trauma care

MDPI

Review

Skin Substitutes: Filling the Gap in the Reconstructive Algorithm

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Abstract: Background: Skin substitutes play a crucial role in wound care by actively modulating the wound healing process, promoting angiogenesis, and protecting the integrity of the native extracellular matrix. Consequently, surgeons have increasingly recognized these resources as excellent complements to improve reconstructive outcomes. This review focuses on the author's experience using these biomaterials in complex cases, highlighting the benefits they bring to patient care. Methods: A literature review was conducted to evaluate the regenerative properties of skin substitutes and their applicability in head and neck, upper and lower extremities, and trunk reconstruction. Results: The reviewed literature, along with the authors' experience, supports the adjunct use of skin substitutes in various reconstructive situations. Combining them with skin grafts improves resulting skin quality and may also enhance donor site healing. They have proven to be effective in addressing chronic venous ulcers, traumatic wounds with limited donor tissues for coverage, extensive burns, diabetic foot ulcers, and oncological resections in the face and scalp. Furthermore, combining them with autologous tissue shows promising results in achieving stable closure. Conclusions: Incorporating skin substitutes in complex reconstructive scenarios offers multiple benefits. Their regenerative properties and ability to modulate the healing process contribute to enhanced outcomes and reduced overall costs.

Keywords: skin substitutes; dermal matrices; wound healing; reconstructive surgery; biomaterials

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1. Introduction

Historically, plastic surgeons rely on a step-like approach known as the "Reconstructive Ladder" when planning reconstruction procedures. Starting with the simplest technique available, this would then progressively escalate to more complex interventions when appropriate [1,2]. In 1994, Gotlieb and Krieger proposed the "Reconstructive Elevator", which allowed surgeons to select the most suitable primary reconstructive technique, regardless of complexity [3]. Then, in a more recent development, came the "Reconstructive Grid", which considered factors such as wound complexity, surgeon expertise, available resources, and patient preferences when deciding on a method for wound closure [4–6].

Over the last twenty years, there has been a remarkable advancement in the development of skin substitutes, leading to their gradual integration into clinical practice. This evolution has significantly transformed the approach to managing soft tissue deficits in contemporary medical settings [7]. Several studies have indicated that the use of skin substitutes is associated with a reduction in the time required for wound closure [8], and their inherent biological properties have been shown to effectively address a range of complexities in the wound care process, including inflammation, re-epithelialization, angiogenesis, wound contraction, and extracellular matrix remodeling [9]. In our experience, skin substitutes can provide temporal coverage when there is limited native tissue available and can also offer a simpler alternative to complex reconstructive procedures in situations

when they are contraindicated or unsafe, particularly in frail or unstable patients [10,11]. This review emphasizes the benefits of integrating skin substitutes as adjunctive components in complex reconstructive scenarios without proposing specific standards for locoregional reconstruction.

2. Skin Substitutes for Reconstruction and Wound Care: Properties and Types

2.1. Properties

Skin substitutes have become essential for tissue reinforcement in reconstruction and wound care because of their regenerative properties, active modulation of the wound healing process, and remodeling of the extracellular matrix (ECM) [12]. When applied to the wound, these tridimensional scaffolds are quickly infiltrated by cellular components and growth factors that stimulate angiogenesis and help promote wound healing [13,14]. Studies have shown that wounds treated with dermal matrices exhibit increased expression of various growth factors such as EGF, FGF, PDGF, and TGF-β [7,9,15]. This increase in expression is due to natural cytokines stored within the scaffold and their cumulative effect on the local production of molecules by native cells in the recipient tissue [11]. Additionally, these matrices offer immediate protection of the native ECM against dehydration, microorganism colonization, exposure to toxins, and external environmental factors that can disrupt the healing process [15].

2.2. Types

According to their composition, currently, there are two main families of skin substitutes, biologicals, and biosynthetics (Figure 1). Biologicals contain dermal components and can be subcategorized based on their donor origin into autografts, allografts, and xenografts. Allografts are derived from cadaveric and neonatal donors, whereas xenografts are typically sourced from bovine and porcine sources. Although xenografts could be derived from a variety of species, they are invariably acellular. This feature ensures that they are immunologically inert, thus avoiding any allergic reactions in the host [16]. Biologicals can be composed of a single layer or multiple layers to incorporate an epidermal element that mimics the native epidermis. This can be of cellular origin, such as living keratinocytes, or a synthetic temporary outer layer composed of a thin silicone film to protect the underlying dermal scaffold. In contrast, biosynthetic skin substitutes, also known as hybrids, include absorbable or non-absorbable materials, such as polyglycolic acid and others, to reinforce the biological matrix, providing additional support and structure.

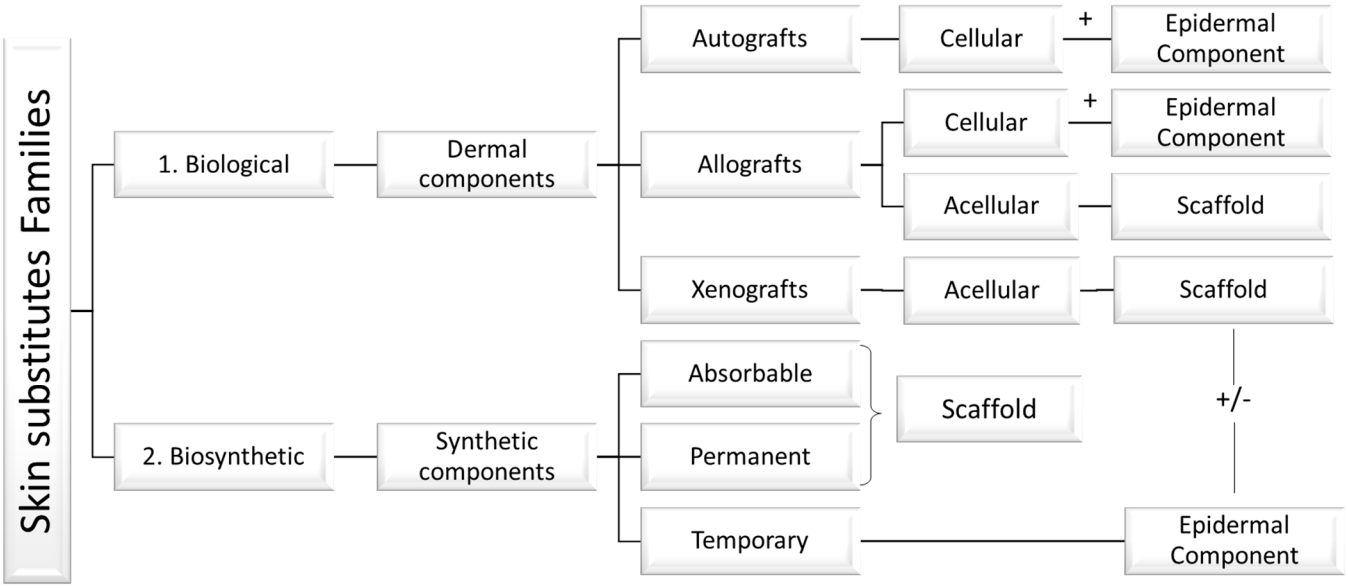


Figure 1. Skin substitute families according to their composition.

