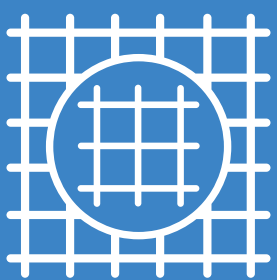
NEW TECHNOLOGIES FOR TISSUE DAMAGE REPAIR

DERMAL MATRICES AND EMERGING BIOMATERIALS FOR WOUND MANAGEMENT



HEALTH ECONOMICS AND REGULATORY ISSUES

The European Wound Management Association
EWMA

New technologies for tissue damage repair

Dermal matrices and emerging biomaterials for wound management

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Abbreviations

AGE	Advanced glycation end products
ATMP	Advanced therapeutic medicinal products
BTM	Biodegradable temporising matrix
CAGR	Compound annual growth rate
CAT	Collagen alginate therapy
CD31	Cluster of differentiation 31 (endothelial cell marker)
ECM	Extracellular matrix
EGF	Epidermal growth factor
ELP	Elastin-like polypeptides
EMA	European Medicines Agency
EUDAMED	European Database on Medical Devices
FBADM	Foetal bovine acellular dermal matrix
FdeU	Fragmented dermo-epidermal units
FGF	Fibroblast growth factor
FSG	Fish skin graft
FTO	Fat mass and obesity-associated protein
GAG	Glycosaminoglycans
GCA	Grancalcin
H&E	Haematoxylin and eosin
IFN-γ	Interferon gamma
Ki67	Ki-67 proliferation marker
m(6)A	N6-methyladenosine
MMP	Matrix metalloproteinase
NO	Nitric oxide
NPWT	Negative pressure wound therapy
OFM	Ovine forestomach matrix
ORC	Oxidised regenerated cellulose
PDGF	Platelet-derived growth factor
PDGF-BB	Platelet-derived growth factor B-chain homodimer
PRP	Platelet-rich plasma
RAGE	Receptor for advanced glycation end-products
ROI	Region of interest
ROS	Reactive oxygen species
SDF-1	Stromal cell-derived factor 1
sHA	High-sulphated hyaluronan
SOC	Standard of care
TBSA	Total body surface area
TGF-β	Transforming growth factor beta
TNF	Tumour necrosis factor
UBM	Urinary bladder matrix
VEGF	Vascular endothelial growth factor
VLU	Venous leg ulcer
vRAGE	Variant receptor for advanced glycation end-products

1. Introduction

In 2018, an EWMA document on Advanced Therapies in Wound Management was released, focusing on the many important new technologies proposed for the management of chronic and acute wounds, with the aim of bridging the needs of an increasing number of patients across the world with solutions that might increase the chances of healing and improve the quality of care and life.[1]

The interest in, and dissemination of, that document within the field of wound management led to a second document, released in 2023, on technologies for tissue repair, targeting tissue defect repair. This was to respond to requests in this area from the surgical community of our multidisciplinary association.[2]

An increasing number of new technologies have been proposed for tissue repair in chronic wound management, and new evidence for already existing technologies emerged since the publication of the 2023 EWMA document, driving the rationale for a new updated release focused on dermal matrices.

Matrices are no longer intended solely to be scaffolds or interfaces; a number of new physiological mechanisms and interactions have been postulated that broaden their indications in wound healing.

At the same time, the number of patients and their recurrences have increased, with more complex cases requiring safer and more cost-effective solutions. Consequently, the management of chronic wounds has evolved towards more integrated, multi-dimensional strategies that take into account this "longitudinal" evolution of the cases, requiring management accordingly not only from a pathological perspective, but also over time.

Finally, a completely new regulatory paradigm for medical devices and technologies has been issued and implemented, with important consequences for clinical practice. The access to modern, up-to-date, effective, and safer therapies for patients with complex chronic wounds requiring adequate management is in danger, not only from a resource-consumption perspective, but also from a resource-availability one. The increasing complexity of the bureaucratic process to access and remain in a fast-evolving market, the variability in registration and reimbursement procedures between different countries in the EU, as well as the inconsistent classification of products that may be considered medical devices in one EU country or drugs in another, limits the circulation of newer products and consequently the possibility for patients to benefit from their application. Taken together with the technical, scientific and clinical considerations mentioned above, this justified the development of the present document, in which regulatory and economic aspects are discussed extensively alongside the previously addressed issues.

Following an initial section revisiting the pathophysiology of wound healing, in which the role of the extracellular matrix has significantly changed, highlighting its functional roles that derive from its structure, a chapter on biotechnologies and biomaterials follows. This chapter introduces the central section of the document, in which some of the newest and most frequently used matrices are extensively discussed, with a new classification in line with the much more complex and diversified catalogue of solutions that the evolution of technology and manufacturing has produced in the last few years.

The sections on regulatory and economic aspects of these important components of wound management conclude the document. They provide interesting arguments for reflection and discussion that may be relevant not only for clinicians and caregivers, but also for administrators and policymakers, in line with the advocacy mission that always characterises EWMA's initiatives.

We, as authors, recognise that this document, although conceived as general and as systematic as possible, cannot comprehensively address all the areas, clinical and technical, of tissue damage repair. This is not only due to limitations in space and time, but also to the fact that certain aspects, like paediatric wounds or war/disaster-related wounds, have such specific and complex dimensions that they deserve a dedicated, in-depth elaboration and display.

For these reasons, the panel of authors decided not to include these areas within the scope of the present document, leaving them available for potential future analyses.

The document is to be considered as a collective work, authored by the entire group of contributors together. I would like to take this opportunity to thank them for the original effort each has invested in the realisation of a publication that we think will be read and consulted by a number of specialists and clinicians with different backgrounds, united by the commitment to caring for and healing patients with chronic wounds in Europe and beyond in these difficult times.

Alberto Piaggesi, MD
Editor

Methodology

The search strategy presented in Table 1 was designed to identify relevant literature on new technologies for tissue damage repair. A structured literature search was conducted in PubMed and Embase for each topic included in the document. The search covered the period 2020–2025. Authors responsible for each section reviewed the retrieved literature and selected relevant publications in accordance with the agreed scope of the document. Additional literature could be included by the authors to describe biological mechanisms, concepts or emerging approaches relevant to tissue damage repair, even if outside the predefined search period. The literature was evaluated with reference to the GRADE methodology.[3] A table summarising the evaluation of evidence is included at the end of the Dermal Matrices section. Supplementary material related to the use of selected new matrices, including a series of online videos demonstrating their application, is available on the EWMA website (www.ewma.org/resource-library).

Table 1. Literature search strategy. All searches were performed in titles and abstracts

General wound
1. General wound: all related terms covering chronic wounds (pressure ulcers, leg ulcers, diabetic foot ulcers, atypical, inflammatory, and malignant ulcers) and acute wounds (traumatic, surgical, and infectious wounds), combined using OR
2. NOT heart surgery OR neurosurgery (included in all searches)
Combined with the following search terms in separate searches:
Biomaterials and Biotechnologies
1. AND
3. Matrices OR acellular matrices OR acellular dermal matrices OR acellular dermis OR dermal matrix OR dermal template OR dermal regeneration template OR dermal substitute OR artificial dermis OR dermis-like tissue OR synthetic dermal matrices OR decellularised matrices OR dermal replacement OR dermal repair OR skin replacement OR skin repair OR skin regeneration OR skin healing OR bone regeneration OR bone repair OR bone healing OR tendon repair OR tendon regeneration OR tendon healing AND materials OR biomaterials OR polymers OR biopolymers OR ceramics OR nanomaterials OR smart materials OR composites OR hydrogel OR particles OR nanoparticles OR microparticles OR scaffold OR self-assembly OR 3D printing OR printing OR additive manufacturing OR biofabrication OR microfluidics OR electrospinning OR decellularisation OR freeze drying OR nanotechnology OR biotechnology OR drug delivery OR delivery systems OR NOT tissue engineering AND pre-clinical OR animals OR animal models OR in vivo OR mice OR rats OR pigs
Matrices
1. AND
3.dermal matrices OR acellular matrices OR skin substitute NOT cell therapies AND collagen matrix OR dermal matrix OR acellular matrix OR skin replacement OR biological matrix OR dermal template AND porcine matrix AND collagen matrix OR dermal matrix OR acellular matrix OR skin replacement OR biological matrix OR dermal template AND bovine matrix AND collagen matrix OR dermal matrix OR acellular matrix OR skin replacement OR biological matrix OR dermal template AND fish matrix
Economy, Organisation and Cost Effectiveness
1. ALL of the above sections/search strings with OR in between AND 2. health economics OR costs OR cost-effectiveness OR cost-utility OR cost-benefit OR budget impact OR economic resources OR resources OR economic analysis OR economic implications OR cost of illness OR organisational implications OR organisational implications OR organisation implications OR organisation implications OR organisational dimension OR organisational dimension OR organisation dimension OR organisation dimension OR health organisation OR health delivery OR health services OR health service
Physiopathology of Wound Repair
1. Wound biology OR wound physiology OR wound pathology OR wound physiopathology AND 2. wound repair OR tissue repair OR wound healing OR cutaneous wound healing OR Skin repair OR Dermal repair OR tissue repair

2. Physiopathology of tissue repair and the role of extracellular matrix

Physiology of tissue repair

Wound healing is a biologically complex process involving numerous cells and molecules that come into play at different times, activating different mechanisms to ensure effective and optimal tissue repair.[4,5] Considered as a whole, the wound repair process can be summarised in four main, successive and overlapping phases: haemostasis, inflammation, proliferation and remodelling[6,7] (Figure 1).

The first phase of haemostasis begins immediately after a trauma or other injuries interrupt the continuity of tissues, when blood cells come into contact with the subendothelial lining of blood vessels. Platelets, recruited by extracellular matrix proteins that interact with platelet receptors, are activated by thrombin and adhere to the wall of the damaged blood vessel, aggregating and forming an initial haemostatic clot.[6,8]

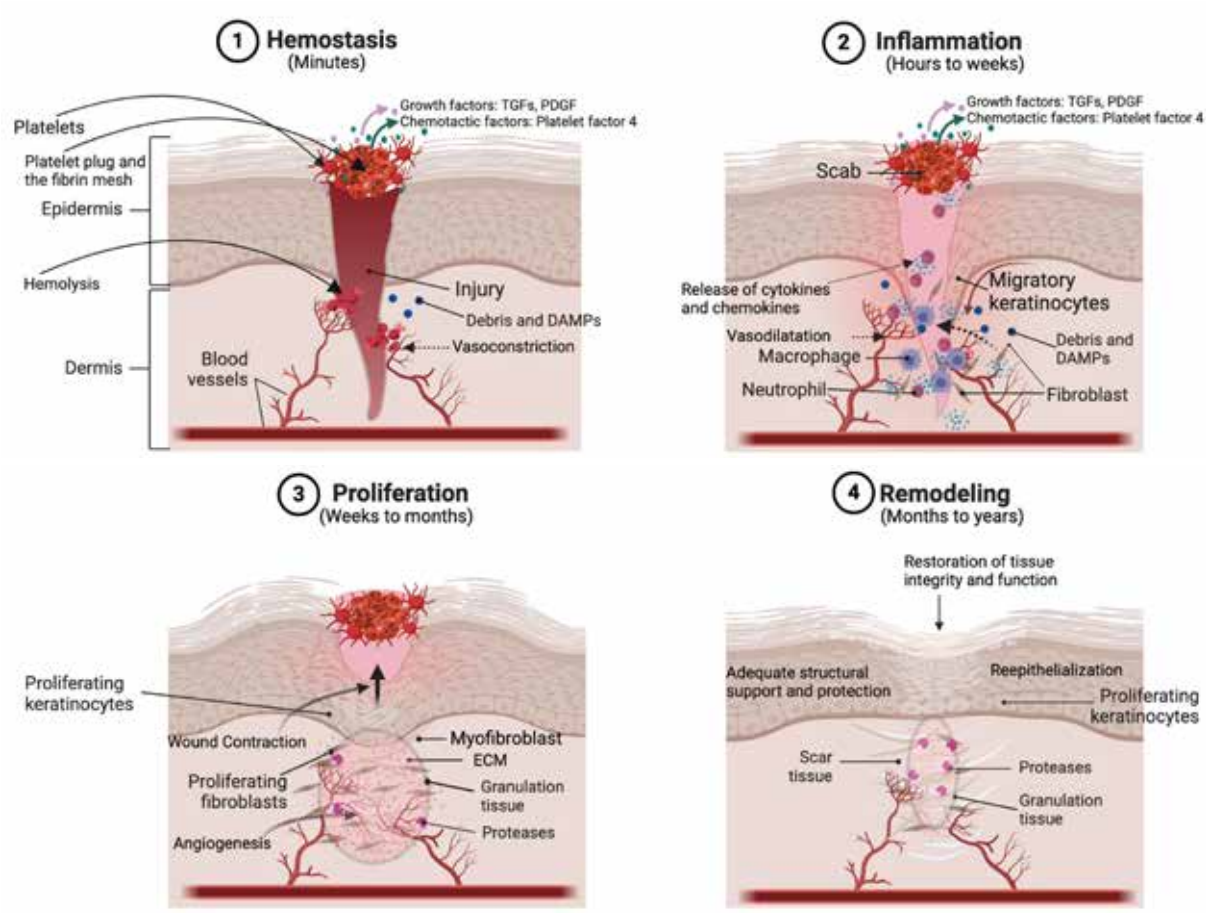

Figure 1. Wound repair physiology. Wound healing can be schematically divided into four sequential phases: Haemostasis, Inflammation, Proliferation and Remodelling (see text). These aspects largely coexist in the wound at the same time, with zones that are more advanced and zones that are still progressing, in a much more scattered pattern compared to a schematic description. In physiological conditions, the wound in its complexity gradually progresses toward re-epithelialisation, while in pathological states, the process is altered, either in its temporal organisation, with a delay or even a stop in its progression, or even in a spatial dimension, with atrophy/hypertrophy, fibrosis or necrosis eventually taking over and disrupting the healing process. Reproduced from Choundhari et al 2024[16] under CC BY 4.0.

