and running sutures, single stitches, metal clips, K-wires, or conformed splints⁴⁷. The importance of continuous wound care was also emphasized.^{8,24,26,42,43} With respect to infection control, some authors recommended antiseptic compresses⁵⁶ and/or antimicrobial therapy^{55,56}. Variability in the time to second stage procedure was observed. Two studies suggested a 2 week interval between DRM and epidermal grafting procedures, in order to reduce the risk of future hypertrophic scarring.^{30,40} In contrast, two other studies recommended delaying the second stage procedure until four weeks after initial DRM placement to ensure adequate vascularization.^{8,29} The thickness of the STSG varied between 0.05mm and 0.25mm, with a mean of 0.16mm.

DISCUSSION

DRM is one of several artificial skin substitutes available for wound coverage with indications in acute burn surgery and post-burn reconstruction. The body of literature currently available on DRM use in burn injury is variable with respect to study design, sample size, and reported outcomes. Age and sex was not reported for almost half of the total number of patients included for analysis. The outcomes across studies are not standardised, and subjective measurements are more frequently described than objective ones, making it challenging to quantify post-operative improvement.

Amongst the 72 studies included for analysis, DRM was applied successfully and safely to a variety of body sites in both acute and reconstructive settings. The literature review supports the clinical use of DRM as a valid alternative in the burn reconstruction patient population, both for its functional benefits, as well as its apparent reduction of recontracture rates compared to available alternatives.

Of the twelve studies that commented on post-operative changes in ROM, only a minority of patients (<16%) were found to have suboptimal functional outcomes and none experienced loss of function. An important consideration that may limit postoperative improvement in ROM is the severity of the initial injury. Given that DRM is recommended in instances where autograft is scarce, often with full-thickness burns covering >40% TBSA,⁶ the preoperative functional status of this patient population is likely to be quite limited. Thus,

careful evaluation of a patient's preoperative morbidity is paramount when drawing post-operative conclusions.

With successful application and take, DRM can produce excellent cosmetic results.^{12,21,30} The forty-five studies that commented on aesthetic outcomes indicate positive and encouraging results in acute and reconstruction burn patients. With respect to colour match, an important consideration is that the final result is more dependent on the epidermal skin graft than the DRM, therefore the area of the donor site was important. Other factors, such as time between first- and second-stage procedures may also play a role in affecting post-operative colouration. It has been proposed that shortening the time to autografting from 14 days to 7–10 days in regions of high vascularity (e.g. the face) may reduce complications of hyperpigmentation, due to faster neodermis formation.⁴³

Invasive infection is the primary cause of death in the acute period following a burn injury, accounting for about 51% of mortality.⁷⁷ It is unknown whether the risk of infection with DRM is related mainly to its intrinsic properties, or as a consequence of the patient population that it is applied to (severe, full-thickness burns). While both factors likely contribute, the severity of initial injury no doubt has an impact on a patient's risk of developing an infection. In fact, one study included in our analysis was terminated early due to the high incidence of infection associated with DRM in patients with burns covering more than 45% TBSA.⁵ Based on these results, Pham et al.⁷⁸ subsequently suggested that DRM may be better suited for patients with less extensive burn injuries. In contrast, numerous other studies included for analysis had a mean %TBSA >45% without reporting infection as a complication. Thus, future work towards identifying specific patients at risk of developing infection with DRM is needed to help guide surgeon clinical decision making.

The overall mortality observed amongst included studies was 8.3%, with a wide range of reported mortality rates amongst individual studies. Factors cited to have played a potential role in the death of patients were: higher (than usual) multiresistant infection rates⁶, relative surgeon inexperience in handling DRM^{5,6}, burn immunosuppression⁵, and surgical site infections due to seeding from distant sites⁵. Although unlikely, there exists the potential for patients to develop toxic shock syndrome following DRM application – a complication that carries a high mortality risk amongst burn patients.⁵⁸ Thus, burn care specialists must exercise caution when using DRMs, especially in non-life threatening situations. Strict adherence to infection control measures and prophylactic nasal Mupirocin or Chlorhexidine to reduce staphylococcal nasal carriage has been suggested to further reduce the likelihood of this outcome.⁵⁸ In addition, increasing surgeon experience with DRM is paramount in improving take and reducing infection rates, ultimately leading to reduced mortality amongst burn patients. In a retrospective review of 1665 acute burn injury patients, Ryan et al.⁷⁹ identified three risk factors associated with mortality: 1) age >60 years, 2) burn injury >40% TBSA, and 3) inhalational injury. In a separate study by Ryan et al.,⁵⁷ equivalent mortality rates were noted amongst the control and DRM groups (30%), despite the DRM-treated patients having more baseline risk factors for death (significantly higher incidence of inhalational injury and %TBSA burned).