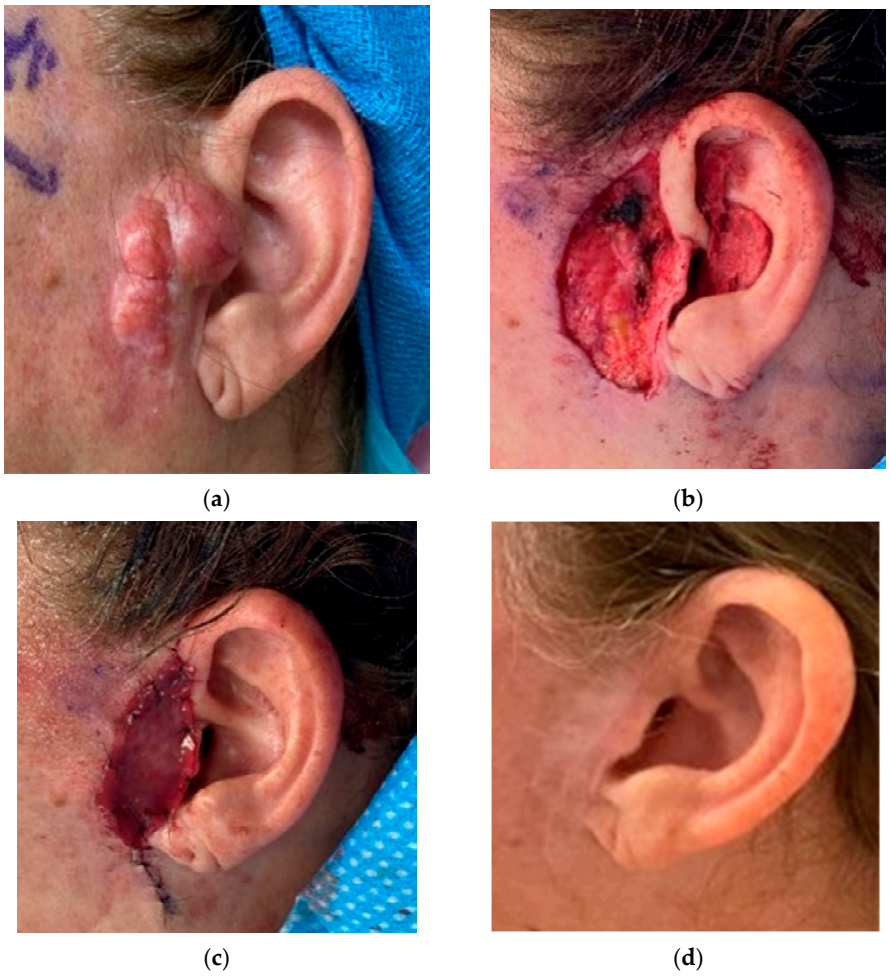
Acellular Dermal Matrices (ADMs) are obtained from allogeneic and xenogeneic donors and retain numerous ECM components, including collagen, elastin, laminin, hyaluronic acid, and glycosaminoglycans [16]. Allogenic ADMs are classified as banked human tissue by the Food and Drug Administration (FDA) because they are produced from cadaveric donor skin. Xenogeneic ADMs are classified as medical devices. Certain alternative products involve additional processing, such as collagen cross-linking, which aids in minimizing degradation by native collagenases [17]. A recently developed scaffold derived from porcine urinary bladder extracellular matrix has been found to be advantageous in various respects. Studies have shown that they enhance progenitor cell migration, proliferation, and differentiation while promoting angiogenesis, reinnervation, and minimal foreign body reaction [18]. Particulate and paste presentations are currently available and can be used to treat tunneled or irregular wounds, although they have comparatively shorter absorption times. Cellular dermal matrices are composed primarily of human neonatal fibroblasts and keratinocytes cultured on a bovine collagen matrix or a biodegradable polyglactin mesh. They are mainly used in non-infected venous leg ulcers and neuropathic diabetic foot ulcers without tendon, muscle, capsule, or bone exposure.

3. Current Uses of Skin Substitutes

3.1. Scalp, Face, and Neck Reconstruction after Oncological Resection, Trauma, and Burns

Scalp reconstruction is a challenging task, especially following wide excisions for cancer treatment, which can result in defects that disrupt the blood supply of potential local flaps. Several articles in the literature discuss comprehensive algorithms for scalp reconstruction; however, such detailed approaches are beyond the scope of this review [19–21]. Local and regional flaps typically provide stable coverage of scalp defects, but their availability may be limited due to prior surgery, radiotherapy, or scarring (Figure 2) [22,23]. Free tissue flaps have high survival rates and may be necessary for large scalp defects, which can result in donor-site morbidity, increased hospitalization length, and higher overall cost [24,25]. However, when temporary coverage is indicated or a previous reconstruction attempt has failed, skin substitutes become viable alternatives [26–28]. In full-thickness defects with an exposed skull, skin substitutes can be considered an initial step in the reconstructive strategy. A single-stage reconstruction can be achieved by placing a dermal matrix and a thin split-thickness skin graft (STSG) over the burred external table, while some authors recommend holding skin grafting for about six weeks until granulation tissue is optimal for graft take [29]. When possible, vascularized pericranial flaps can be mobilized to cover the exposed skull before skin substitute placement [28–31]. Cost-analysis studies have demonstrated that treating scalp defects larger than 100 cm^2 with the use of dermal matrices is more cost-effective than free and local flaps [32]. Furthermore, the use of temporal synthetic biodegradable matrices has proven beneficial in facilitating the closure of large and infected scalp defects (Figure 3) [33].

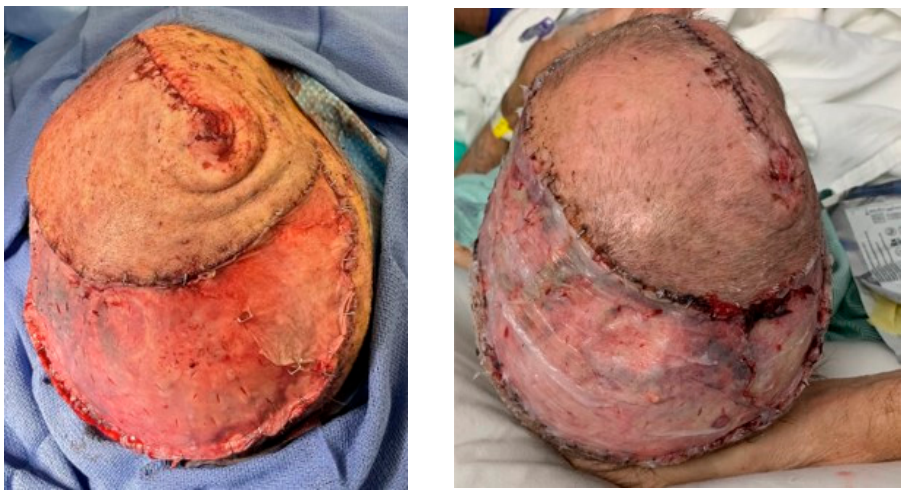
The many aesthetic subunits of the face require complex reconstructions after cancer resection defects or trauma or as a result of burns. Defects over the lower eyelids, inner cantus, cheek, and neck can potentially benefit from incorporating skin substitutes as an adjunct to reconstructive procedures to assist in covering the defect. For example, the application of dehydrated human amniotic membrane over defects in the lower eyelids or a bilayer dermal matrix over defects on the inner cantus has shown promising results, providing stable closure of the wounds and improving overall scar healing pain scores [34]. Similarly, in reconstructions of large neck defects with complex regional flaps, the use of skin substitutes such as bilayer dermal matrices and others can facilitate and reinforce the closure and temporalize the wound bed in preparation for subsequent skin grafting (Figure 4).



(**a**) (**b**)

(**c**) (**d**)

Figure 2. Use of bilayer dermal regeneration template in the face. (**a**). A 50-year-old female with a preauricular benign histiocytoma from a facelift scar. (**b**). Resection of the lesion resulted in a full-thickness defect of 6 × 4 cm. (**c**). The absence of facial skin laxity due to the previous facelift did not allow the advancement of a flap over the defect, which was covered with a bilayer dermal regeneration template (**d**). Successful wound healing with acceptable aesthetic results.