The activation of platelets determines a modification of their conformation and the release of alpha granules containing bioactive molecules that support the coagulation process.[9] The secretion released by platelets also contains attractive chemokines that promote the recruitment of immune cells to the injury site, stimulate fibroblasts and keratinocytes thanks to growth factors.[4,9,10] At this point, the formation of a clot composed of fibrin, fibronectin, vitronectin and thrombospondin occurs, with a haemostatic, protective and reserve function for cytokines and growth factors.[11,12] The coagulation phase is interrupted by the inhibition of platelet aggregation by prostacyclin, the release of antithrombin III which acts on thrombin and the degradation of coagulation factors (V and VII) by activated protein C.[13] At the same time, platelet-derived growth factor (PDGF) promotes the proliferation of smooth muscle and endothelial cells and their progenitors at the site of damage in the blood vessel wall.[14,15]

The subsequent inflammatory phase represents a defensive phase against the possible contamination of the lesion by pathogenic agents and is composed of a series of events, which are triggered to recruit immune-competent cells and promote molecular interactions to eliminate non-viable tissue, foreign bodies and pathogenic agents.[4]

Necrotic cells, debris of the lesion and damaged tissues, as well as bacterial components, activate molecular signals respectively defined as DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) which recruit and activate mast cells, Langerhans cells, T-lymphocytes and macrophages.[17] Neutrophil leukocytes are recruited by the release of pro-inflammatory cytokines and chemokines [interleukin 1 (IL-1), tumour necrosis factor alpha (TNF-α)] and bacterial endotoxins [lipopolysaccharide (LPS)];[18,19] Neutrophils release reactive oxygen species (ROS), antimicrobial peptides, eicosanoids and proteolytic enzymes, phagocytose necrotic tissues and pathogens, and eliminate them through extracellular traps (DNA networks coated with antimicrobial peptides and cytotoxic histones).[20,21]

At the end of their action, neutrophils are eliminated from the lesion site by adhesion to the fibrin crust or by the action of macrophages (macrophagic efferocytosis) or through a process of apoptosis, necrosis or phagocytosis.[6,22] Macrophages are activated by pro-inflammatory molecules such as LPS and IFN-γ (interferon-gamma) and release ROS, inflammatory cytokines (IL-1, IL-6 and TNF-α) and growth factors (vascular endothelial growth factor (VEGF) and PDGF).[12] Subsequently, macrophages undergo a transition to an anti-inflammatory phenotype and release cytokines (IL-4, IL-10, IL-13), enzymes (arginase) and growth factors that promote re-epithelialisation, fibroplasia and angiogenesis.[6,12,23–25]

In the proliferative phase, keratocytes, fibroblasts, macrophages and endothelial cells are activated to form granulation connective tissue and initiate the processes of re-epithelialisation, neo-angiogenesis and immunomodulation.[5,6] The presence of hydrogen peroxide, pathogens, growth factors and cytokines, the variation in mechanical tension and the electrical gradients present in the lesional environment activate the keratinocytes present on the edges of the lesion, which polarise in an antero-posterior direction and migrate, triggering the re-epithelialisation process.[26,27] Keratinocyte migration is facilitated by the release of matrix-metalloproteinases (MMPs) and plasmin, that degrade fibrin inside the wound bed;[28] migration stops when keratinocytes from the opposite edges meet and form a thin epithelial layer.[6] Fibroblasts activity is triggered by molecules secreted by platelets, endothelial cells and macrophages, such as transforming growth factor (TGF-β) and PDGF which induce fibroblasts to deposit extracellular matrix (ECM) proteins and differentiate into myofibroblasts, useful for wound contraction.[29] Fibroblasts produce granulation tissue composed of fibronectin, immature collagen and proteoglycans, that supports cell migration and differentiation, stimulates the neo-angiogenesis and the deposition of new ECM.[6,30] The process of neo-angiogenesis is initiated by the hypoxic condition present in the lesional environment which determines the release of hypoxia-inducible factors, cyclooxygenase-2 and VEGF, which prevents the apoptosis of endothelial cells.[31,32] Macrophages intervene in the process of neo-angiogenesis by releasing metalloproteinases (MMPs) and chemotactic factors (TNF-α, VEGF and TGF-β), which facilitate the movement of endothelial cells;[33] furthermore, they phagocytise vessels in excess, modulating the angiogenic response.[34,35] The neovascularisation that is established following the neo angiogenesis process supports Schwann cells in the differentiation for the reconstruction of axons and the restoration of nerve function after lesion damage.[8]

The final phase of remodelling begins with the formation of a fibrin clot that is subsequently replaced by the

action of fibroblasts with hyaluronic acid, fibronectin and proteoglycans, which in turn facilitate the formation of collagen fibrils with a cross-linked structure.[36,37] The newly formed tissue is composed mainly of type III collagen, which over time is replaced by type I with a parallel bundle orientation, which increases the tensile strength of the scar.[38,39] Collagen degradation during the remodelling process is regulated by collagenases expressed by macrophages, fibroblasts and anti-inflammatory keratinocytes, while elastin is responsible for the synthesis of new fibres.[36] Myofibroblasts in granulation tissue adhere to each other (via desmosomes) and bind to matrix fibrils, solidifying it in a mechanism called wound contracture.[40] The peak response of the remodelling phase ends when macrophages, endothelial cells, and fibroblasts undergo apoptosis, leaving a scar as a result.[41]

Pathology of tissue repair

If, in the cascade of events that characterise the healing process of acute wounds, alterations occur that change the balance and progress of the process and compromise the healing of the wound, the wound becomes chronic.[6] In several circumstances, like diabetes, advanced age or genetic disorders, dysfunctional tissue repair occurs, compromising optimal wound healing and causing chronicity.[5,6] A lesion is defined as chronic when it does not heal within 12 weeks of its onset.[6,8] One factor that determines the chronicity of wounds is the senescence of mitotic cells, which lose their proliferative capacity and secrete pro-inflammatory cytokines and proteases that degrade tissue.[42,43] However, one of the major factors contributing to chronicity is inflammation, which causes continuous destruction of the injured tissue and often persists due to the presence of infections, caused by pathogenic microorganisms that aggregate in a polymeric matrix (biofilm) resistant to common antibiotics.[6,44] Chronic lesions contain Langerhans cells, proteases, neutrophils that produce cytotoxic extracellular traps, and pro-inflammatory macrophages. The latter are involved in ineffective efferocytosis of apoptotic cells and bacterial phagocytosis and have a poor ability to polarise towards an anti-inflammatory state[44–56]; proteases degrade dermal ECM components, growth factors, and cytokines.[57–59] Cellular damage in chronic lesions also extends to the process of re-epithelialisation and remodelling, particularly in diabetic lesions, which present hyperkeratotic margins and for which it has been observed in vitro that the presence of elevated β-catenin and c-myc is observed in the nucleus of keratinocytes, which hinder their migration.[60] Alterations in the expression of cell cycle markers and desmosome differentiation, a modification of growth factor receptor signalling, and the absence of hair follicles have also been observed.[61–63] Fibroblasts are not effective in deposition of ECM because they are not receptive to growth factors.[64–68] Another factor contributing to the chronicity of lesions in diabetic patients is the state of hyperglycaemia, which alters the functionality of leukocytes and determines the non-enzymatic glycation of ECM proteins and the production of advanced glycation end products (AGEs), which modify the structure of the dermis, produce ROS, and fuel the inflammatory state.[69–71] Elevated levels of ROS impair neo-angiogenesis by hindering the proliferation, migration and apoptosis of endothelial cells. Endothelial cell alteration is expressed with the reduction of nitric oxide production, which in turn determines an alteration of the functionality of the vascular barrier, increases platelet coagulation and alters the immune response. Furthermore, in the presence of diabetic pathology, a reduction of stromal cell-derived factor 1 (SDF-1) is observed, a factor that normally contributes to the recruitment of endothelial progenitor cells to the site of the lesion, and a modification in the expression of pattern recognition receptors, which trigger a reaction in the host, is also observed.[72–74]

The role of extracellular matrix (ECM)

In this context, the role of ECM has recently been redefined. New and more detailed insights have been gained from basic and translational studies, which changed perspectives of it from a scaffold into a proactive component of the healing process of chronic wounds with pro-regenerative properties[75] (Figure 2).

ECM has been demonstrated to have an immunomodulatory effect, being able to downregulate the pro-inflammatory version of macrophages, shifting their phenotype from M1 to M2, thus unblocking the reparative phase of tissue repair, 'frozen' into a low-intensity inflammatory state.[76,77]

A similar finding has been reported for a pro-angiogenic role of ECM: the production, differentiation and homing of progenitor into endothelial cells and the forming of neo-vessels has been observed in vitro and in vivo, where it was associated with a pro-reparative switch in chronic wound models.[78]

More recently, antibacterial properties have also been associated with ECM, which has been shown to derepress genes encoding for bactericidal peptides of the innate immune system.[79,80]

These achievements on the complex interaction between ECM and tissue repair, which established a link between the structure of ECM and its functions, have already been transferred from lab to bench, with a variety of new constructs that promise to change not only the way ECM could be inserted into a therapeutic program in a chronic wounded patient, but also to broaden the indication for their use, both for the different aetiologies and the timing.[82,83]

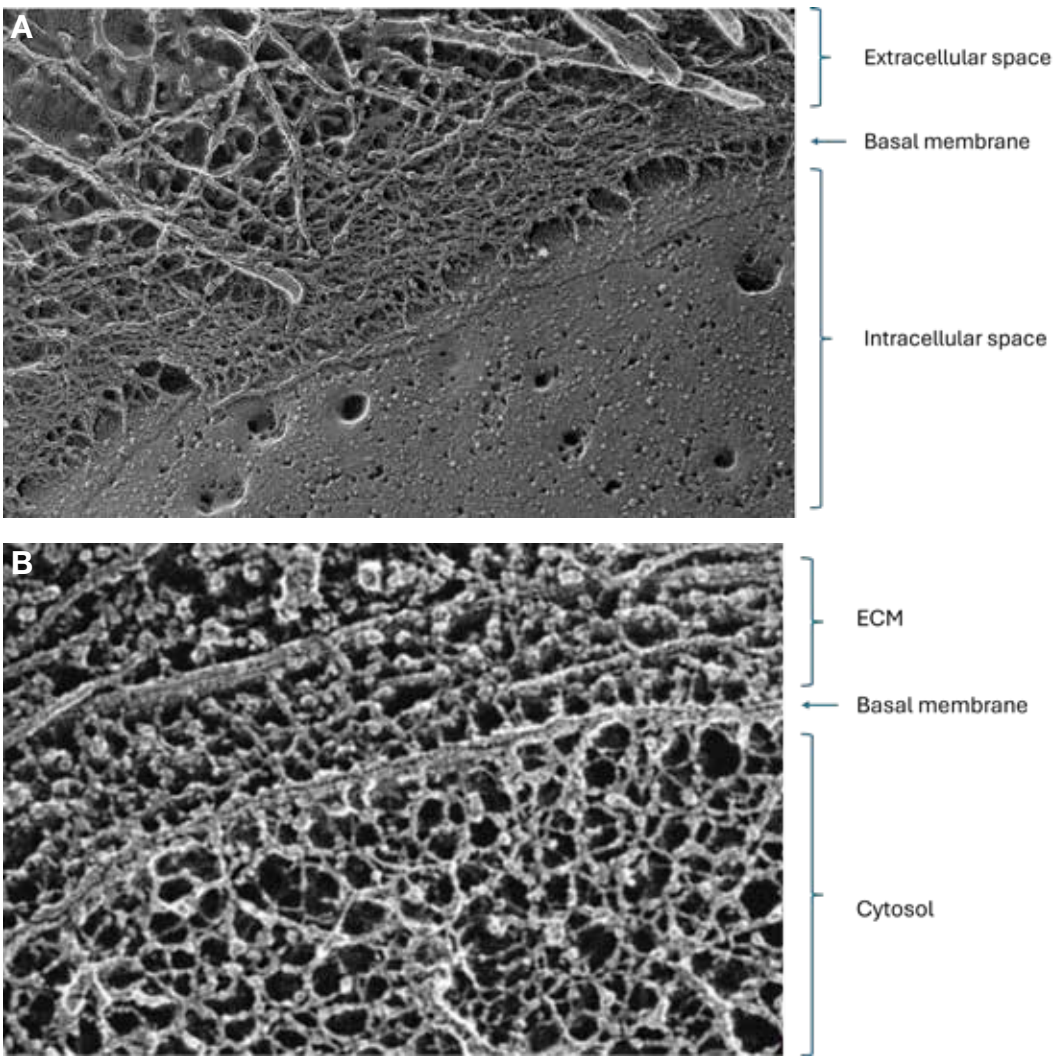

Figure 2. Extracellular matrix (ECM) structural features at a microscopic dimension reveal its intimate connection with cells and help in understanding its multidimensional role in the biology of wound healing. a) ECM is strictly interconnected with the basal membrane of the cells, such that a cleavage plane is not distinguishable. b) ECM and cytosol share the same structural architecture; this allows the mechanical stimuli to overcome the barrier of the basal membrane and to exert their effects also inside the cell and its nucleus, activating or repressing genes, thus changing the proteomic and the whole biology of the wound. Adapted from Leppert et al 2014[81] under CC BY 3.0.

3. Materials

Introduction

The development of wound healing products closely mirrors the trajectory of biomaterials science, evolving from inert synthetic dressings to biologically active, tissue-derived templates.[84] Early generations of products were predominantly made of polymers, such as polyurethane or silicone sheets, which provided mechanical protection and moisture balance but did not actively participate in tissue repair.[85]

As understanding of the ECM deepened, and its regenerative potential was demonstrated with the clinical use of allogeneic and xenogeneic grafts (such as cadaveric skin or porcine dermis), biomaterials research progressively shifted toward designs that could emulate its structural and biochemical functions.[86,87] In the late 1980s and early 1990s, processing techniques were refined to remove cellular components while preserving ECM architecture, culminating in the introduction of the first acellular human dermal matrix.[88] Shortly thereafter, a major milestone was reached with the development of the first hybrid matrix combining animal-derived collagen and glycosaminoglycans with engineered microarchitecture, including optimised porosity and pore size.[88] This product established the principle that engineered matrices could serve as bioactive templates, providing both mechanical stability and a permissive environment for cellular infiltration, neovascularisation and matrix remodelling, thus moving beyond the passive role of synthetic materials.

Building on these biological foundations, the 2000s saw the emergence of fully synthetic dermal matrices composed of degradable polymers, such as polylactic acid, polyglycolic acid and polycaprolactone.[89] These synthetic systems offered high reproducibility, tuneable degradation kinetics, and independence from donor-derived variability. In parallel, new generations of decellularised matrices were developed from non-dermal xenogeneic tissues and using processing methods that preserved not only structural components, such as collagen, elastin and glycosaminoglycans, but also other bioactive elements.[90] These refinements increased resistance to proteolytic degradation, extended persistence within the wound, and enhanced support for cell ingrowth. At the same time, engineered hybrids continued to advance, combining the reproducibility and mechanical control of synthetic polymers with the biological complexity of ECM-derived components.

With the advent of advanced biomaterial processing and modification technologies,[91] the field entered an era where previously unattainable levels of precision in scaffold design are possible. In parallel, the systematic collection of patient data and the development of new analytical tools will be decisive in fostering cross-pollination between biomaterials science and clinical practice, ultimately enabling wound-informed biomaterial design and therapeutic strategies. Looking ahead, a broader repertoire of dermal matrices is expected to emerge, but one principle is now firmly established: dermal matrices should not be conceived as passive templates, but as active biomaterials capable of modulating the wound microenvironment and orchestrating the cellular and molecular events that underpin high-quality tissue repair.

Biological matrices

Evidence published over the past five years provides a heterogeneous but increasingly informative picture of the role of decellularised tissue–derived matrices across wound types.

Human-derived dermal matrices show promise as active scaffolds that can enhance wound healing, particularly when combined with autografts in burn and trauma patients, where they improve closure rates and scar quality.[92] However, clinical efficacy in chronic wounds such as venous leg ulcers remains uncertain. A recent randomised controlled trial failed to demonstrate benefit,[93] although the small sample size (71 patients) and early termination prevent definitive conclusions. Preclinical data further support human-derived dermal matrices' bioactivity, demonstrating accelerated re-epithelialisation, neovascularisation and matrix remodelling,[94] consistent with earlier clinical observations in diabetic foot ulcers.