Despite some inconsistency in preferred application techniques, several common themes were identified. Authors unanimously preferred the use of thin autograft during the second stage procedure for improved cosmesis, and emphasized the importance of adequate immobilization of DRM to the wound bed to improve take. Various methods for immobilization were reported, with a heavy emphasis on the use of VAC techniques. Of course, surgeon experience with DRM has a significant impact on patient outcome. To facilitate this, Malic et al.⁹ have generated a nationwide protocol on wound healing and DRMs using expertise from several Canadian burn care specialists. Their expert panel has recommended certain minimum training requirements for surgeons without previous experience handling DRMs. A detailed protocol was also developed for reference, via nationwide specialist agreement. By applying the techniques recommended by those experienced with handling DRM in burn injury, one can expect substantial reductions in complication rates in the future.

Limitations and future directions

There are several limitations to this review. First, the quality of studies included for qualitative analysis was variable, with the majority being case series and case reports (79%). Consequently, this impacts the power of our conclusions. Second, there was inconsistency in reporting of demographic and outcome data amongst included studies, which complicated interpretation of the data and limited our ability to perform a meta-analysis. Amongst the four randomized controlled trials (RCTs), only two reported on objective measures of aesthetic outcome^{2,6} and only one commented subjectively¹². None commented on functional outcome. Clearly, there is a need for future RCTs that document post-operative functional and cosmetic outcomes to better understand the role of DRM in full-thickness burn injuries. Third, the geographic distribution of articles included in this study was heavily skewed towards developed regions in North America and Europe (80.5%). This is likely attributable to its high cost and our analysis being restricted to include only English-language articles. Thus, this article is limited by pre-exclusion of data from other countries whose outcomes associated with DRM are reported in other languages. Lastly, none of the included articles conducted a cost-benefit analysis of DRM. This analysis is important to investigate moving forward, given that a major limitation of DRM use is its significant cost – both the material itself, and the lengthy hospital stay that is often required following application. Such analyses would provide burn specialists with the concrete data necessary to make more informed treatment decisions when allocating their healthcare system's resources.

CONCLUSION

Since its introduction in 1981,⁷ DRM has been successfully used for a variety of applications, mainly burn injury. The objective of this work was to perform a systematic review of the literature to assess the clinical efficacy and safety of DRM use in patients with full-thickness burn injury. This review demonstrated improved functional and aesthetic outcomes amongst the majority of patients treated for acute burn injury as well as post-burn reconstruction. Both minor and major complications were observed across included studies with low incidence. Infection was the most commonly cited complication. We believe that

the benefits of DRM from a survival, functional, and cosmetic point of view outweigh the risks of the aforementioned potential complications. In concordance with previous reports, DRM can be safely applied both in the acute and reconstructive phases of burn injury, at a variety of anatomic regions. A focus should be placed on improving certain, modifiable factors – namely surgical expertise in handling DRM, and post-operative patient compliance – in order to see further advancements in outcomes. Future, high level evidence studies with objective functional and cosmetic outcomes of DRM in burn injury are required, in order to improve our understanding of expected patient outcomes and provide patients with tangible, realistic goals for recovery.

APPENDICES

APPENDIX 1.

Systematic search strategies of databases

MEDLINE	EMBASE	CINAHL	The Cochrane Library
1. exp Burns/	1. burn/	((MH "Burns+") OR	1. burn.mp.
2. (thermal adj3 injur*).tw.	2. (thermal adj3 injur*).tw.	(burn OR burns OR burned OR scald*)	2. integra.mp.
3. (burn or burns or burned or scald*).tw.	3. (burn or burns or burned or scald*).tw.	AND ((MH "Skin, Artificial") OR (integra	3. artificial skin.mp.
4. 1 or 2 or 3	4. thermal injury/	OR (skin substitute) OR (artificial skin))	4. skin substitute.mp.
5. Skin, Artificial/	5. 1 or 2 or 3 or 4		5. 2 or 3 or 4
6. (artificial* adj3 skin).tw.	6. artificial skin/		6. 1 and 5
(substitute adj3 skin).tw.	7. (artificial* adj3 skin).tw.		
8. integra.tw.	8. (substitute adj3 skin).tw.		
9. 5 or 6 or 7 or 8	9. integra.tw.		
10. 4 and 9	10. 6 or 7 or 8 or 9		
	11. 5 and 10		