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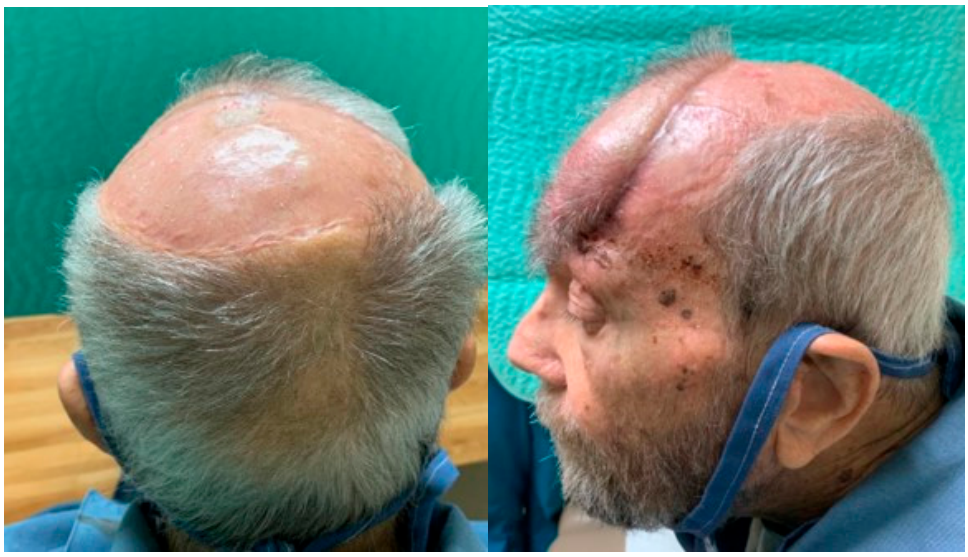
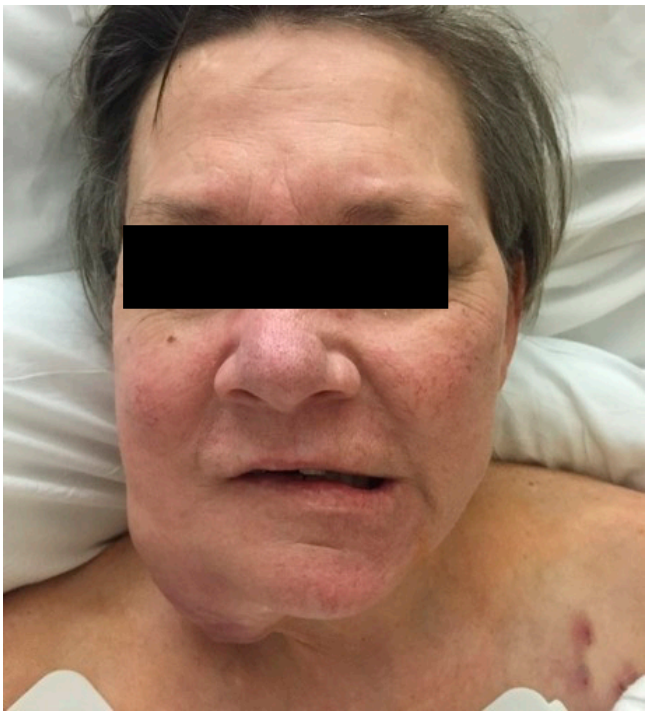


(**c**)

Figure 3. Scalp Reconstruction After Large Squamous Cell Carcinoma Resection with Local Transposition Flap. (**a**). A hyaluronic acid-based matrix was used to cover the donor defect over a previously burred skull. (**b**). After full integration of the dermal matrix, it was covered with a split-thickness skin graft (not shown). (**c**). The wound remained stable after 6 months.

Facial burns, especially in infants and children, benefit from the application of certain skin substitutes such as human amniotic membranes. Studies have shown that the regenerative characteristics of these biomaterials are safe and enhance the wound healing process in this vulnerable population where donor skin is limited or not available [35].



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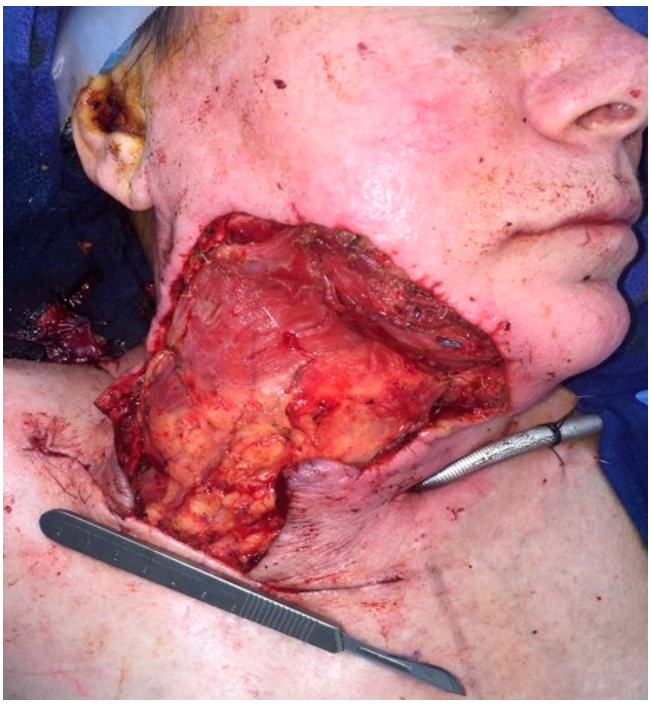

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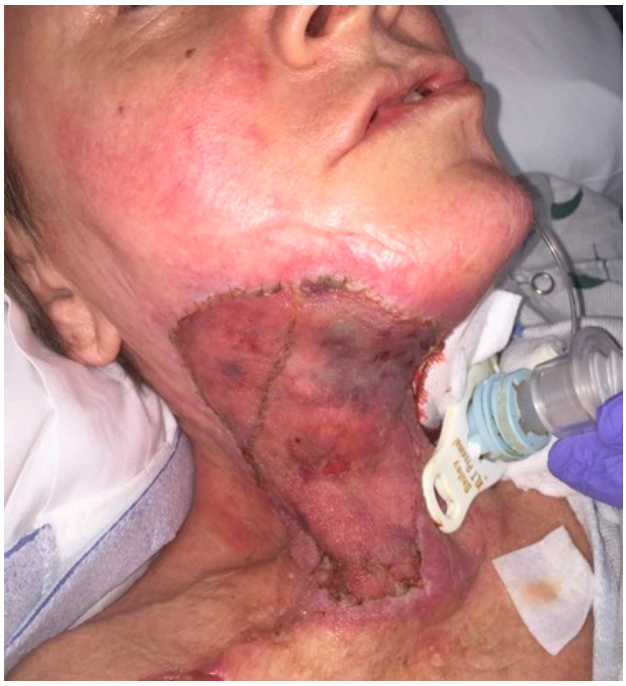


(**d**)

Figure 4. Utilization of bilayer dermal regeneration template, negative pressure wound therapy, and split-thickness skin graft in the neck. (**a**). A 60-year-old female with an oropharyngeal squamous cell carcinoma extending to the neck. (**b**) Extensive mandibular resection defect covered with a pediculated pectoralis major muscle flap. (**c**) Bilayer dermal regeneration template applied to the exposed muscle flap. (**d**) Skin graft performed three weeks later provided stable coverage for adjuvant radiotherapy.