Among other dermal matrices, foetal bovine acellular dermal matrices (FBADMs) have emerged as effective options for diabetic foot ulcers (DFUs). In the randomised controlled trial of 207 patients (103 assigned to FBADM, 79 completed the study), healing rates were significantly higher in the FBADM group, with nearly half of ulcers closed by 12 weeks, and many requiring only a single application.[95] Supportive retrospective evidence from 256 patients demonstrated that FBADM use within multidisciplinary wound care algorithms was associated with reduced minor and major amputation rates, improved limb salvage and fewer hospital readmissions.[96] In addition, a prospective series of 20 high-risk patients (older age, high body mass index, diabetic population) reported rapid and durable wound closure, with an 83% mean wound reduction by week 9 and sustained closure at 6 months.[97]

Biological matrices derived from non-dermal tissues have also been investigated as alternatives to traditional dermal-based products. These products provide ECM structures that support cellular infiltration, modulate protease activity, and promote tissue remodelling, though their efficacy appears to depend on both tissue source and processing methodology. Ovine forestomach matrix (OFM) demonstrated favourable outcomes in a prospective study of 29 patients with 33 chronic wounds of varying aetiologies.[98] OFM was applied every 3–7 days, achieving ≥50% wound reduction in 64% of cases at 4 weeks and complete closure in 73% by 12 weeks, with no adverse events. Mechanistic insights were provided by a comparative preclinical study showing that OFM degraded rapidly (less than 3h) in a chronic wound model, while porcine small intestinal submucosa matrices persisted more than 7 days and continued to support fibroblast activity.[99] This suggests collagen crosslinking of the porcine small intestinal submucosa matrices critically influence efficacy. Urinary bladder matrix (UBM), another xenogeneic scaffold, has shown particular promise in complex wounds. Case reports described successful closure of a cerebrospinal fluid fistula and a deep postoperative infection using porcine UBM.[100] A larger retrospective case series of 21 high-risk patients confirmed these findings. UBM facilitated robust soft tissue remodelling, with all wounds achieving either complete re-epithelialisation or successful preparation for grafting or flap coverage.[101] These results highlight UBM's ability to provide a stable, vascularised wound bed in cases where flap surgery is contraindicated. Other non-dermal matrices include a hepatic-derived porcine liver matrix, tested in a multicentre prospective trial of 53 patients with hard-to-heal DFUs. Of the 38 patients who completed the study, 57.9% achieved complete closure within 12 weeks, with a mean closure time of 8.1 weeks, typically after a single application.[102] Human-derived adipose matrix has shown potential in niche applications such as recurrent pressure injuries. In one case study, injection of adipose ECM into a trochanteric ulcer provided subcutaneous cushioning, resulting in durable closure and no recurrence after 24 months.[103]

In the last few years, a growing body of evidence supports the efficacy of fish skin grafts (FSGs), a distinct class of xenograft rich in omega-3 polyunsaturated fatty acids, in the treatment of chronic and complex wounds, particularly DFUs. Data from a randomised trial of 49 patients with treatment-resistant superficial DFUs showed 67% of FSG-treated ulcers fully closed compared with 32% in the standard of care group at 12 weeks, with significantly greater wound area reduction at 6 weeks (72.8% vs 41.2%).[104] Interim results from a larger randomised controlled trial of 94 patients confirmed superior outcomes: 63% closure with FSG versus 31.3% with standard of care at 12 weeks, with a median of six applications required and mean healing time was 7 weeks in both groups.[105] The final analysis of 102 patients showed 56.9% closure in the FSG group versus 31.4% in standard of care, with significantly greater wound area reduction (86.3% vs 64%).[97] Beyond DFUs, case reports extend FSG utility to complex wounds: one contaminated necrotising wound achieved complete healing within 28 days[106], while an upper extremity wound with exposed tendons and nerve was successfully reconstructed with full functional recovery.[107]

A large retrospective cohort study involving more than 34,000 patients with DFUs reported comparative outcomes between a porcine placental matrix and a pooled group that included porcine small intestinal submucosa, fish skin xenografts, FBADMs, several human acellular dermal matrices, and amniotic/umbilical tissue–derived matrices. Patients treated with porcine placental matrix were found to have fewer outpatient amputations, lower bacteraemia rates, and reduced hospital utilisation.[108] However, because all non–placental matrices were grouped together as a single comparator, this analysis does not provide a true head-to-head evaluation of efficacy between specific matrix types. The heterogeneity of the comparator group and the

retrospective design represent major limitations, meaning the findings should be interpreted with caution.

Overall, although most of the available studies are small trials, retrospective cohorts, or case series, the evidence suggests that certain biological matrices may offer advantages in specific chronic wound settings. FBADMs and FSGs have shown particularly encouraging results in DFUs, while for complex surgical or contaminated wounds, as well as pressure and venous leg ulcers, further research is still needed.

Bioengineered matrices

Hybrid

In contrast to tissue-decellularised biological matrices, hybrid artificial matrices are prepared from tissue ECM-derived components and engineered to consistent specifications, such as composition, porosity and degradation or resorption profile.

Evidence suggests the benefit of some hybrid dermal matrices in improving the healing of chronic wounds. A bovine collagen-chondroitin-6-sulfate matrix not only showed a role in reducing postoperative infection rates and shortening healing time in DFUs, but also in activating key molecular pathways of tissue regeneration, including upregulation of collagen I, collagen III, and elastin synthesis.[109] Similarly, a bovine collagen-laminin matrix additionally impregnated with resveratrol-loaded hyaluronic acid and dipalmitoylphosphatidylcholine-based microparticles, was evaluated in an open, prospective, comparative clinical study of 48 patients with Wagner grade 1–2 DFUs.[110] After four weeks, wound closure reached 57.8% in the treatment group versus 26.6% in the standard of care group, with significant improvements in oxidative stress biomarkers. A pre-clinical study in a sheep wound model also showed the benefits of a porcine atelocollagen-gelatine matrix in exudate management and tissue regeneration, despite the lack of differences in the rate of healing compared to conventional methods.[111] These findings are consistent with clinical data where hybrid dermal templates were used to improve the efficacy of other approaches. For example, in 30 patients with chronic leg ulcers, prospective multicentre observational data demonstrated that combining a bovine collagen-chondroitin-6-sulfate matrix with skin grafting significantly accelerated wound closure, achieving a 54.5% wound surface reduction at three months after surgery.[112] In another example, in a retrospective review of six patients (mean age 61.3 years) with chronic vascular leg ulcers, application of a porcine atelocollagen-gelatine-based matrix led to satisfactory granulation within 10 days and complete wound healing after an average of 14 weeks.[113] In a case series of 12 patients (nine tumour resections and three chronic ulcers), the same type of matrix promoted dermal regeneration within approximately three weeks, with nearly all wounds becoming ready for grafting.[114] These findings were further extended to oncologic heel defects, where in four patients a staged approach combining the porcine atelocollagen-gelatine-based matrix with negative pressure wound therapy enabled reliable healing, acceptable cosmetic outcomes, and no tumour recurrence at 12 months.[115]

A retrospective study (122 included out of 453 patients) comparing three hybrid dermal matrices in the management of critical lower limb wounds showed that the matrices combining bovine collagen with or without shark chondroitin-6-sulfate consistently demonstrated the highest rates of skin graft viability and graft take[116] (Figure 3). In contrast, the matrix composed of porcine atelocollagen-gelatine was associated with faster induction of secondary healing in acute wounds. Despite this, no differences were observed among the three matrices in terms of wound healing 30 days after the skin graft or following removal of the external silicon layer.

The addition of biologically active components appears to improve the performance of these matrices. Clinically, the combination of porcine atelocollagen/gelatine matrix with platelet-rich plasma (PRP) accelerated the healing of refractory wounds (16 patients). While the overall rate of complete closure was not significantly different (87.5% vs 75.0%), the addition of PRP significantly shortened healing time, accelerated vascularisation, improved infection control, and reduced hospitalisation, highlighting its responsiveness to biological augmentation.[117] Pre-clinical data has shown the same trend of enhanced wound healing with the b Fibroblast Growth Factor (FGF)-impregnated matrices relative to the unmodified ones.[118] However, the degree of improvement depends on the intrinsic properties of the matrix. The porcine atelocollagen-gelatine matrix supported extensive fibroblast and capillary infiltration throughout the wound bed, whereas the matrix with only bovine atelocollagen promoted neovascularisation primarily confined to the wound base. By contrast, the

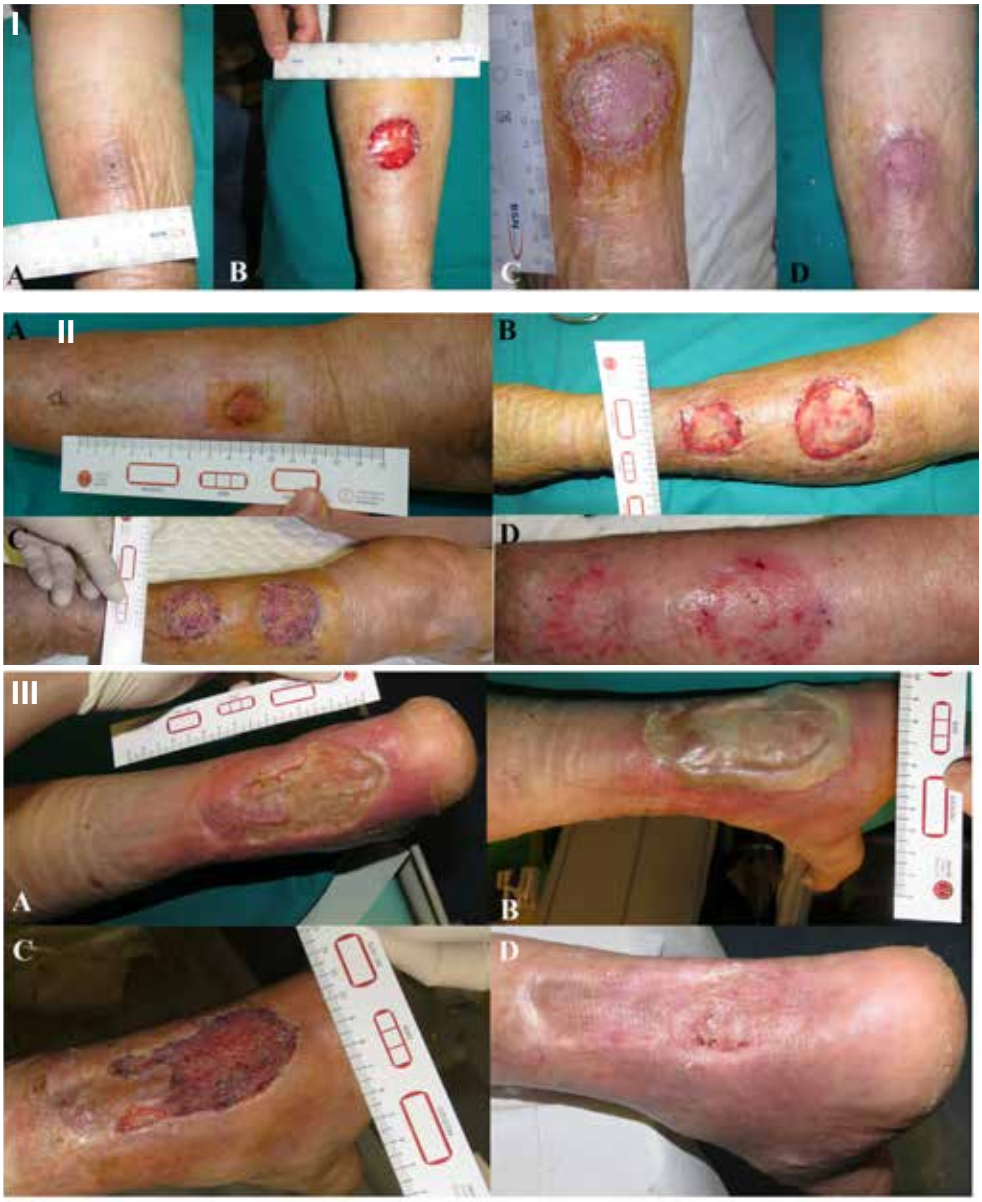

Figure 3. Representative wounds treated with hybrid dermal matrices. Wounds treated with: (I) bovine collagen plus chondroitin-6-sulfate matrix; (II) bovine collagen matrix or (III) porcine atelocollagen-gelatine. For each matrix the illustrations show: (A) the initial wound appearance; (B) the dermal substitute applying; (C) the skin graft take; and (D) and the final closure result at 30 days. Adapted from Cottone et al 2021[116] under CC BY 4.0.

collagen–glycosaminoglycan matrix, despite showing the highest bFGF binding capacity, exhibited only limited cellular infiltration. Taken together, the evidence indicates that although there seems to be a benefit in combining hybrid matrices with bioactive components, most of the data remain pre-clinical.

Synthetic

Unlike biological or hybrid matrices, fully synthetic dermal matrices are engineered scaffolds composed of degradable polymers to offer reproducibility, tuneable degradation kinetics, and independence from donor-derived variability. Recent clinical studies provide growing evidence that these materials are effective in the management of chronic wounds. In a small case series (with 4 cases), a synthetic electrospun ECM made of polyglycolic acid and poly(L-lactide-co-caprolactone) promoted more than 80% diabetic foot wound size reduction after four applications and over 95% closure by six applications when used in combination with amniotic allografts.[119] This study, although limited to a case series, further suggests that synthetic ECMs can synergise with biologically active products. In a prospective randomised controlled trial with 30 participants, DFUs treated with matrices composed of biodegradable polylactide, trimethylene carbonate, and ε-caprolactone achieved complete closure in a median of 9.3 weeks, significantly faster than the 14.8 weeks observed with a bovine collagen/calcium alginate matrix.[120] A larger retrospective review (with 131 wounds) extended these findings, showing that polylactide, trimethylene carbonate, and ε-caprolactone matrices reduced healing times for both diabetic foot and venous leg ulcers compared with collagen dressings and FSGs, achieving 55% and 26% higher closure rates by 12 weeks, respectively.[121]

A synthetic fibre matrix composed of polyglycolic-co-L-lactic acid and polydioxanone, designed to support cellular infiltration, neovascularisation and granulation tissue formation, while minimising the risk of immunogenicity associated with biologic products, has also been investigated. In a retrospective case series of 20 patients with 23 lower extremity wounds—including DFUs, venous leg ulcers, and transmetatarsal amputation sites—