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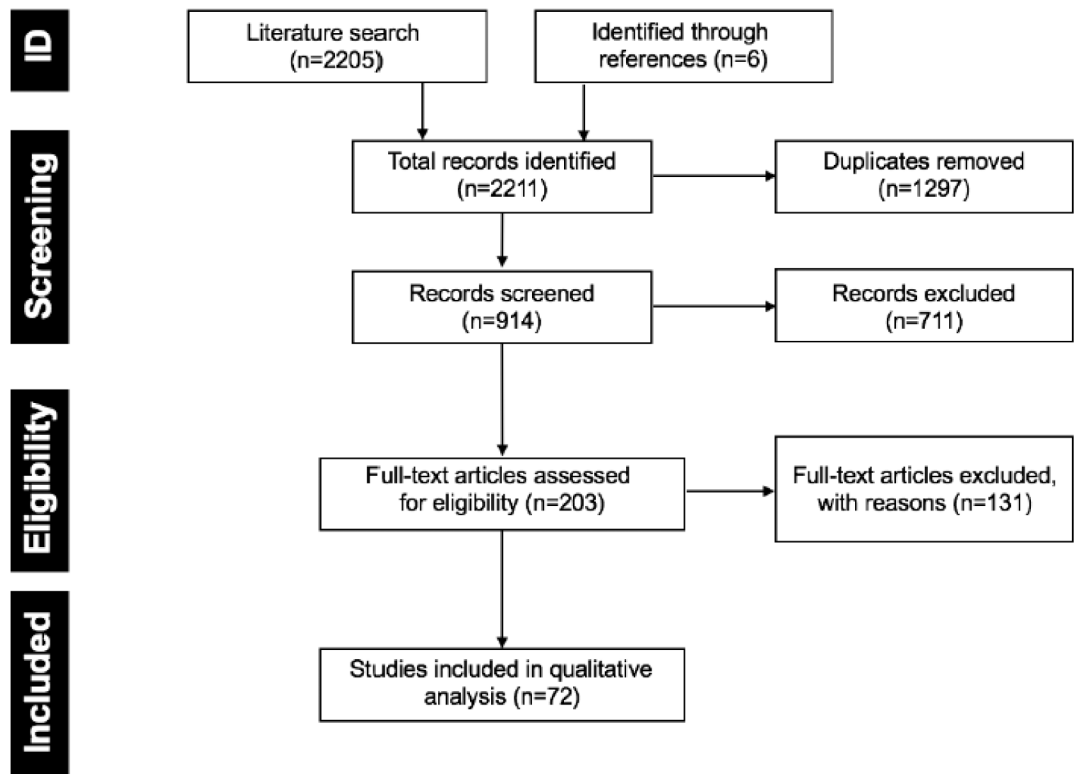


FIGURE 1. Flow diagram depicting the screening of articles for inclusion for qualitative analysis, reported in accordance with the Preferred Reporting Systems for Systematic Reviews and Meta-Analysis (PRISMA) statement.

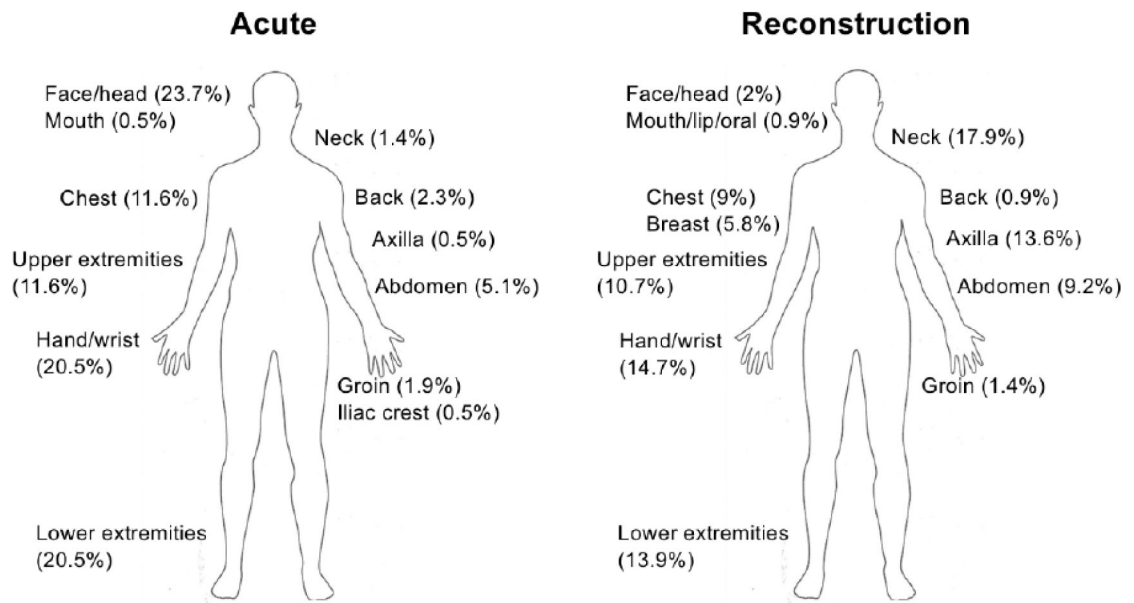


FIGURE 2. Anatomic distribution of DRM application for both acute and reconstructive indications; reported for 561 treated sites (48% of all DRM-treated sites).