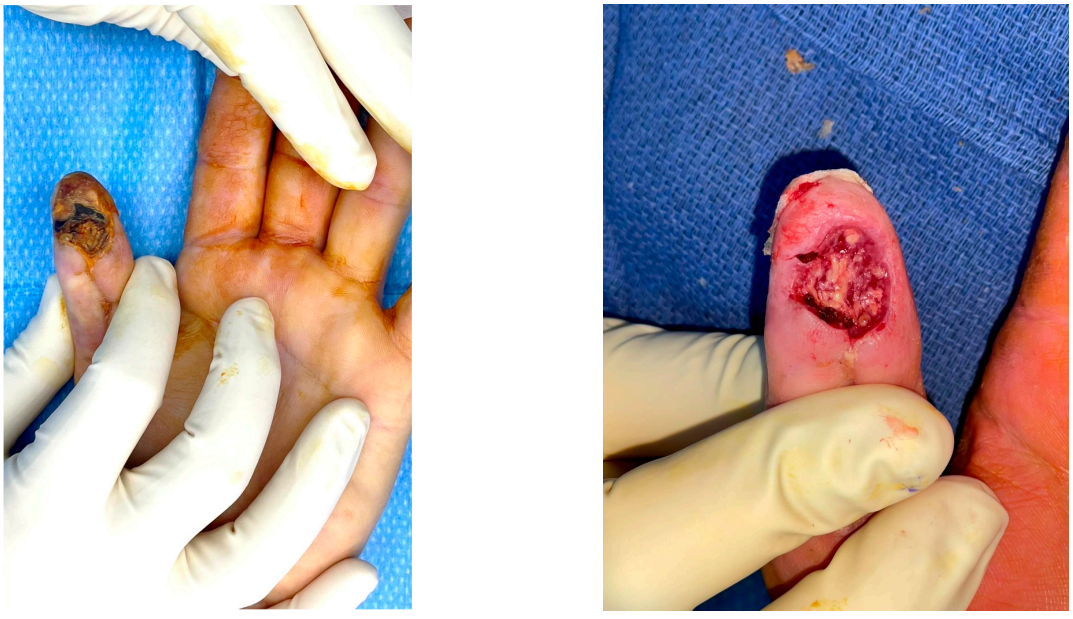
3.2. Upper Extremities Reconstruction after Burns, Trauma, and Chronic Wounds

Traumatic and burn injuries to the upper extremity, particularly the hand, pose significant challenges as they are often associated with high rates of disability and morbidity, often necessitating multiple and complex reconstructive procedures [36–38]. In the context of hand burns, digit scar contractures are a common occurrence, and the standard of care often involves the utilization of local flaps and full-thickness skin grafts for scar release and the return of range of motion. The incorporation of skin substitutes, specifically bilayer dermal matrices, can serve as a valuable adjunct to these procedures, providing temporary and definitive coverage for secondary defects and prior to the application of skin grafts [39]. For extensive upper extremity burn wounds, an increasingly popular strategy involves the combination of skin grafts with dermal matrices. This approach has shown promising results in enhancing the quality and elasticity of the skin and ultimately improving the resultant range of motion of the affected joints. The key to this improvement lies in the introduction of a regenerative scaffold of elastin and collagen into the wound bed that serves as a template for new tissue growth [12,40–42]. Furthermore, when this approach is used in conjunction with negative pressure wound therapy (NPWT), the outcomes are even more promising, resulting in a superior scar appearance compared to the use of skin grafts alone [43].

Traumatic fingertip injuries are common. The decision between nonoperative and operative management depends on specific criteria. Secondary intention healing is indicated in patients without exposed bone or tendon and less than 2 cm of skin loss or in children with exposed bone [44]. Operative interventions, including primary closure, full-thickness skin grafting, and flap reconstruction, are tailored based on the extent of tissue loss and exposure of bone or tendon. The goal of fingertip reconstruction lies in the restoration of sensate and durable fingertips with adequate bone support for nail growth. Improper

treatment may lead to stiffness, long-term functional loss, and hook nail deformity [44]. The adjunct use of skin substitutes for second-intention healing of fingertip injuries is a feasible option (Figure 5). In a recent retrospective cohort study, the use of a collagen–elastin template scaffold treated with autologous adipose-derived stromal vascular fraction cells led to promising results, including better scar quality, higher tactile recovery, improved range of motion, higher patient satisfaction, shorter surgical times and hospital stays, and lower surgical costs compared to the reverse digital artery island flap [45]. Cell therapy using autologous cells accelerates wound healing by reducing the invasion time of host cells and early skin synthesis, and while cell-only treatment quickens healing, it does not affect wound contraction; hence, cells are often used with artificial dermal scaffolds to optimize healing and minimize wound contraction without delay in healing for skin and soft tissue defects [46]. Limited case series have indicated that complex cases with exposed tendons and joints following burns, traumatic injuries, and oncological resections have been successfully treated with either single or staged composite applications of dermal substitutes and split-thickness skin grafts [37,47–49]. Some of these injuries necessitate that the dermal substitutes be piled or stacked to increase the thickness and sturdiness of coverage when applied over exposed bone and tendon [50]. Some of the matrices reported for this use include collagen–elastin templates, esterified hyaluronic acid matrices, and dermal regeneration templates.

Chronic and infected upper extremity wounds are difficult. Treatment involves reconstruction after a full course of antibiotics and serial debridement. Under these circumstances, the resulting defects are often extensive and complex. The use of temporary skin substitutes, such as synthetic biodegradable polyurethane matrices, has proven to be beneficial. It increases the success rates of reconstruction and reduces morbidity in patients with chronic wounds, including those complicated by osteomyelitis [51–53]. Another example noteworthy to highlight is the management of severe axillary hidradenitis suppurativa, which necessitates extensive full-thickness skin resection of the axillary region, resulting in undesirable scarring and contracture despite local flaps and the application of full-thickness skin grafts [54]. Studies have shown that applying a bilayer dermal matrix followed by skin grafts has positive outcomes, including a low recurrence rate, improved range of motion at the shoulder, better aesthetic results, and lower pain scores compared to skin grafts alone [55–58].



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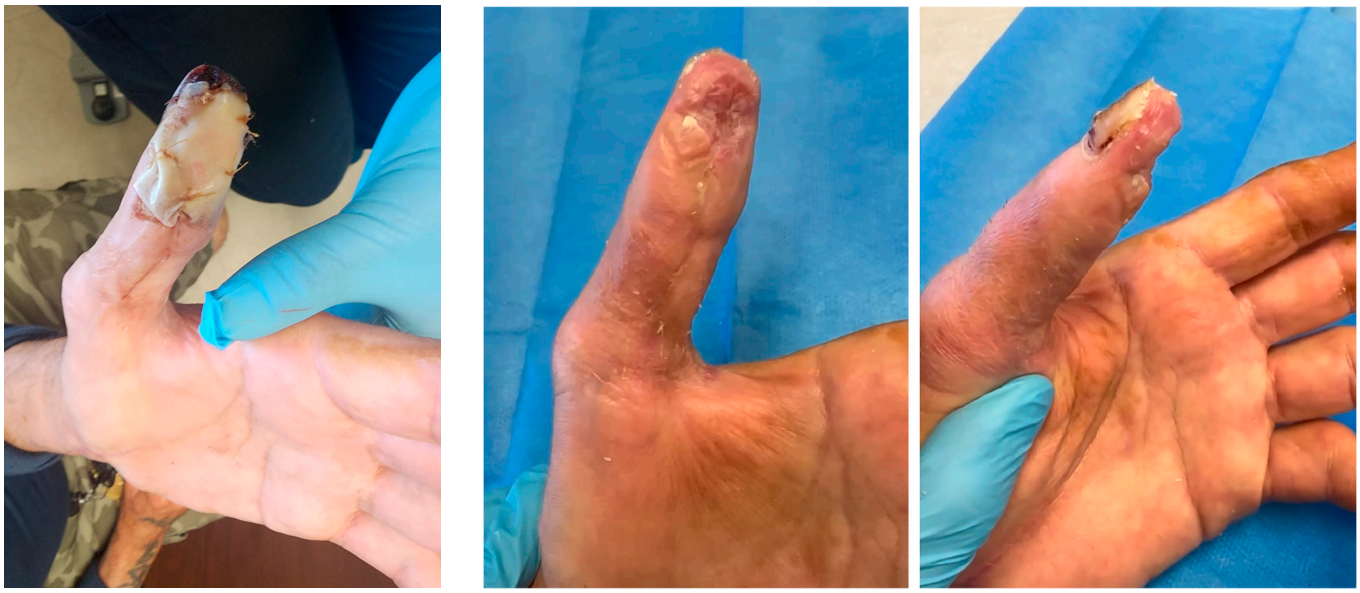