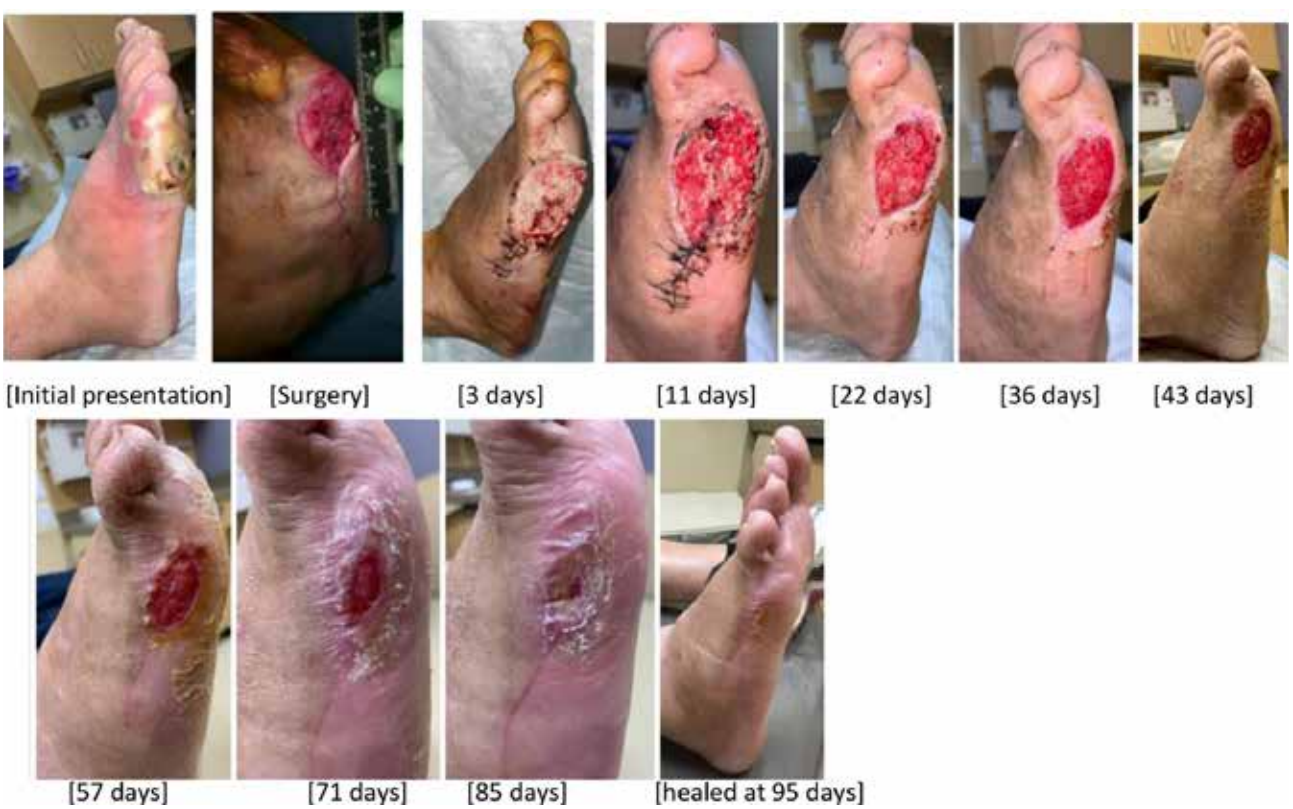

Figure 4. Healing progression of a partial ray amputation wound treated with the synthetic polyglycolic-co-L-lactic acid and polydioxanone matrix. Reproduced from Barton and Abicht 2021[122] under CC BY NC ND 4.0.

complete healing was achieved in 96% of wounds (22/23), with a mean time to closure of 96 days[122] (Figure 4). Most wounds required only a single application of the matrix, and minimal scarring was observed. Evidence for DFUs was further strengthened by a prospective multicentre study enrolling 24 patients.[123] At 12 weeks, 75% (18/24) of ulcers had completely healed, with an average closure time of 6.4 weeks. Mean wound area reduction reached 96%±10%, outcomes considered superior to standard care. Other lower extremity wounds have also been treated with polyglycolic-co-L-lactic acid and polydioxanone matrix. In a retrospective series of nine patients with complex operative wounds of the leg, seven achieved complete closure (78%), with a mean time to healing of 136 days and good scar quality.[124] For more challenging presentations, a case report described successful use of polyglycolic-co-L-lactic acid and polydioxanone matrix in a sacral pressure ulcer of >16 years' duration, complicated by exposed spinal segments and peritoneum.[125] Nine applications over 11 weeks led to new epithelial tissue formation, tissue coverage over the exposed bone, infection management, and wound exudate reduction, ultimately allowing discharge without complications.[125] Histological insights from a biopsy at the time of subsequent below-knee amputation (for posttraumatic arthritis rather than wound failure) were provided by a case study of a chronic calcaneal wound in a 16-year-old patient, refractory to multiple prior interventions.[126] Application of polyglycolic-co-L-lactic acid and polydioxanone promoted granulation and epithelialisation, revealing mature collagen deposition, angiogenesis, and absence of bacterial colonisation or foreign-body reaction.

A prospective multicentre, single-arm clinical trial evaluated the efficacy and safety of a silk elastin sponge, a recombinant protein-based biomaterial designed to form an irreversible gel upon contact with the wound.[127] The study, enrolling 25 patients, including 20 with chronic wounds and five with acute wounds, showed that by day 14, 90% of patients with chronic wounds demonstrated adequate wound bed preparation. Overall, 24 of 25 patients completed the study, with one discontinuation due to local infection. No major safety concerns were reported.

Together, these studies suggest that synthetic matrices are evolving beyond their original role as inert scaffolds, demonstrating the capacity to actively support wound healing and, in some cases, to serve as platforms for combination approaches with biologically active products. However, while the short- to mid-term efficacy data are encouraging, the overall evidence base remains smaller than that for biologic or hybrid matrices, and larger, long-term comparative studies will be needed to consolidate their role in chronic wound care. Recent pre-clinical studies are further highlighting key differences in the effect of different dermal matrices, confirming previous data or generating valuable knowledge to support future clinical studies. A bovine dermal collagen matrix demonstrated superior structural performance compared to a collagen–glycosaminoglycan scaffold and a FSG, enabling rapid cellular infiltration, early vascularisation, and highly consistent autograft take.[128] In another study, a hybrid matrix composed of bovine collagen and elastin proved more effective than a fully synthetic biodegradable polyurethane scaffold in attracting fibroblasts and macrophages and in restoring a balanced secretion of inflammatory mediators, underscoring its immunomodulatory capacity.[129] Together, these findings suggest that optimal clinical outcomes in chronic wounds may require matrices that combine durable structural scaffolding with active immunoregulatory functions.

Bioengineered advanced scaffolds

Materials already used in dermal matrices, or closely related derivatives, remain under active investigation. Collagen, from mammalian or alternative marine sources, continues to serve as the structural backbone of many scaffolds, with gelatine, its derivative, also widely explored.[130–132] These biopolymers are frequently combined with additional components such as chitosan–glucan complexes to improve structural and biological properties.[133] Other established polymers in wound-care products, like alginate, have been reinforced with ultralong hydroxyapatite nanowires to improve mechanical resilience and enable ion release.[134] Such approaches build on the extensive clinical experience with dermal matrices, but it remains unclear how these modified or hybrid versions can surpass or complement the performance of current products.

Parallel efforts explore hybrid scaffolds and unconventional biomaterials that combine natural and synthetic polymers, and functional additives. Natural silk sericin-based hydrogels crosslinked enzymatically have been investigated for their antioxidant activity,[135] while polysaccharide-based hydrogels such as glucomannan, have been explored for their ability to mimic extracellular matrix features.[136] Hybrid constructs combining polycaprolactone nanofibers with

gelatine-based layers have been proposed to simultaneously provide structural support and moisture retention.[137] Similarly, bilayer structures integrating a chitosan-gelatine hydrogel base with peptide-loaded poly(lactic-co-glycolic acid) nanoparticles and a top nanofiber layer functionalised with antimicrobial peptides, combine natural and synthetic materials and bioactive compounds to simultaneously address antimicrobial protection and stimulate skin cell proliferation.[138]

These studies reflect the growing interest in combining multiple materials to achieve multifunctional scaffolds. However, despite these advances, the rationale for material selection often remains grounded in broad attributes such as biocompatibility, antibacterial capacity, or ECM mimicry, without detailed mechanistic evidence.

Advanced drug delivery strategies

In addition to providing structural support, biomaterial platforms have been designed to function as active delivery vehicles for therapeutic molecules. Growth factors, antibodies and small molecules remain attractive payloads to accelerate wound repair.[139–142] However, major challenges persist in preserving their stability and bioactivity within the proteolytic wound environment and in sustaining their therapeutic effect over clinically relevant time frames. To address these challenges, several strategies have been explored. One approach focuses on shielding and stabilising molecules within the matrix; polyphenol-activated protein coatings have been developed to preserve lysozyme structure and activity while co-embedding it with other bioactive molecules in a nanocomposite, thereby shielding them from degradation.[143] Similarly, chitosan hydrogels were functionalised with heparin or its derivatives, exploiting their ability to bind and stabilise both endogenous and exogenous growth factors, protecting them from proteolysis and extending their bioactivity.[144] Another strategy relies on tethering bioactive molecules to the matrix to achieve sustained local presentation. For instance, pro-angiogenic peptides with collagen-binding domains were tethered to acellular dermal matrices, where they remain sequestered until gradual enzymatic remodelling triggers their release.[145] Gene-activated matrices, composed of VEGF-encoding polyplexes retained within a hyaluronic acid–collagen network through collagen-mimetic peptides, host cells to internalise the genetic material and produce VEGF locally, sustaining growth factor signalling over time.[146] Other systems achieve bioactivity through the material itself rather than delivered molecules; PDGF-mimetic peptides self-assembled into fibril-rich hydrogels that present receptor-binding epitopes, enable the directly engaging PDGF receptors on host cells to trigger sustained signalling.[147] An innovative approach has explored incorporating bioactive molecules during material synthesis, thereby avoiding additional post-processing modifications. In this strategy, transgenic silkworm strains were engineered to biosynthesise epidermal growth factor (EGF) and PDGF B-chain homodimer (PDGF-BB) enriched silk fibres, which are processed into sericin hydrogels that release both growth factors in a sustained and synergistic manner[148] (Figure 5 and Figure 6).

Collectively, these approaches illustrate a spectrum of relevant strategies aimed at overcoming the challenges associated with active therapeutic platforms, yet further advances are needed to ensure precise spatiotemporal control and long-term stability.

Intrinsically bioactive materials

The intrinsic chemistry and architecture of a material can be exploited to directly target key pathological processes, enabling predictable, mechanism-driven wound repair. Moreover, certain biomaterials can be deliberately engineered so that their inherent physicochemical and biochemical properties themselves elicit therapeutic effects, eliminating the need for supplementary drugs or growth factors. High-sulphated hyaluronan has been proposed to exert strong immunoregulatory effects by modulating macrophage phenotype when released from hyaluronan/collagen hydrogels[149] (Figure 7). Similarly, natural snail mucus gel, which consists of a network of positively charged protein and polyanionic glycosaminoglycans, has been investigated for its ability to regulate wound inflammation.[150] Hydrogels combining snail glycosaminoglycan with methacrylated gelatine harness the glycosaminoglycan's cytokine binding capacity to sequester proinflammatory mediators, while the gelatine network mimics ECM proteins to support cell adhesion and proliferation.[151]

Mechanism-targeted and precision-medicine biomaterials designs

An increasing number of biomaterial-based therapeutic designs are guided by detailed insights into the molecular and cellular abnormalities underlying chronic wound pathology, particularly in diabetic ulcers, enabling the development of materials tailored to directly target these

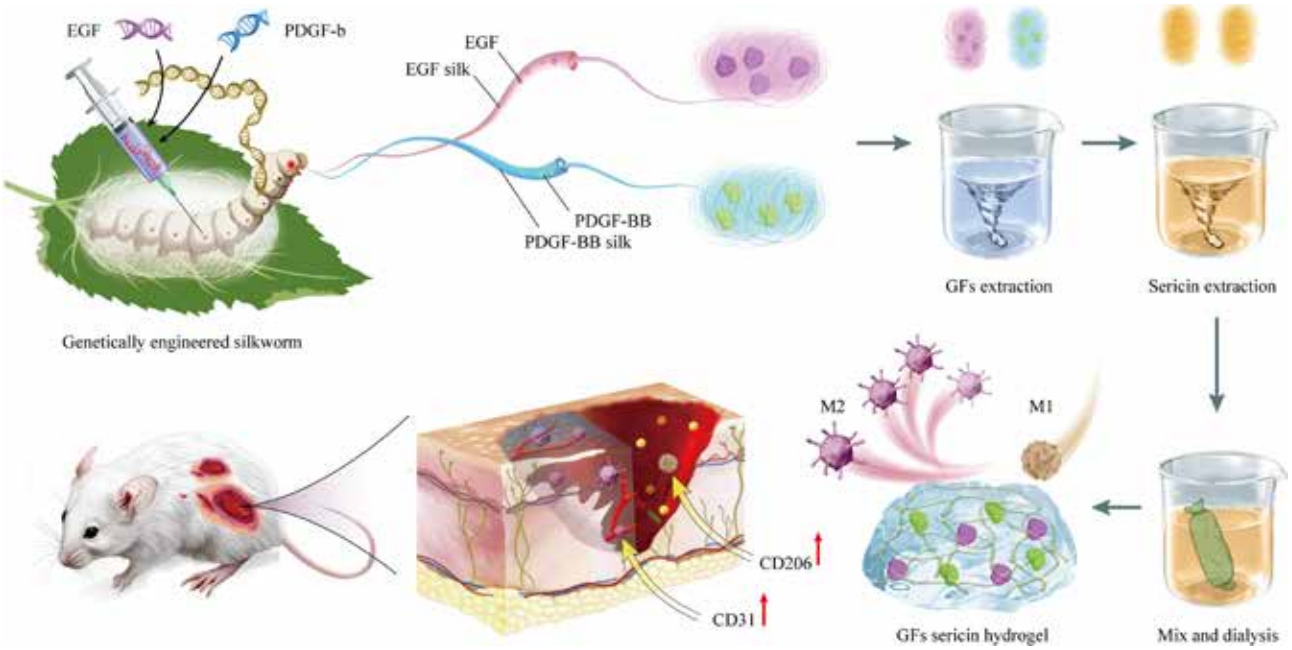

Figure 5. Schematic of genetic engineering of transgenic silkworms for synthesising EGF and PDGF-BB silk fibres, processed into sericin hydrogels for dual growth factor (GF) delivery in diabetic mice with non-healing wounds. Reproduced from Deng et al. 2025[148] under CC BY NC ND 4.0.

mechanisms. One example is the targeting of grancalcin (GCA), a pro-inflammatory protein elevated in diabetic ulcer tissue that impairs angiogenesis by binding to transient receptor potential melastatin 8 (TRPM8) and suppressing its downstream signalling. To counter this, a gelatine methacrylamide hydrogel was engineered for the sustained release of a GCA-neutralising antibody, providing prolonged local inhibition of GCA activity and directly addressing the angiogenic deficit in diabetic wounds.[152] Another well characterised pathological driver of DFUs is the accumulation of advanced glycation end products (AGEs), which activate RAGE-mediated proinflammatory signalling and hinder the proliferative phase of healing.[153] To address this, a recombinant fusion protein comprising the RAGE binding domain (vRAGE) linked to elastin-like polypeptides (ELPs) was developed as a competitive inhibitor.[154] Building on this approach, a dual-protein coacervate combining vRAGE-ELP with SDF1-ELP was engineered to simultaneously block AGE-RAGE signalling and promote revascularisation, thereby uniting inflammation resolution with angiogenesis stimulation in a single treatment[155] (Figure 8). Similarly, MMP9, a protease with a high capacity to degrade collagen, has been identified as a key contributor to impaired healing in diabetic wounds.[156] One of its principal regulatory mechanisms is N6-methyladenosine (m(6)A) RNA methylation, which involves the demethylase fat mass and obesity-associated protein (FTO); in diabetic foot ulcers, m(6)A levels are markedly reduced while FTO expression is elevated. To address this imbalance, a nanocolloidal hydrogel loaded with an FTO inhibitor was developed to restore m(6)A methylation on MMP9 transcripts, thereby normalising its expression and promoting proper progression of the healing process.[157] The skin of patients with diabetic ulcers is also characterised by low levels of cortistatin (CST), prompting the design of a strategy to restore its activity. While not yet incorporated into a matrix, CST-loaded pDMA-pEPEMA nanoparticles were developed to release CST rapidly in the acidic microenvironment of chronic wounds.[158]

In summary, these strategies exemplify a precision-medicine approach to wound biomaterials: each is explicitly designed around a validated pathological mechanism and incorporates delivery systems or material properties that directly counteract these defects to restore the healing cascade. However, translating these targeted interventions into routine clinical use will require overcoming challenges, such as ensuring long-term stability and bioactivity in complex wound environments.