Table 1.

Authors' affiliation

Continent	No. of studies	No. of acute cases	No. of reconstructive cases
Europe	37	107	216
North America	21	665	17
Asia	9	14	36
Australia/Oceania	4	7	8
South America	1	7	7

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Table 2.

Functional Outcome – Range of Motion (Objective) (n=4)

Article	Body Site	Outcome
Chou et al., 2001 (n=13)	Elbow	+30°, n=6
	Axilla	+65°, n=2
	Wrist	+31°, n=4
	Upper arm	+45°, n=1
Figus et al., 2007 (n=1)	Axilla	0°–30° → 0°–120°
	Antecubital fossa	120°–160° → 0°–160°
	Wrist	–160°––140° → –45°– +45°
	Neck	90° fixed flexion → 0°–90°
Moieman et al., 2001 (n=20)	Axilla, neck, groin, thigh, knee, foot, chest, back, abdomen, ankle, arm	Patients reported a 72% increase in ROM
Young et al., 2004 (n=8)	Wrist	“Excellent” results (75–100% ROM); n=5
	Axilla	“Good” results (50–74% ROM); n=1
	Elbow	“Poor” results (no change in ROM); n=2 Wrist: 2 sites FFD (+15°, +20°) Elbow: 2 sites FFD (+55°, +90°)

* FFD=fixed flexion deformity

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Table 3.

Functional Outcome – Range of Motion (Subjective) (n=8)

Article	Acute / Reconstruction (n=number of patients)	Outcome
Cedidi et al., 2002	Acute (n=1)	Functional ROM was complete and “excellent”
Verolino et al., 2008	Acute (n=1)	Normal mobility with right hand, good thumb opposition Active ROM was normal 2 years post-op Active flexion of the IP joints was limited (5–15°) Passive motion quasi normal in flexion and extension for all IP and MP joints
Pontini et al., 2015	Acute (n=1)	Satisfactory oral ROM at 12 months
Frame et al., 2004	Reconstruction (n=89)	Post-treatment ROM (rated by <i>physicians</i>): Excellent (46%, 59 sites) Good (29%, 37 sites) Average (9%, 11 sites) Below average (16%, 20 sites) Post-treatment ROM (rated by <i>patients</i>): 86% satisfied
Popescu et al., 2007	Reconstruction (n=1)	Extension of neck was significantly improved Mouth opening was almost normal
Lynch et al., 2008	Reconstruction (n=1)	Contracture release improved the patient’s neck ROM
Park et al., 2009	Reconstruction (n=3)	Significant improvement in shoulder abduction and extension Improved ROM Good ROM at ankle
Cuadra et al., 2012	Acute (n=7), Reconstruction (n=7)	Range of articular motion was complete in 15/17 cases (88%) Moderate motility limitation in both active and passive movements of 5 th digit; n=1 Limited flexion of fingers; n=1

Table 4.

Scar Cosmesis (Scar Scales) (n=9)

Article	Acute vs. Reconstruction (n=number of patients)	Outcome
Anderson et al., 2011	Acute (n=5 (DRM)); n=8 (control))	Median VSS DRM: 6 Median VSS control (CEA +STSG): 4 <i>*Not a significant difference</i>
Branski et al., 2007	Acute (n= 10)	Mean Hamilton-burn scar score: DRM: 4.2 Autograft-allograft (control): 6.6
Danin et al., 2012	Acute (n=22)	Mean VSS: 2.08
Lagus et al., 2013	Acute (n= 10)	Mean VSS: DRM: 2.5 → 1.3 STSG: 2.5 → 0.8 Cellonex: 2.9 → 0.8
Zajicek et al., 2017	Acute (n=11)	Mean VSS score: DRM: 1.4 DE graft (control): 4
Chou et al., 2001	Reconstruction (n=13)	Mean VSS: 8.7 → 2.5
Moiemen et al., 2001	Reconstruction (n=20)	Mean VSS: 13.3 → 9
Palao et al., 2003	Reconstruction (n=12)	Mean VSS: 8.1 → 2.5
Dantzer et al., 2003	Acute (n= 11), Reconstruction (n=11)	Acute: Mean VSS of 3.1 Reconstructive: Median VSS from 10 → 2