(**c**) (**d**)

Figure 5. Utilization of a Hyaluronic Acid-Based Biological Bilaminar Matrix for Secondary Wound Healing of the Fingertip After a Necrotizing Infection. (**a**). A 58-year-old male patient, who is diabetic, presented with a necrotizing infection in his left thumb. (**b**). Debridement and wet-to-dry dressing changes were performed until an appropriate wound bed was obtained. (**c**). A bilaminar hyaluronic acid matrix was applied to the wound and left in place for 3 weeks. (**d**). A month after the initial presentation, patients display full healing of the wound and initial return of protective sensation. Although a volume deficiency is still evident, the patient can now start hand occupational therapy and return to work.

3.3. Applications on Lower Extremities Reconstruction

Most chronic non-healing wounds in the lower extremities are the consequence of multiple conditions, including venous insufficiency, diabetic foot ulcers, osteomyelitis, peripheral artery disease, deep burns, necrotizing infections, tumor resection defects, and severe trauma. Providing care for these wounds is particularly challenging, as patients are subject to significant disability and recurrence [59]. Reconstruction involves the use of local or free flaps, with favorable outcomes and high rates of limb salvage. Nevertheless, difficulties can arise due to the limited availability of donor tissues, particularly in complex cases involving significant soft tissue loss [60,61]. Most skin substitutes are available off the shelf, making their use especially convenient in urgent situations. They can be used as temporary biological coverage, for wound bed preparation for future skin grafting, or in conjunction with flaps in complex wounds, often with satisfactory results [62] (Figure 6). The retrospective study by Kozac et al. [63] analyzed the success of three reconstructive procedures, namely bilayer wound matrix, local tissue rearrangement, and free flap reconstruction, in over 300 adult patients with lower extremity wounds. Success was defined differently for each procedure, with the primary outcome being graft success at 180 days. Secondary outcomes included amputation rates, readmissions, reoperations, and costs. The study found varying success rates: 69.2% for bilayer wound matrix, 91.3% for local tissue rearrangement, and 93.3% for free flaps. Despite longer hospital stays and higher costs, free flap reconstructions had the lowest amputation rates. However, the study acknowledged significant data heterogeneity, including comparability of injuries and patient factors between groups, suggesting the need for further studies for a more comprehensive understanding. Reconstructive success is associated with avoiding amputation and includes other factors such as graft success, readmissions, reoperations, and costs. While this study is retrospective, other study designs could also provide valuable insights into this field.

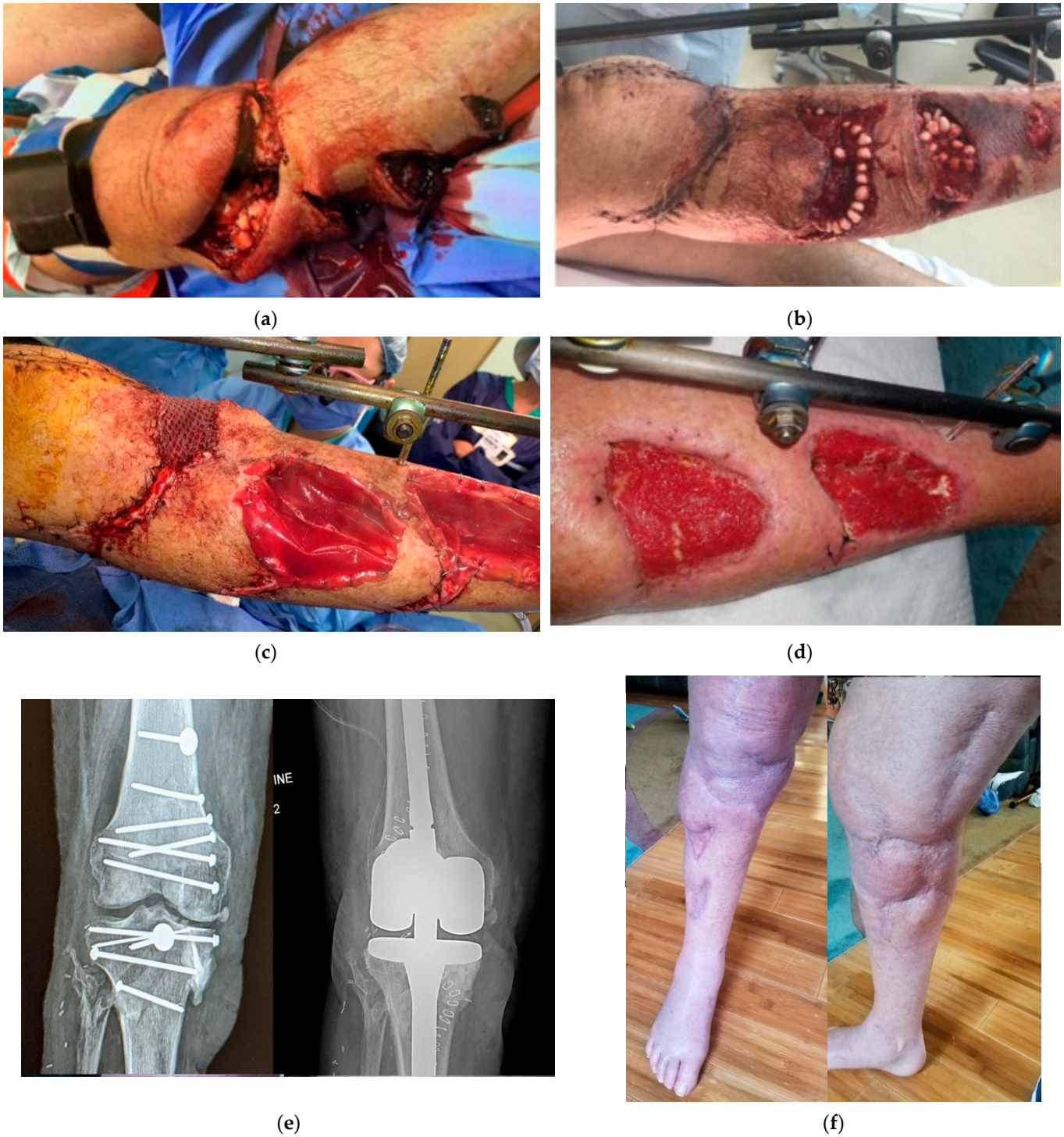
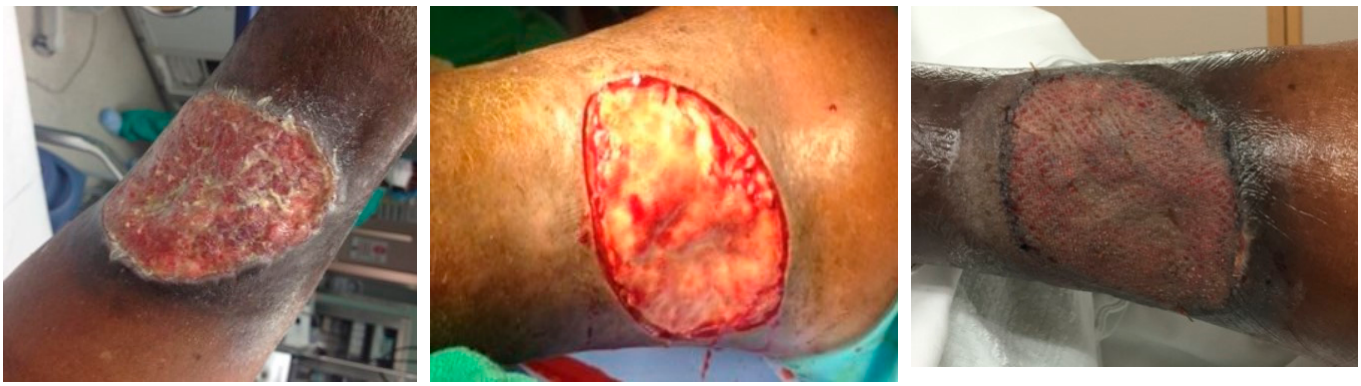