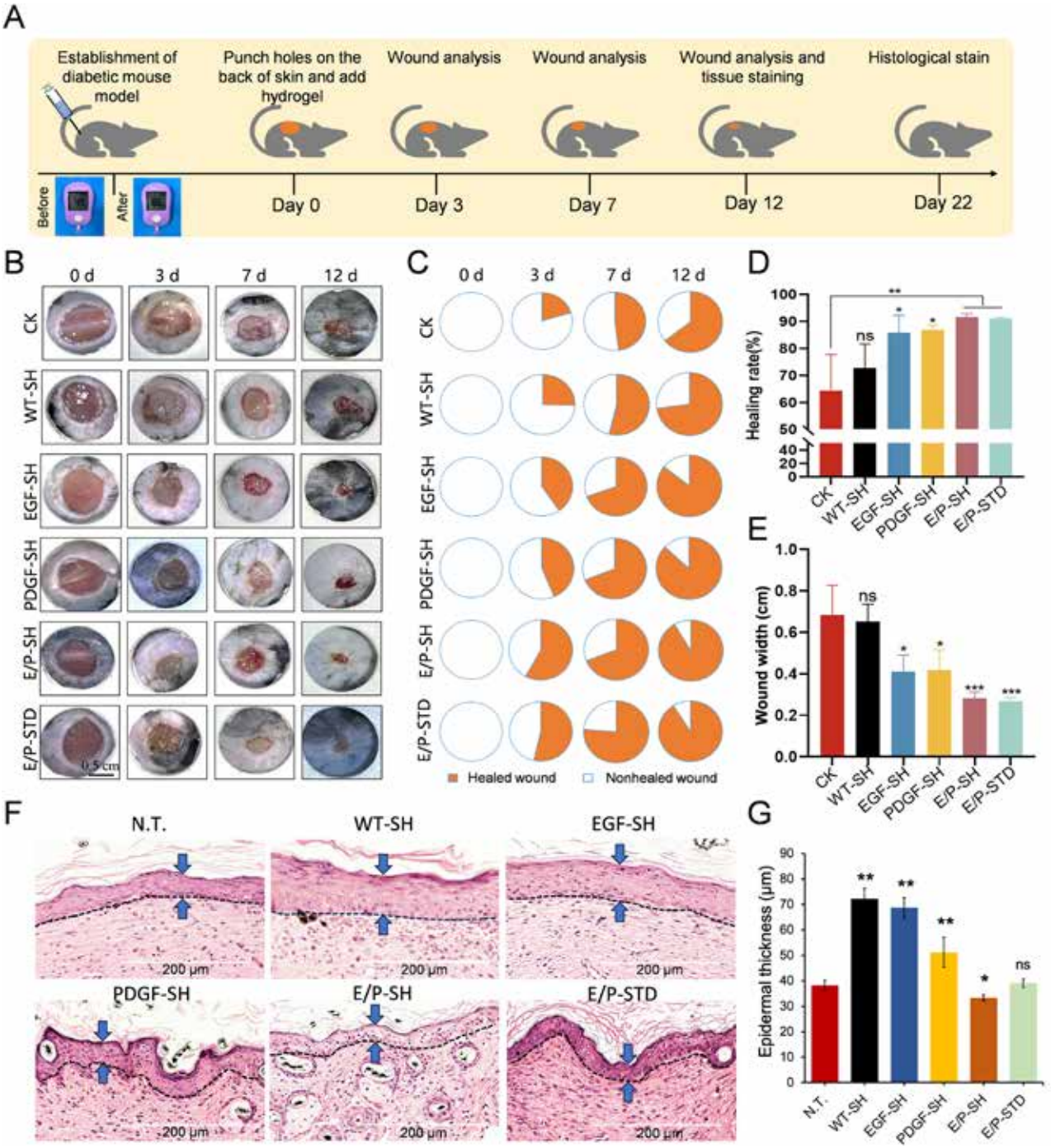

Figure 6. Full-thickness wound healing in diabetic mice was promoted by the growth factors containing sericin hydrogels.
a) Timeline for establishing a diabetic mouse model for the assessment of wound healing after application of growth factors sericin hydrogels.
b-c) Representative images from the wounds of the different treatment groups at days 0, 3, 7, and 12.
c-e) Evaluation of wound healing areas and wound widths at day 12 in the different treatment groups.
f) Histology through haematoxylin and eosin staining of fully healed tissue on day 22.
g) Epidermal thickness of completely healed full-thickness diabetic mouse wounds treated with the hydrogels: wild-type sericin hydrogel (WT-SH); EGF-sericin hydrogel (EGF-SH); PDGF-sericin hydrogel (PDGF-SH); and EGF/PDGF-sericin hydrogel (E/P-SH).
Reproduced from Deng et al 2025[148] under CC BY NC ND 4.0.

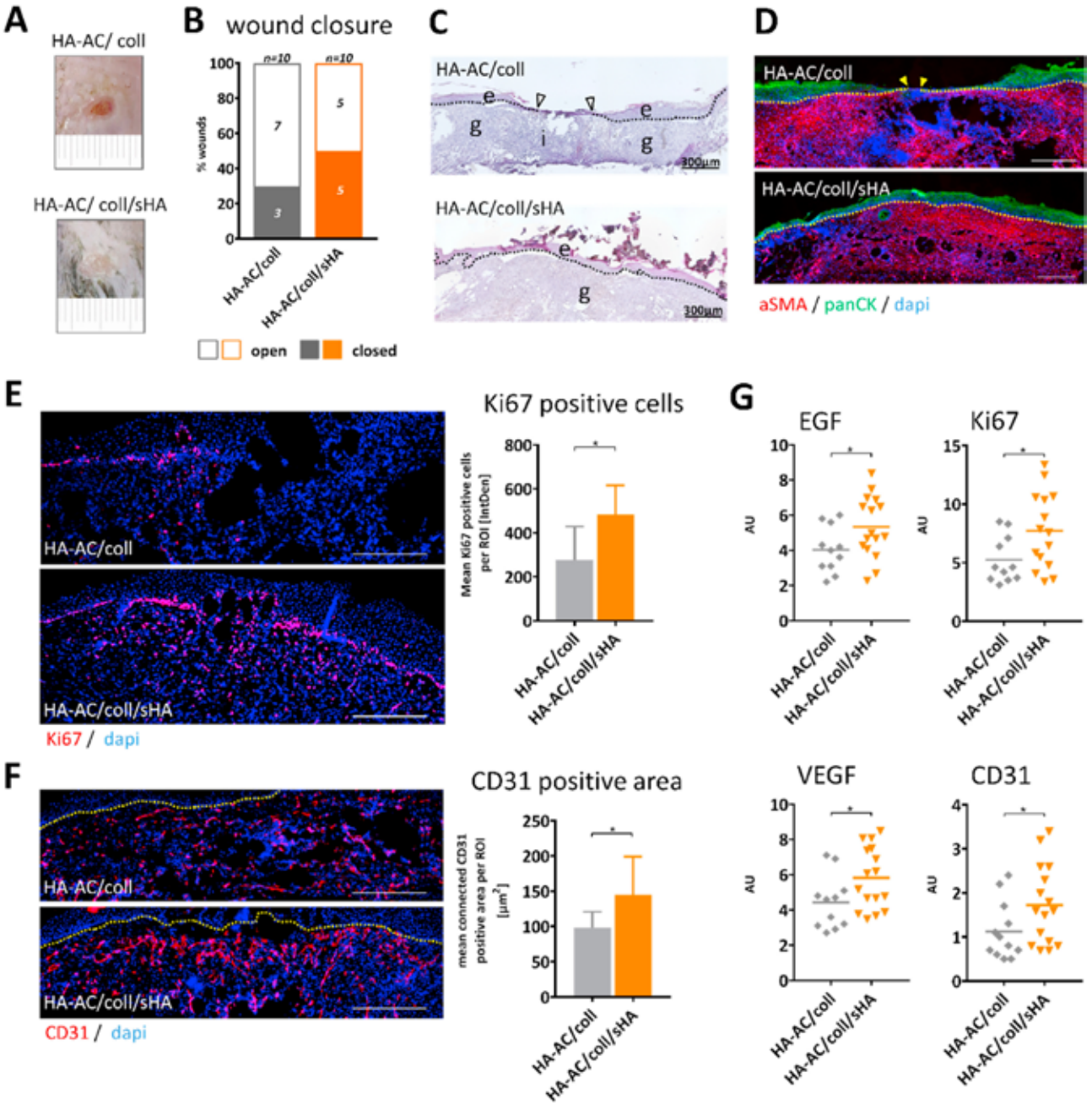

Figure 7. Hydrogels releasing sHA accelerate re-epithelialisation, tissue formation and angiogenesis in wounds in diabetic db/db mice. a) Macroscopic appearance of wounds. b) Quantification of wound closure. c) H&E staining of wound sections. d) Immunofluorescence staining of aSMA and panCK in wound sections visualising granulation tissue and neoepithelium, respectively. e) Immunofluorescence staining of Ki67 in wound sections visualising proliferating cells and quantification of Ki67+ cells. Epidermal layer and granulation tissue were defined as region of interest (ROI).
f) Immunofluorescence staining of endothelial cell marker CD31 in wound sections visualising newly formed vessels and quantification of connected CD31+ area. Granulation tissue was defined as ROI.
g) Gene expression relative to reference gene GAPDH of angiogenic markers (VEGF/CD31) and pro-regenerative tissue markers (EGF/Ki67) in wound tissue. g=granulation tissue; e=epidermis; i=immune cell infiltrate. Arrowhead marks epithelial tip. Dotted line marks border between epidermis and dermis. Scale bars: 300µm. Each symbol represents one wound. Unpaired t-test: *p≤0.05. AU=arbitrary unit. IntDen=integrated density. Reproduced from Hauck et al 2021[149] under CC BY-NC-ND 4.0.

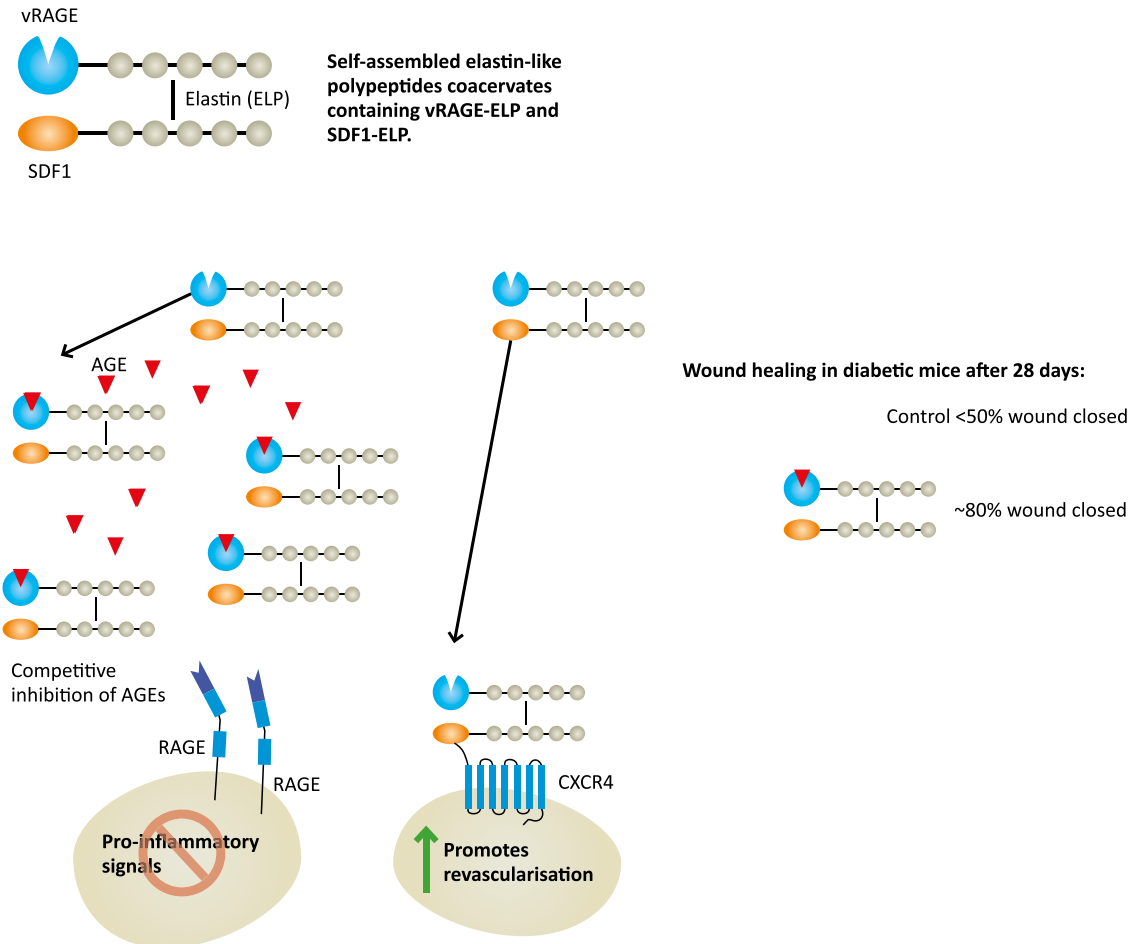

Figure 8. Dual-protein coacervate to block AGE-RAGE signalling. A dual-protein coacervate combining vRAGE-ELP with SDF1-ELP was engineered to simultaneously block AGE-RAGE signalling and promote revascularisation.[155]

Redox and oxygen-modulating strategies

Chronic wounds are characterised by a persistent imbalance between oxidative stress and oxygen availability, in which sustained overproduction of reactive oxygen species (ROS) occurs alongside inadequate tissue oxygenation. Recognising that redox homeostasis and oxygen supply are closely interlinked determinants of healing quality,[159] a wide range of biomaterial based designs have increasingly integrated antioxidant systems to neutralise excess ROS. This has been achieved primarily through the delivery of radical-scavenging compounds or the development of stimuli-responsive matrices capable of switching from ROS generation to scavenging.[160–162]

Building on the same principle of control of wound microenvironments, other systems harness oxygen related signalling molecules, particularly nitric oxide (NO), as therapeutic agents. In one approach, stable NO-containing microbubbles were incorporated into a poloxamer 407 solution that transitions into a hydrogel at body temperature after being sprayed onto the wound.[163] In another, wound ROS are used to trigger the release of the anti-inflammatory doxycycline hydrochloride from a ROS-responsive polyurethane nanofibrous membrane.[164] A combinatory strategy co-delivers the AGE-inhibiting rosiglitazone and the NO donating S-nitroso glutathione from nanoparticle/hydrogel composites, simultaneously blocking AGE-mediated damage, replenishing NO, and reducing oxidative stress.[165] Another dual release design employs a gel that alternately produces NO and O_2 to relieve inflammation and hypoxia, using *Weissella cibaria* (a probiotic bacterium) as the NO donor and *Chlorella vulgaris* (a microalga) as the oxygen donor[166] (Figure 9).

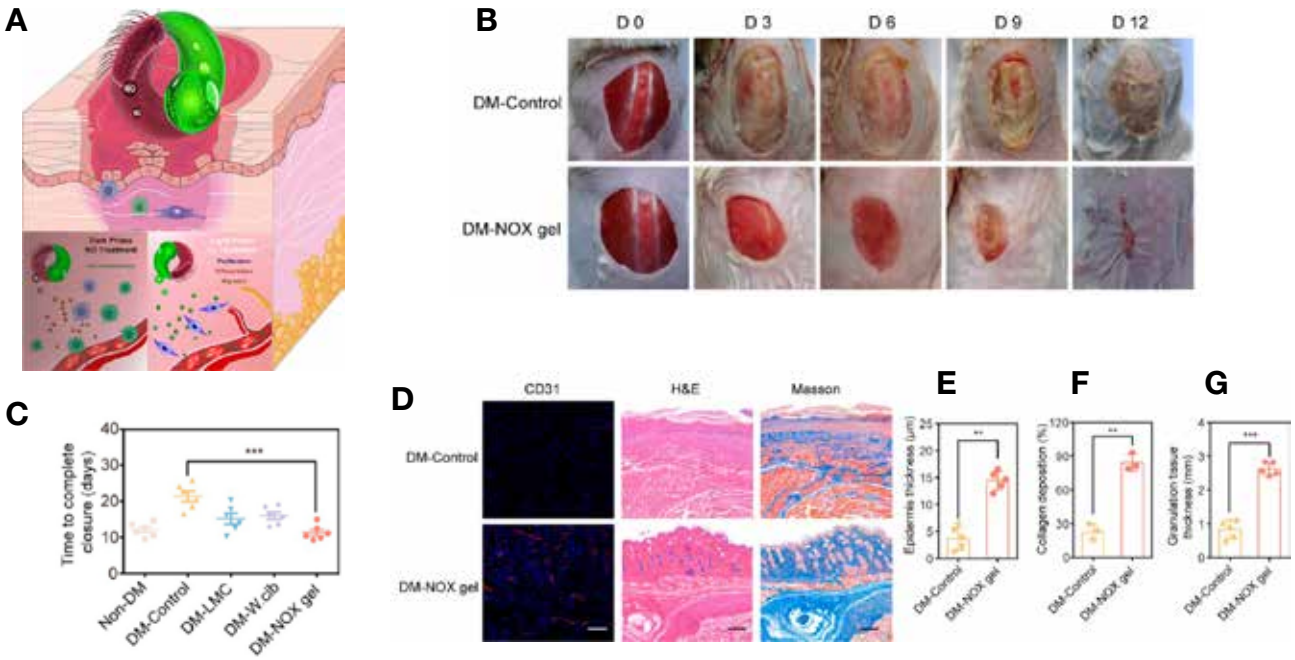

Figure 9. Dual release NOX gel. a) Schematic illustration of NOX gel as an algae-bacteria dressing for delivery of O_2 and NO for diabetic wound healing. b) Representative images of the diabetic wound area treated with NOX gel or not. c) Days of the complete wound-closure times. d) Immunofluorescence images of blood vessel CD31-positive endothelial cells (red) and H&E and Masson staining of wound tissues in different groups at day 12. Scale bar: 100μm. e–g) Quantification of the epidermis thickness, collagen deposition and granulation tissue in different groups at day 12. Significantly different (one-way ANOVA): *p<0.05; **p<0.01; ***p<0.001. Adapted from Chen et al 2023.[166] Reprinted (adapted/in part) with permission from the American Chemical Society, © 2023 American Chemical Society.

Together, these redox and oxygen modulating biomaterials illustrate the potential to break the cycle of chronicity by restoring a pro-healing microenvironment; however, future progress will depend on optimising the precision, duration and safety of their effects.

Biomaterial-physical stimuli interfaces for precision healing

An emerging direction in the design of biomaterials is the development of systems, many building on the principles discussed above, that respond to external physical stimuli, enabling precise, on-demand activation of biological responses to overcome persistent barriers in chronic wound repair. Recent advances have demonstrated how the intrinsic properties of biomaterials can be engineered to interface with adjuvant stimuli such as light, mechanical forces or ultrasound. One example is the incorporation of polypyrrole into a polyvinyl alcohol/polyethylene glycol/hyaluronan hybrid hydrogel to impart photothermal capability under near infrared light. Upon irradiation, the hydrogel surface generates localised heat that effectively kills bacteria.[167] Mechanical actuation has been achieved using strain-programmed scaffolds with a hydration-based shape-memory mechanism, in which a pre-stretched hydrophilic elastomer is linked to a dried adhesive layer of crosslinked polymer networks to draw wound edges together in a controlled manner[168] (Figure 10). Another approach leverages piezoelectric stimulation via dopamine modified polyvinylidene fluoride electrospun membranes activated by low intensity pulsed ultrasound. The mechanical waves generated by ultrasound deform the piezoelectric fibres, producing localised electrical signals that mimic the skin's natural bioelectric field.[169]

By coupling tailored biomaterial properties with targeted external stimuli, these material–physical hybrids expand the therapeutic toolkit for chronic wound management, offering new opportunities to integrate multiple functions into a single, responsive platform.

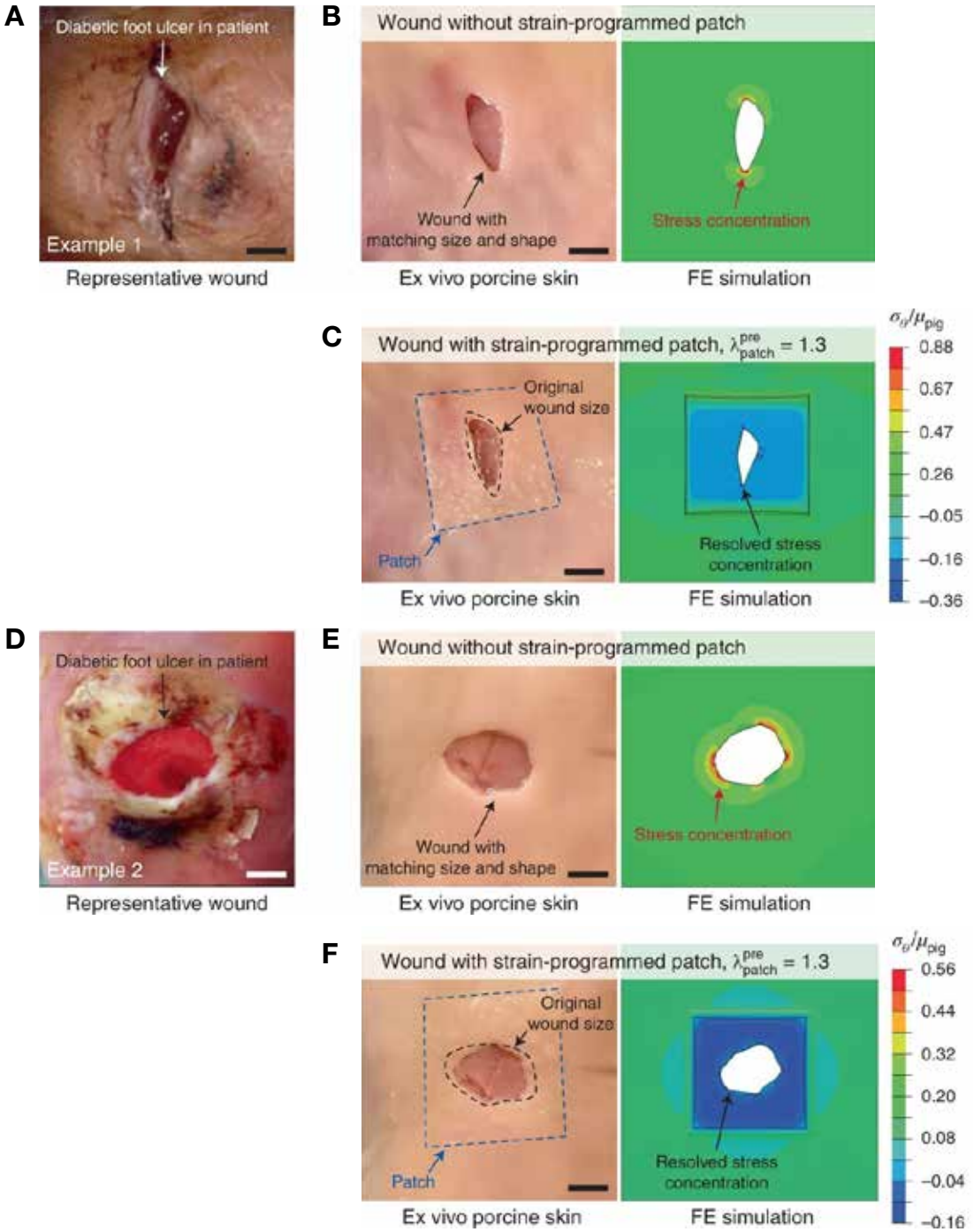

Figure 10. Mechanical modulation of human skin wounds. a,d) Representative examples of DFU with varying shapes in patients. b,e) Ex vivo porcine skin wounds and finite-element results based on the DFU examples. c,f) Mechanical modulation of ex vivo porcine skin wounds and the corresponding finite-element results by the strain-programmed patch. Wound contraction and removal of wound-edge stress concentration are indicated in the experimental images and finite-element results. Adapted from Nature Biomedical Engineering, Theocharidis et al 2022,[168] with permission from Springer Nature.

Conclusion

Over the past four decades, dermal matrices have evolved from inert protective barriers into sophisticated, bioactive platforms capable of modulating the wound microenvironment and actively guiding tissue repair. Biological, hybrid, and fully synthetic systems now

coexist, each offering distinct advantages in terms of structural support, immunomodulation, and integration with adjunctive therapies. While foetal bovine acellular dermal matrices and FSGs have shown particularly strong evidence in DFUs, synthetic and hybrid designs are rapidly closing the gap, offering reproducibility, tuneable degradation, and compatibility with precision-medicine strategies.

Emerging biomaterial designs are advancing towards:
1) mechanism-targeted scaffolds engineered to modulate key biological processes, such as inflammation resolution, angiogenesis, and ECM remodelling,
2) redox-modulating systems aimed at restoring oxidative balance in chronic wounds, and
3) material–physical stimulus interfaces capable of on-demand therapeutic activation with synergistic integration into adjunctive modalities.
Collectively, these approaches signal a paradigm shift toward multifunctional, patient-tailored solutions that can be tuned to the biochemical and biomechanical profile of individual wounds. However, their successful translation into routine clinical use will require progression beyond the proof-of-concept pre-clinical studies conducted to date.
Looking ahead, the next generation of dermal matrices will be shaped by advances in processing methodologies, nanotechnology, and material chemistry that allow precise control over bio functionality at the molecular and cellular scale. High-resolution 3D bioprinting, microfluidic patterning, and nanoscale surface engineering will enable spatially resolved deposition of biomolecules, gradients in mechanical stiffness, and controlled topographies to guide cell behaviour. Parallel progress in polymer chemistry, including modular crosslinking strategies, stimuli-responsive linkers, and bio-orthogonal functionalisation, will make it possible to program the release of growth factors, modulate immune responses, and tailor degradation kinetics to the wound's healing trajectory. By integrating next-generation biosensing platforms, these materials could not only monitor pH, oxygenation, inflammatory mediators and microbial load, but also perform continuous multi-parameter profiling, including metabolic, proteomic and microbiome signatures, to anticipate potential complications. Coupled with embedded logic circuits or wireless links to AI-driven control systems, they could dynamically adjust therapeutic payloads, release sequences and even their own mechanical or biochemical properties in real time, creating a self-optimising wound-healing environment.

The convergence of synthetic biology, nanotechnology, and materials science may yield living matrices seeded with engineered cells programmed to secrete regenerative factors in response to environmental signals, or to self-destruct once their role is complete. Coupled with AI-driven design algorithms, future dermal matrices could be computationally optimised for each patient's genetic profile, comorbidities, and wound characteristics, ushering in a new era of precision regenerative medicine.

4. Technologies for tissue repair

Dermal matrices

Advances in wound care have consistently pushed the boundaries of innovation, introducing materials and techniques that enhance healing and improve patient outcomes. Among these breakthroughs, biologic and bioengineered matrices have emerged as transformative solutions, redefining the approach to tissue regeneration. These matrices, whether derived from natural sources or synthetically constructed, have provided clinicians with versatile tools to address chronic and acute wounds.

The introduction of matrices over the last three decades has resulted in a myriad of products and classifications based on features such as durability, the skin layer to be replaced, cellularity, layering and the origin of the material, but there is still no consensus about these classifications.[170,171]

However, it is now clear that what is commonly defined as a "matrix" is a three-dimensional scaffold designed to mimic the structure of natural ECM of the skin. Ideally, the matrix should be conformable and customisable to different wounds, resistant to infection, cost-effective, durable, stable, widely available and should protect from fluid loss and external injuries.

Far from possessing these ideal features, an ideal matrix does not yet exist; the available matrices are featured by specific key physical characteristics including:

Porosity and pore size: A matrix has an interconnected porous network that allows cell migration, vascular ingrowth, and nutrient diffusion. Optimal pore size is usually in the range of 50–200µm.

Thickness: The thickness can vary depending on the application, typically ranging from a few hundred micrometres to several millimetres, to provide structural support without impairing integration.

Mechanical strength and elasticity: It possesses enough tensile strength to withstand handling during surgery, while remaining flexible and elastic to adapt to the wound bed.

Surface: The surface is usually rough or fibrous to facilitate cell adhesion and proliferation.

Hydration capacity: A matrix can absorb and retain fluids, maintaining a moist environment that supports healing.

Biodegradability: Many matrices are designed to gradually degrade or remodel, being replaced by newly formed host tissue over time.

Transparency or opacity: Depending on the material and thickness, it can appear semi-transparent or opaque.

Moreover, as already mentioned previously, the ECM, which is the biologic "material" that matrices are used to replace, has been demonstrated to have immunomodulatory, pro-angiogenic and even anti-bacterial properties, establishing a link between the structure of ECM and its functions, and thus, substantially changing the profile of what matrices are intended to deliver, which is no longer only related to the structural aspects of the wound but also to its functional behaviour.

In view of the sharp increase in number of products available, coming from different sources, with significantly different features and indications, and considering the new insights and achievements gathered in recent years on the physiology and pathology of wound repair and regeneration, the previous differentiation between permanent matrices and granulation tissue bioinductors is outdated and a new, more refined classification of the matrices is needed, to adequately describe the characteristics of these medical devices and to help users in selecting the best possible option to match the specific clinical conditions to be treated.