Figure 6. Bilayer dermal regeneration template, particulate urinary bladder matrix, and split-thickness skin grafts for coverage of a complex lower extremity injury. (**a**). A mid-60s male with a propeller injury. Vascular and orthopedic intervention was required due to Gustilo IIIC tibial fracture. (**b**). The patient underwent multiple debridement, application of wound antibiotic beads, and negative pressure wound dressing. (**c**). A large knee defect was covered with a reverse gracilis muscle flap and skin graft, while two large defects over the leg were temporarily covered with the bilayer dermal matrix. (**d**). Wound bed optimized for skin graft take. (**e**). Patient required total knee arthroplasty 12 months later due to the severity of the injury. (**f**). Patient ultimately had a full restoration of function.

Pontell et al. [64] conducted a study comparing two groups of patients with foot and ankle wounds. The first group, consisting of four patients, received a reverse sural adipofascial flap (RSAF) with immediate split-thickness skin grafting, taking an average of 141.2 days to heal. The second group, also of four patients, was treated with RSAF in combination with an acellular dermal matrix and negative-pressure wound therapy, followed by STSG at a later date, with an average healing time of 104.5 days. This latter approach resulted in a healing time reduction of 36.7 days on average, a 25% decrease compared to the first group. The study suggests that the use of ADM and NPWT, along with RSAF, could potentially reduce the overall healing time compared to RSAF with immediate STSG. However, further comprehensive studies are required to validate these results [64]. Similarly, in chronic venous ulcers, bilayer dermal matrices have shown advantageous results, decreasing healing time compared to controls treated with standard wound care [65] (Figure 7).



(**a**) (**b**) (**c**)

Figure 7. Particulate and laminated urinary bladder matrix under negative pressure wound therapy to treat lower extremity venous ulcer. (**a**). A mid-40s morbidly obese female with a large infected venous ulcer that failed to improve after months of wound care and pressure dressing. (**b**). IV antibiotics, surgical debridement, and wound preparation were performed before skin substitute application. (**c**). A split-thickness skin graft provided final coverage, improving the patient's quality of life.

Likewise, in a study by Kavros et al. [66], a fetal bovine acellular dermal matrix was used to treat 46 patients with chronic diabetic foot ulcers. The study found that 76% of the patients healed within 12 weeks, with an average healing time of 53.1 days, a relatively brief period considering that these chronic ulcers had persisted for an average of 286 days. Most healed wounds required only one or two applications of the ADM. Even for ulcers not fully healed within 12 weeks, the wound area was reduced by 71.4% on average. The study suggests that this ADM, combined with standard care, can effectively treat diabetic foot ulcers, although results may vary and further research is needed. Furthermore, studies indicate that skin substitutes can boost tissue oxygen pressure in these poorly vascularized wound beds [67] (Figure 8).

3.4. Applications on Trunk and Spinal Reconstruction

The use of dermal matrices in abdominal reconstruction has become increasingly common as local and free flaps are utilized for the repair of large and complex abdominal wall defects following oncologic resections and catastrophic abdominal complications [68,69]. Strategies for the reconstruction of partial and complete defects of the abdominal wall encompass the utilization of autologous tissue for local and free flaps [70]. These strategies can include the addition of synthetic and biological materials for reinforcement. Promising results have been observed when full-thickness abdominal wall defects were addressed with component separation in a multilayer fashion using an acellular dermal allograft [71,72].

This approach suggests a safe profile and good integration with the surrounding tissues, as well as a low rate of infection, erosion, extrusion, and rejection compared to synthetic materials [73]. However, it can be associated with hernia recurrence rates of 11.5% and 14.6% at 3- and 5-year follow-ups, respectively, according to a single-center prospective series of 191 patients [74].