For this purpose, the matrices have been grouped according to their structural and manufacturing features in three categories: biologic, synthetic and mixed. Table 2 shows a schematisation of such classification, reporting the products covered in the present document. Of course, this must be considered provisional since – as we said – not all presently existing matrices have been discussed in this document and, even more relevant in consideration of the

Table 2. Classification of matrices and related technologies according to their bio-physical categories, origin and characteristics as stated by their manufacturers

Name	Category	Origin	Characteristic
Endoform	Biological	Ovine forestomach	Primarily composed of 85% collagen and 15% other important secondary molecules found in the natural extracellular matrix (ECM) of tissue such as collagen I and III, fibronectin, laminin, collagen IV and glycosaminoglycans (GAGs), which bind water to maintain hydration. Reabsorption 7 days. Pore size is not declared
Hy-Tissue Micrograft Technology	Skin micrografting medical device	N/A	Sterile single use medical device for the fragmentation of tissue biopsies, such as skin biopsies, obtained by rotating the fragmentation area of the device itself
Integra Dermal Regeneration Template — single layer	Biological	Bovine	Atelocollagen with a controlled pore structure (diameter ranging 20–125µm), and presence of glycosaminoglicans (chondroitin-6-sulfate) a degradation half-life approximating 14±7 days and scaffold remains present long-term (over years). Can be immediately covered with skin graft
Integra Dermal Regeneration Template — bilayer	Hybrid	Bovine plus silicone	Atelocollagen, controlled porous matrix of fibres of cross-linked bovine tendon collagen and glycosaminoglycan (chondroitin-6-sulfate) The epidermal substitute layer is made of a thin polysiloxane (silicone) layer pore structure (diameter ranging 20–125µm), a degradation half-life approximating 14±7 days and scaffold remains present long-term (over years). Present also in the meshed version
Kerecis	Biological	Cod *(Gadus morhua)*	Decellularised fish skin rich in omega-3 fatty acid, collagen, glycans and elastin. Pore size 10–150µm. Biodegradable, the surface can be meshed. High water storage capacity. Reabsorption in 7–14 days
Matriderm	Biological	Bovine	3-dimensional acellular porous dermal matrix composed of types I, III, and IV bovine collagen and elastin. Thicknesses of 1, 2 and 3mm with pore sizes between 18–34µm, reabsorption 14±7 days
Micromatrix/ Cytal	Biological	Porcine urinary bladder	Acellular matrix that preserves ECM and structural components derived from porcine bladder tissue with a bimodal structure including lamina propria and epithelial basement membrane, particularly collagen (types I, III, IV, V), fibronectin, laminin and glycosaminoglycan
Myriad	Biological	Ovine Forestomach	Non-reconstituted collagen with ECM-associated macromolecules including elastin, fibronectin, glycosaminoglycans and laminin. The pore size is not declared
Novosorb BTM	Synthetic	Porous biodegradable polyurethane foam	Average pore size 188µm. 2mm-thick open-cell polyurethane foam completely re-absorbable, covered by a non-degradable sealing membrane
Pelnac — single layer	Biological	Porcine	Composed of a biodegradable (14±7 days) scaffold of porcine tendon-derived atelocollagen sponge layer (~3mm thick, porosity of 70–110µm). Can be immediately covered with skin graft
Pelnac — bilayer and reinforced bilayer	Mixed	Porcine plus silicone layer	Composed of a biodegradable (14±7 days) scaffold of porcine tendon-derived atelocollagen sponge layer (~3mm thick), and a reinforced silicone film layer. Porosity of 70–110µm

rapid turnover that this sector is facing, the new products that are about to be licensed have not been evaluated.

As previously mentioned, one of the most important features is the availability for clinical use, but not all matrices are available worldwide. For example, a wide variety of biological matrices are available in the United States, while the South American market offers fewer options. Many of these products are not approved or sold in the European Union (EU). Distribution within the EU is often restricted by the complexity and difficulty of achieving CE mark approval, the need for additional research (randomised Level I clinical trials) and the significant costs associated with entering a new market.

The section dedicated to regulatory aspects will address and discuss the issue of access to care for the increasing number of patients suffering from chronic and complex wounds. These patients deserve to be treated safely and effectively with technologies that ensure the best standard of care, but cannot afford them, or are impeded by regulatory boundaries. This will be discussed also from the perspective of the ethical issues raised by the present situation.

In the following pages, we present the most widely used and worldwide available products, aiming to provide a clearer understanding of their features, classification, mechanisms of action and range of application, based on clinical evidence and literature.

Endoform

Endoform is derived from decellularised ovine forestomach matrix (OFM), preserving a rich and bioactive ECM structure. It contains over 150 matrix proteins, including collagens (types I, III, IV), elastin, fibronectin, glycosaminoglycans, basement membrane components, and growth factors such as VEGF, FGF, and PDGF. This scaffold mimics native tissue, enabling cellular adhesion, migration, and proliferation — key steps in constructive wound healing. Endoform retains the porous architecture and residual vascular channels of native ECM, which act as conduits for angio-conduction. These structural features facilitate rapid ingrowth of endothelial cells and capillaries, promoting revascularisation of the wound bed. Chronic wounds often suffer from elevated protease activity that destroys native ECM and inhibits tissue healing. Used as an “advanced dressing”, Endoform plays a key role by being degraded preferentially by proteases, thereby protecting the patient’s own ECM. The presence or absence of Endoform remnants provides clinicians with a direct, visual assessment of protease activity. Persistent remnants imply reduced proteolytic activity and progression towards healing; rapid disappearance indicates high proteolytic activity and a need for more frequent application.

Due to its composition and structure, Endoform supports wound healing across all phases – stabilisation, inflammatory modulation, proliferation and tissue remodelling. It restores ECM balance, encourages granulation tissue formation,

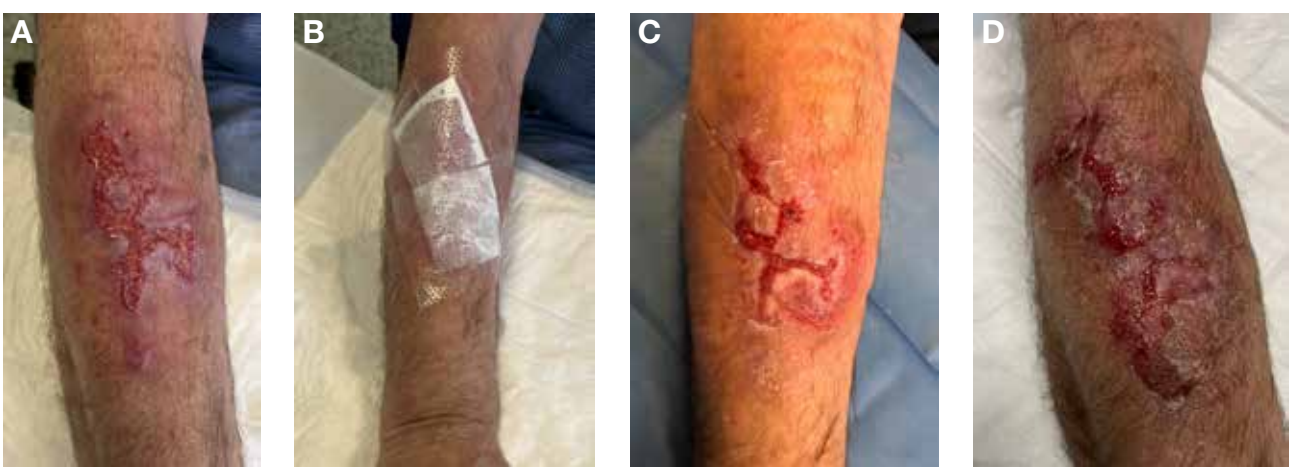

Figure 11. Endoform case. a) Male patient affected by not re-epithelialised second degree burn after 1 month treated with standard of care. b) Application of Endoform and activation with saline solution. c) After 1 week, re-epithelialisation started requiring a new application. d) 2 weeks after the first application: almost fully re-epithelialised.

and supports re-epithelialisation. An antimicrobial version of Endoform, containing 0.3% ionic silver, aims to provide broad-spectrum antimicrobial activity for up to seven days. It helps prevent biofilm formation without being cytotoxic to dermal cells, making it suitable for wounds with a higher risk of infection.

In 2020, Raizman et al[98] published a multicentre study on 27 wounds (initially 33 on 29 patients, but six wounds were lost during the study). These wounds included venous leg ulcers, DFUs, pressure injuries, surgical wounds, traumatic wounds and others, such as pilonidal sinus, necrotising fasciitis, and radiation-induced injury. Following the application, the average time to wound closure was 8.2 weeks (range, 2.7–19.7 weeks); the percentage of reduced wounds at 4 weeks was 64%, the average wound area reduction at 4 weeks was 66%, and 73% of wounds had closed at 12 weeks.

In 2022, Bosque et al[172] published a retrospective pragmatic real-world data study that compared the healing outcomes of DFUs treated with either ovine forestomach matrix (OFM) (n=1150) or collagen/oxidised regenerated cellulose (ORC) (n=1072) in outpatient wound care centres. The median time to wound closure was significantly (P=0.0015) faster in the OFM group (14.6±0.5 weeks); DFUs treated with OFM healed up to 5.3 weeks faster. Cox proportional hazards analysis showed that OFM-treated wounds had an 18% greater probability of healing versus wounds managed with collagen/ORC, and this probability increased to 21% when the analysis was adjusted for multiple variables.

In summary, Endoform can be used “as dressing” in all kinds of wounds, with a particular efficacy on those affected by high proteolytic activity.

Integra

Conceptualised in 1969 by Burke and Yannas and commercialised in the 1980s, Integra was the first matrix by modern standards and definitions. Integra is a bovine-derived acellular dermal matrix composed of bovine tendon collagen and shark-derived glycosaminoglycan (chondroitin-6-sulfate). This structure acts as a biodegradable scaffold that guides cellular ingrowth. Host fibroblasts, endothelial cells and macrophages infiltrate the matrix, gradually replacing it with vascularised neodermis (a new dermal layer). During this process, the collagen-glycosaminoglycan scaffold is degraded by enzymes and resorbed by the body.

According to the available evidence, the efficacy of the Integra matrix is attributable to an optimal pore structure (diameter ranging 20–125µm) and biomaterial stability, with a degradation half-life of approximately 14±7 days and scaffold remaining present long-term. The presence of ligands for integrins $\alpha1\beta1$ and $\alpha2\beta1$ at sufficient densities promotes cellular adhesion, facilitating dermal regeneration accompanied by vascularisation and innervation, ultimately leading to re-epithelialisation and epidermal formation.

It is available in both a dual-step version (covered by a silicone layer which prevents fluid loss, protects against bacterial invasion, provides mechanical stability, and maintains a moist environment conducive to healing) and a one-step version, which can be grafted immediately and is typically used when there is already a good wound bed but the replacement area needs thickening.

Over the last five years, many studies have been published as case reports, case series, case controls, retrospective studies, and one randomised controlled trial on possible complications associated with the use of Integra. In 2020, authors Hicks[173] and Dalla Paola[174] described two case series. The first was a prospective case series of 107 diabetic foot patients treated with Integra. In this case series, they noted that after 18 months, 93+/-3.3% of patients were healed. Meanwhile, Dalla Paola et al reported a retrospective case control study on patients affected by critical limb ischaemia post-revascularisation: Integra promoted faster healing (83 days versus 139 in the control group).

In the same year, Scalise et al[175] reported a retrospective case series of 111 patients affected by different wounds. In this study, the authors divided the patients into two categories according to complications. The authors reported no difference in complications and suggested the possibility of using only Integra without skin graft with patients who were elderly or who had multi-comorbidities. These results confirmed the recommendation published in 2019 by Magnoni et al[176], who recommended the use of Integra in elderly patients with comorbidities, large and complex bone exposure, radiation and recurrent and/or aggressive tumours, to allow a better and faster view of the area.

Meanwhile, other experiences have been reported on burned patients, scalp reconstruction, elderly patients,

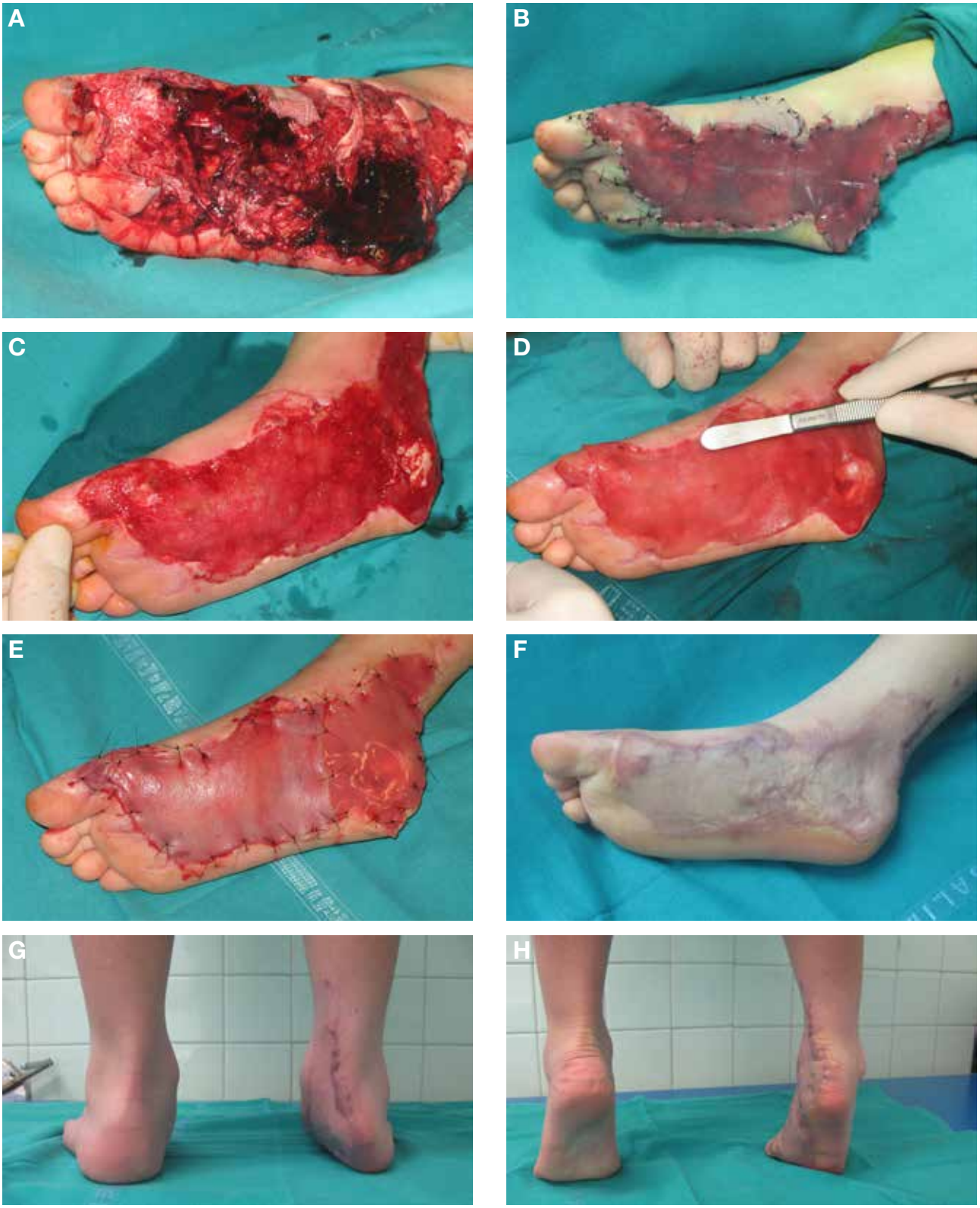

Figure 12. Integra case 1. A 45-year-old man with severe foot injury: a) preoperative; b) Application of Integra bilayer after debridement. c) Very good quality and thickness of the neodermis ready for skin graft after 3 weeks. d,e) Application of Integra single layer and immediate coverage with a split-thickness skin graft. f–h) After 2 years: function restored.