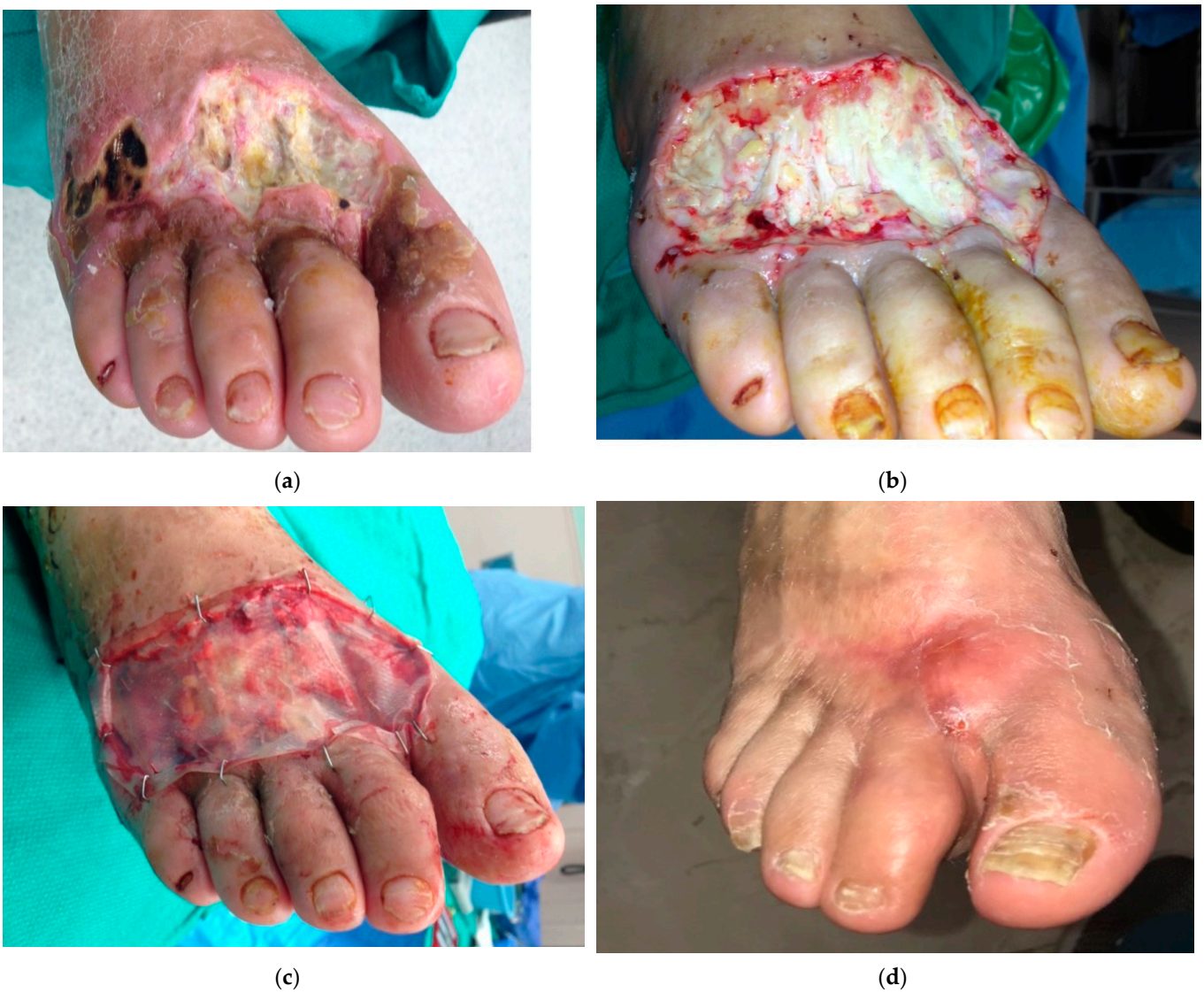


Figure 8. Application of porcine urinary bladder matrix and split-thickness skin graft in a diabetic foot ulcer. (**a**). A 28-year-old male, with type I diabetes, presented with a necrotizing infection. (**b**). Multiple debridements were performed for local infection control, which exposed the extensor tendons. (**c**). Urinary bladder ECM was applied over the wound 10 days after the initial presentation. STSG was applied 6 weeks later over a healthy granulated wound bed as an outpatient procedure (not shown). (**d**). Eight months after the initial presentation, the patient achieved complete healing and foot salvage, despite an initially poor prognosis.

Indications for employing dermal matrices or other biomaterials as surgical meshes or regeneration scaffolds include previously failed reconstructions and contaminated surgical fields [75–77] (Figure 9). Biological dermal matrices promote revascularization and integrate into native tissues more quickly than synthetic materials [76,77]. This allows for the formation of a robust tissue layer that supports lower rates of visceral erosion, intra-abdominal adhesion formation, and infections when compared to synthetic meshes [78,79].

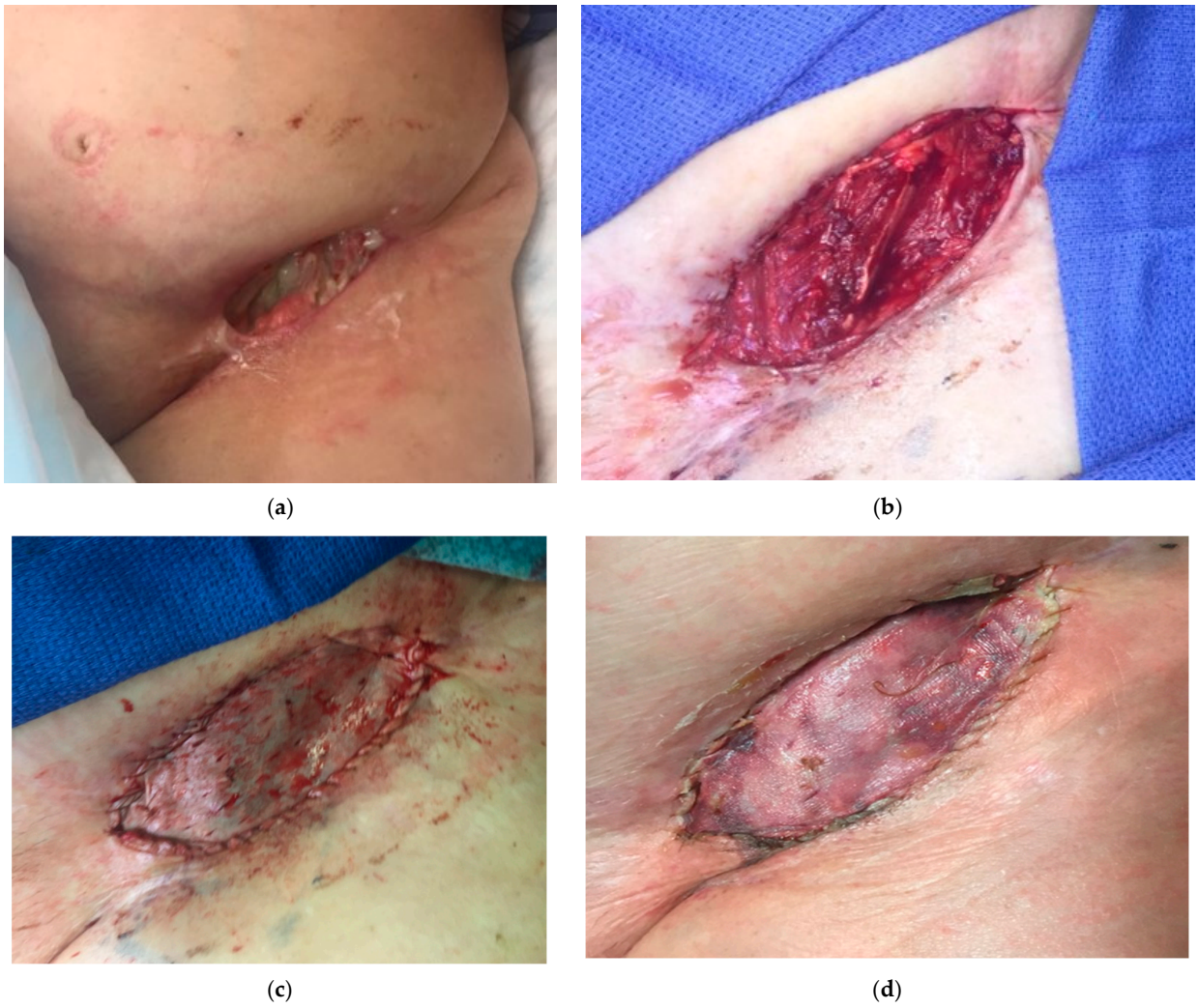


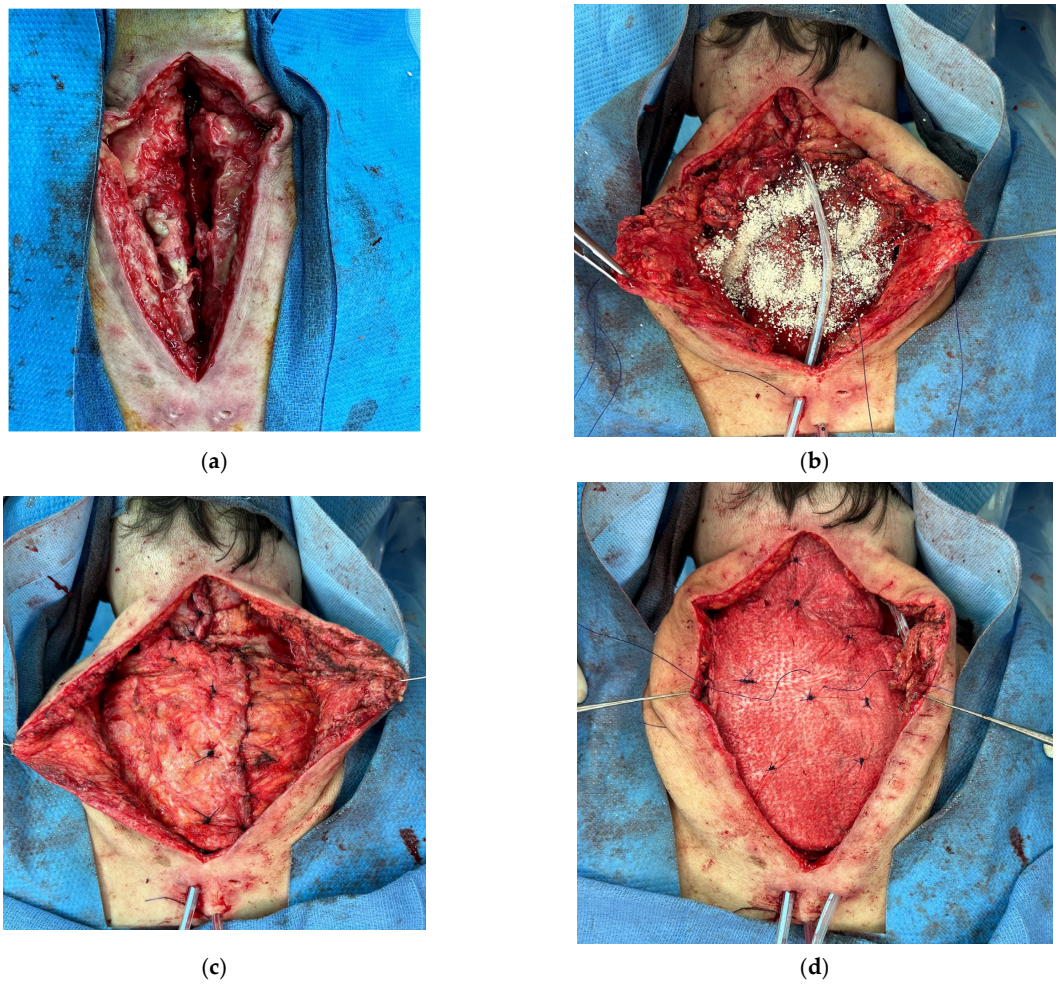
Figure 9. Urinary bladder matrix reinforcement of pediculated gracilis muscle flap. (**a**). A 43-year-old female with recurrent melanoma and previous radiation to the left groin. Presented with a non-healing, infected, and painful wound, with failed previous reconstruction attempts. (**b**). A gracilis muscle flap was used to fill the volume defect. (**c**). UBM temporarily covering an irregular wound bed. (**d**). Wound ultimately covered with a skin graft. Despite successful wound management, the patient's unfortunate passing was attributed to disease progression.

The current research on abdominal wall hernia repair indicates that the location of mesh placement significantly impacts the recurrence rates of hernias. Sosin et al. have shown that retromuscular (5.8%) and underlay (10.9%) mesh placements have lower recurrence rates compared to onlay (12.9%) and interposition (21.6%) placements [80]. Furthermore, a systematic review from John Hopkins University concluded that underlay or retrorectus mesh placements are associated with lower recurrence rates, with the lowest seroma rates observed following a retrorectus repair [81]. Additionally, a study on robotic ventral/incisional hernia repair with hernia defect closure and intraperitoneal onlay mesh showed a hernia recurrence rate of 14.81% [82]. Therefore, while the choice of technique depends on various factors, including patient-specific circumstances and the surgeon's expertise, retromuscular or underlay mesh placements are generally associated with lower hernia recurrence rates [82].

Hybrid meshes, which have been recently developed, combine biological materials with a permanent synthetic component to create a durable mesh that facilitates tissue ingrowth and reduces foreign-body reaction [83]. The addition of biosynthetic or biological materials could potentially decrease the need for permanent materials in abdominal wall

repairs, thereby providing better tissue integration and infection protection [84]. Moreover, the use of biosynthetic meshes in certain scenarios, including component separation, has resulted in improved outcomes and reduced costs compared to using biologicals alone [85]. This is due to their ability to counteract certain downsides of biologicals, such as resorption and high hernia recurrence rates, especially in contaminated wounds or when patient conditions are suboptimal for healing (e.g., uncontrolled diabetes, steroids use, malnutrition, etc.) [85–87]. The advantageous properties of hybrid meshes include serving as a scaffold for fibroblast migration and cellular ingrowth into the pores, followed by a controlled local inflammatory cascade to optimize vascularization and collagen production. They also provide protection to the permanent mesh component from triggering negative effects on surrounding tissue [85]. Despite the limited long-term data available, some authors suggest that the use of these hybrid meshes may lead to increased patient satisfaction through better integrative processes and the potential for lower rates of complications, reintervention, and recurrence [85].

In the same way, immediate reconstruction following complex spinal surgery and oncological spinal wounds can benefit from the adjunct use of particulate extracellular matrices along with local muscular flaps. These presentations are morcellated forms of extracellular matrices from different sources and can assist in obliterating the resultant dead space between the dura and paravertebral muscle flaps [88]. Additionally, other local flaps used for spine reconstruction, such as the trapezium and latissimus, can be reinforced with the application of extracellular matrices with favorable results (Figure 10).



(**a**) (**b**)

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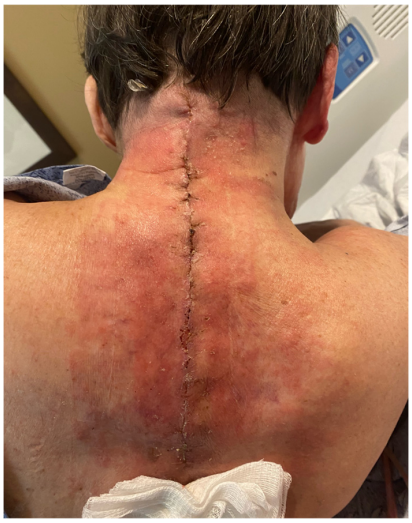
Figure 10. *Cont.*



(**e**)

Figure 10. Particulate extracellular matrix with paravertebral and trapezium muscle flaps. (**a**). A 66-year-old female with multiple cervical spine surgeries, complicated with hardware infection. (**b**–**d**). Following hardware removal and debridement, reconstruction was completed with paravertebral and trapezium muscle flaps, reinforced with morselized and laminated ECM allograft. (**e**). Wound healing after 12 days.

4. The Future of Skin Substitutes

The reconstructive ladder and subsequent models have provided valuable guidance in making optimal choices to expedite patient healing and achieve a balance between function and aesthetics [1,7]. Current scientific and technological advances have facilitated the development of numerous skin substitutes that enhance and modulate the wound healing process through biomodulation effects [89,90]. This includes immune cell recruitment, increased essential cytokines and growth factors, and modified molecular interactions within the wound [7,91,92]. More recently, tridimensional bioprinting has enabled the production of synthetic skin embedded with cells and bioactive molecules, resulting in increased cytokine production at the wound site. This accelerates healing by stimulating cell proliferation, promoting macrophage differentiation, and enhancing neovascularization [93, 94]. Additionally, gene editing technology applied to novel skin substitutes has shown potential for accelerated skin regeneration by targeting growth factors and pluripotent cells [95,96]. Despite these advancements, the challenges surrounding skin substitutes in clinical practice are multifaceted. One hurdle is the incomplete integration with the host tissue as achieving proper vascularization and cellular interactions is crucial for successful wound healing. Another is the uncertain long-term stability of these substitutes, as well as the absence of native skin elements such as epidermal appendages, intrinsic vasculature, innervation, and the lack of capacity to produce melanin [9]. Additionally, the prohibitive cost of skin substitutes presents challenges for generalized availability in low-income and uninsured patients. In contrast, cost analysis studies comparing skin substitutes to traditional wound care strategies have demonstrated a beneficial economic impact, owing to fewer emergency visits and readmissions, shorter hospitalizations, and improved limb salvage rates [97]. Moreover, regulatory considerations associated with the development and commercialization of these products add to their complexity. Overcoming these challenges will require continuous collaboration between scientists, clinicians, industry, and regulatory authorities.

In conclusion, recent technological advancements in skin substitutes have been pivotal in filling the gaps within reconstructive algorithms. These biomaterials offer solutions for reconstructive surgery and wound care while reducing overall treatment costs. Fur-

ther research and development in this field will likely lead to additional advances in the effectiveness and accessibility of skin substitutes for patients.

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Informed Consent Statement: All patients receiving treatment involving skin substitutes and biological materials under the care of the senior author (RC) underwent a thorough informed consent process. Prior to any intervention, these patients were provided with comprehensive information about the nature, purpose, potential risks, and expected outcomes of the proposed procedures. Permission to share photographic documentation of cases and outcomes was also obtained.

Data Availability Statement: This study does not possess a data sheet since it is a narrative review of literature.

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