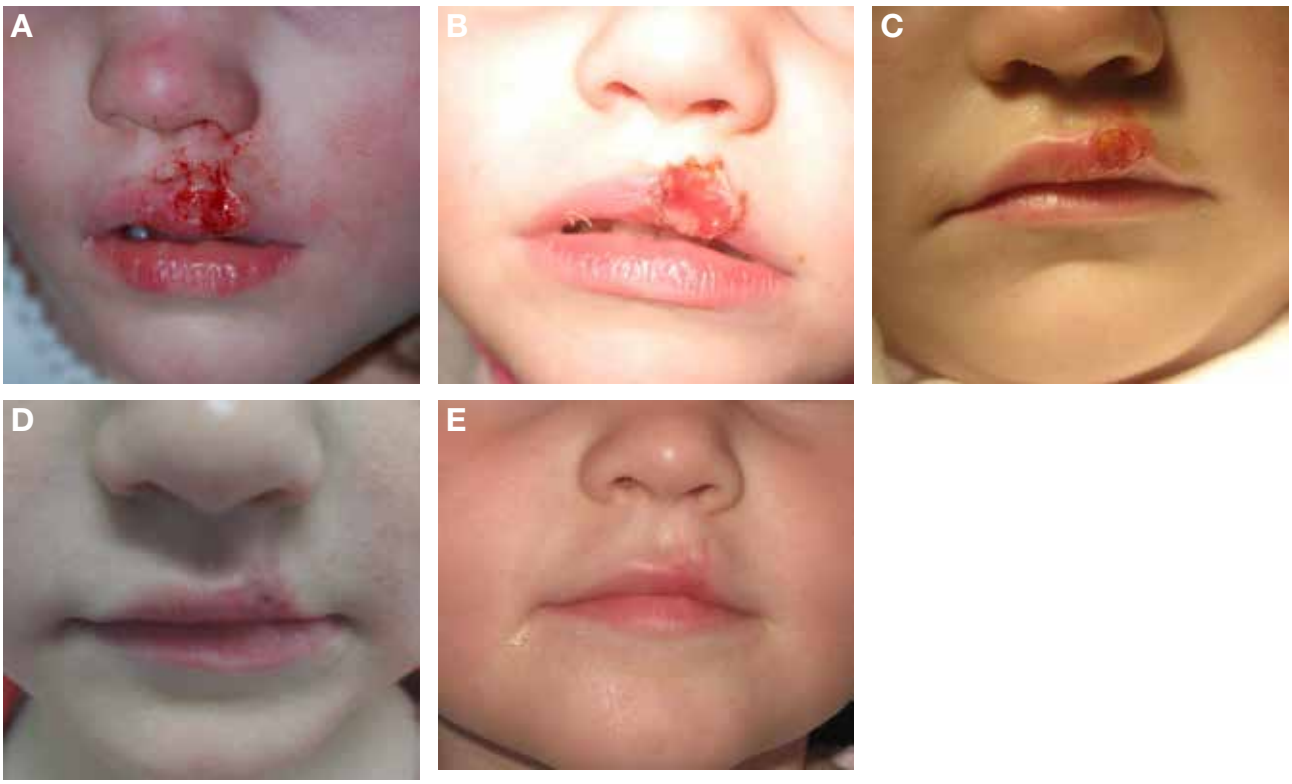

Figure 13. Integra case 2. a) Upper lip wound from a dog bite in child. b) 2 weeks after application of Integra dual layer. c) Silicone removal in the third week. d) After 1 month, almost complete spontaneous healing. e) At 2 months, complete healing, no skin grafting required.

and more. Bernstein et al[177] noted complete healing in 86% of 14 patients treated with Integra plus skin graft. Choughri et al[178] described the possibility of using Integra as a good alternative to flap reconstruction in 14 patients affected by hand lesions after 36 months. During the same year, Shakir et al[179] published a retrospective case control study on 191 wounds, demonstrating 70% healed cases after 180 days. Rudnicki et al[180] used Integra on 13 burned patients immediately after escharectomy with good results. Furthermore, Chaiyasate et al[181] reported their experience on 13 patients in which they demonstrated good scalp reconstruction after 3 months of follow up. Interestingly, a year later, Romano et al[182] reported the same good results after 68 days of follow-up on 20 patients affected by scalp lesions but, most importantly, by comorbidities, aggressive or relapsed tumours.

Regarding complications, in 2020, Gonzalez et al[183] associated Integra with infections in a systematic review of the literature, reporting 212 infections in 602 patients and 1254 treated areas (16.9%), suggesting that its application was not suitable for sites at risk of infections. Finally, in the same year, Vana et al[184] published a prospective study on 24 patients comparing Matriderm and Integra. In this paper, Integra had lower retraction and better skin quality and was still present after 12 months.

In 2022, Prezzavento et al[185] reported a two-year retrospective review in cutaneous oncologic surgery in 13 patients undergoing reconstruction after extensive tumour excision. These patients were treated with Integra Dermal Regeneration Template followed by secondary skin grafting approximately 20 days post-application. The mean graft take rate was approximately 92%, with an average grafting time of 20 days, yielding optimal aesthetic and functional outcomes and no significant infectious complications.

In 2024, Boschetti et al[186] published a retrospective case series on 18 patients affected by scalp full-thickness defects reconstruction following the resection of skin carcinoma and treated with Integra Single Layer followed by split-thickness skin grafting in one-stage procedure. The authors noted a complete graft take rate of 77%, and reduced healing time (<60 days) with consequent possibility of early radiotherapy.

Meanwhile, Turton et al[187] reported a study on 101 scalp reconstructions with a 95% success rate using Integra alone, without the necessity for a secondary surgical stage. The authors also reported postoperative infections in 21% of cases, which were effectively managed with topical and oral antibiotics. Depending on the patients' clinical conditions and comorbidities, median complete healing was observed from 4 months up to one year.

In 2025, Jović et al[188] published a systematic review analysing the use of Integra in exposed bone reconstruction. The review included 40 studies, with a total of 202 defects. The reported average success rate was 87.54% (±25.9), and the average graft take was up to 98.8%.

Bassetto et al[189] recently published an "expert panel recommendation" summarising 25 years of experience in head and neck reconstruction, concluding that Integra can maintain space, promote vascularisation, reduce contraction and fibroblastic infiltration, as well as ensure stable reconstruction, also in complex regions such as the nose and oral cavity.

In summary, in clinical practice, Integra is primarily used for patients who are not at risk of developing infections. It is also indicated when no vital structures are exposed, and in cases such as post-burn escharectomy, where temporary coverage is needed before definitive grafting.

Kerecis

Intact FSG is one of the more recent matrices, more accurately described as a biological tissue graft, developed to act as a matrix to support tissue regeneration in wounds of various aetiologies.

The use of fish skin as a matrix is grounded in its unique biochemical and structural properties, which offer remarkable advantages for wound healing. Unlike traditional matrices derived from synthetic polymers or mammalian tissue, fish skin provides a naturally occurring ECM rich in bioactive components such as collagen, fibrin, glycosaminoglycans, elastin and lipids, including omega-3 fatty acids. These elements are critical in facilitating cellular infiltration, angiogenesis and epithelialisation, processes essential for effective tissue regeneration. Omega-3 fatty acid-derived molecules have anti-inflammatory properties, and the omega-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, in particular, have been shown to accelerate wound healing in animal models.

Furthermore, the acellular nature of fish skin ensures compatibility across diverse patient profiles, eliminating concerns about immunogenic reactions and broadening its therapeutic scope.

Clinical trials have tested Kerecis fish skin in both acute and chronic wounds, including a large prospective randomised controlled trial investigating the use of fish skin to treat deep DFUs on 255 patients. This study demonstrated a higher rate of healing at 16 weeks (44% vs 26%, $p<0.001$), compared to standard of care, in a shorter time (17.3±0.69 vs 19.4±0.66 weeks, respectively).[190] Prior to the introduction of Kerecis fish skin, no similar product was available. The fish skin is a byproduct of processing Icelandic cod *(Gadus morhua)* from sustainably managed wild fish stocks located in the Atlantic Ocean. Since its introduction to the wound care market, its use has increased substantially and expanded to a broader range of applications.

In addition to intact fish skin (Kerecis Solid), which is also available in a pre-fenestrated version to help manage wound fluid production (Kerecis Fenestrated), and is indicated for chronic, surgical and traumatic wounds, Kerecis Micro consists of fragmented intact fish skin that allows greater surface area coverage than non-fragmented versions and is designed to fill deeper and more irregular wound spaces. Kerecis Expanse is a pre-meshed version of the product designed to cover larger surface areas in an outpatient setting.

As FSG is derived from North Atlantic cod, and there is no known risk of viral pathogen transfer from cod to humans, the fish skin only requires light processing. More intensive chemical processing may denature proteins, remove key molecular components, and introduce artificial cross-linking, all of which may adversely affect the efficacy of a skin substitute product. Light processing means that more of the structural and molecular properties of the fish skin are retained in the acellular FSG. Fish skin has a microstructure that resembles that of human skin. Intact FSG is a robust and lightweight material that does not require special storage conditions. The product does not require special equipment or advanced training for use, however the clinician must be aware of which wounds and wound environments provide the most optimal results, as no product, including intact FSG, is a universal dressing optimal for all wounds. Product selection must be

determined based on the patient and the wound aetiology, status and presentation.

The clinician must keep in mind that results are directly influenced by numerous factors, including the patient's medical status, medications, presence and levels of bacteria, inflammation, wound aetiology and wound bed preparation. The mechanism of action and duration of the product will be affected by how, where and when it is applied in the continuum of wound healing and tissue regeneration.

Numerous studies at different levels support the use of intact fish skin graft. The more recently published randomised controlled trial strongly supports the use of intact FSG for the treatment of diabetic ulcers.

Within the diabetic population, the clinician must consider adjunctive therapies including offloading, glucose control, blood flow and wound staging.

Beyond DFU, an increasing body of clinical evidence documents the application of intact fish skin matrices in a wider spectrum of complex wounds. Case series and retrospective analyses report successful outcomes in venous leg ulcers, post-surgical wounds, traumatic injuries, and donor sites, as well as in full-thickness defects with exposed tendon or bone.[191–195] In these settings, the matrix has been shown to support rapid granulation tissue formation and subsequent re-epithelialisation or definitive closure.

The biological profile of intact fish skin represents a distinctive feature of this technology. The matrix naturally contains omega-3 polyunsaturated fatty acids, which have been associated in preclinical and clinical studies with modulation of the inflammatory response, reduction of pain, and resistance to infection.[191,192,196] Clinically, a reduction in analgesic requirements following application has been reported, together with favourable patient-

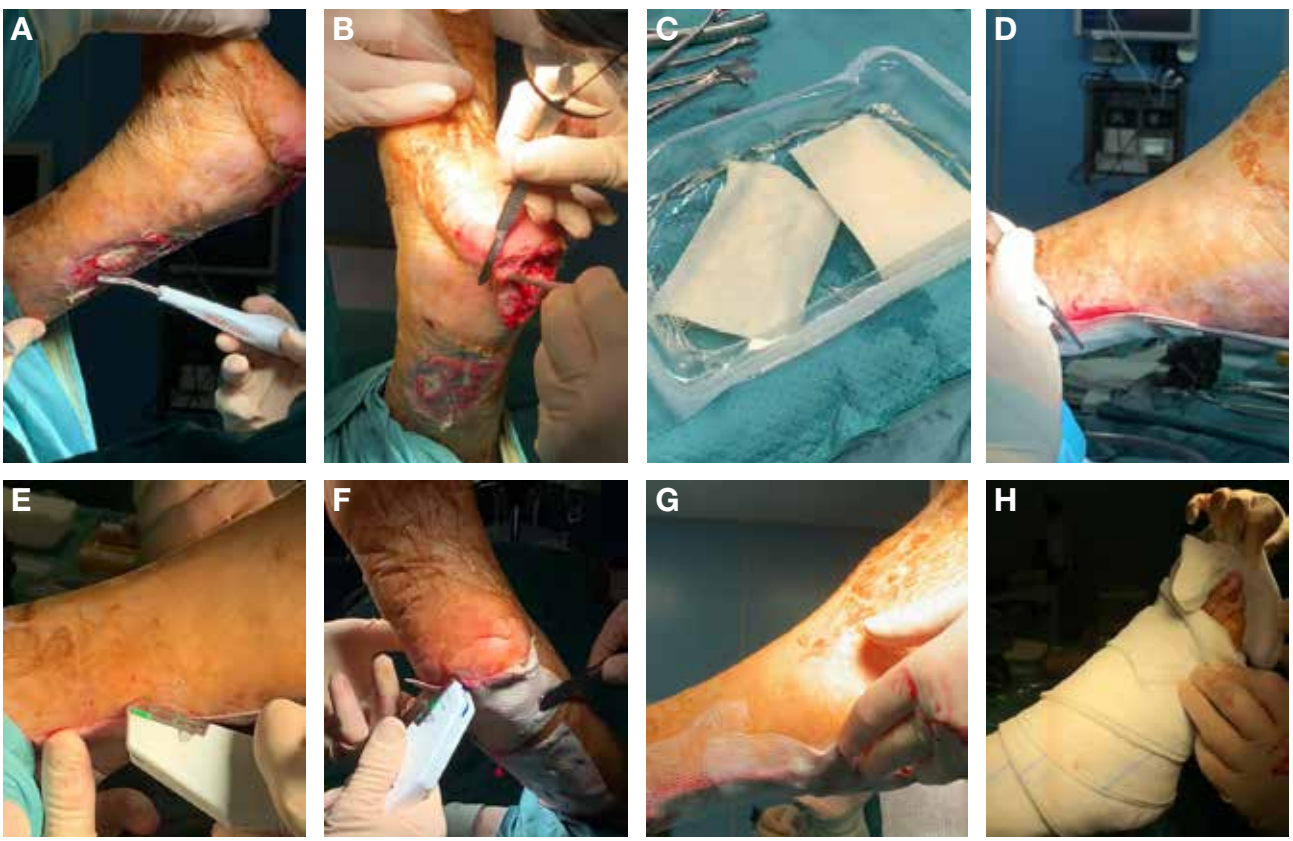

Figure 14. Kerecis case 1. a) Debridement with hydrosurgery of the lesion on the Achilles tendon, exposed within the lesion. The ulcer was neuroischaemic, developed during intensive care unit admission after revascularisation, alongside with the calcaneal one. b) Debridement of the calcaneal lesion. c) Pre-hydration of the lyophilised fish skin. d) Positioning of the hydrated device on the Achilles tendon, debrided. e) Securing the device by stapling it on the lesion's margins. f) Same procedure on the calcaneal lesion. g) Dressing with paraffin gauze. h) Securing of the entire construct with gauze pads.

reported outcomes, particularly in donor sites and painful chronic wounds.[192,195]

The integration of evidence-based practices and emerging technologies, such as negative pressure wound therapy or the application of growth factors, can significantly enhance the healing process. Regular monitoring and adjustments ensure that the chosen interventions remain appropriate as the wound progresses through different stages of healing, ultimately providing a framework for optimised patient care.

From the literature, Kotronoulas et al[191], in 2020, demonstrated Kerecis' suitability for obtaining a very "natural" skin and reducing pain. Alam et al[192] reported an analgesic effect and a 100% re-epithelialisation in 2019 on 10 donor split-thickness sites in burned patients. The same year, Michael et al[193] described a retrospective case series of 58 diabetic ulcers, achieving surface reduction in 87.57% and complete healing in 60.34%. Also in the same year, Woodrow et al[194] presented a prospective

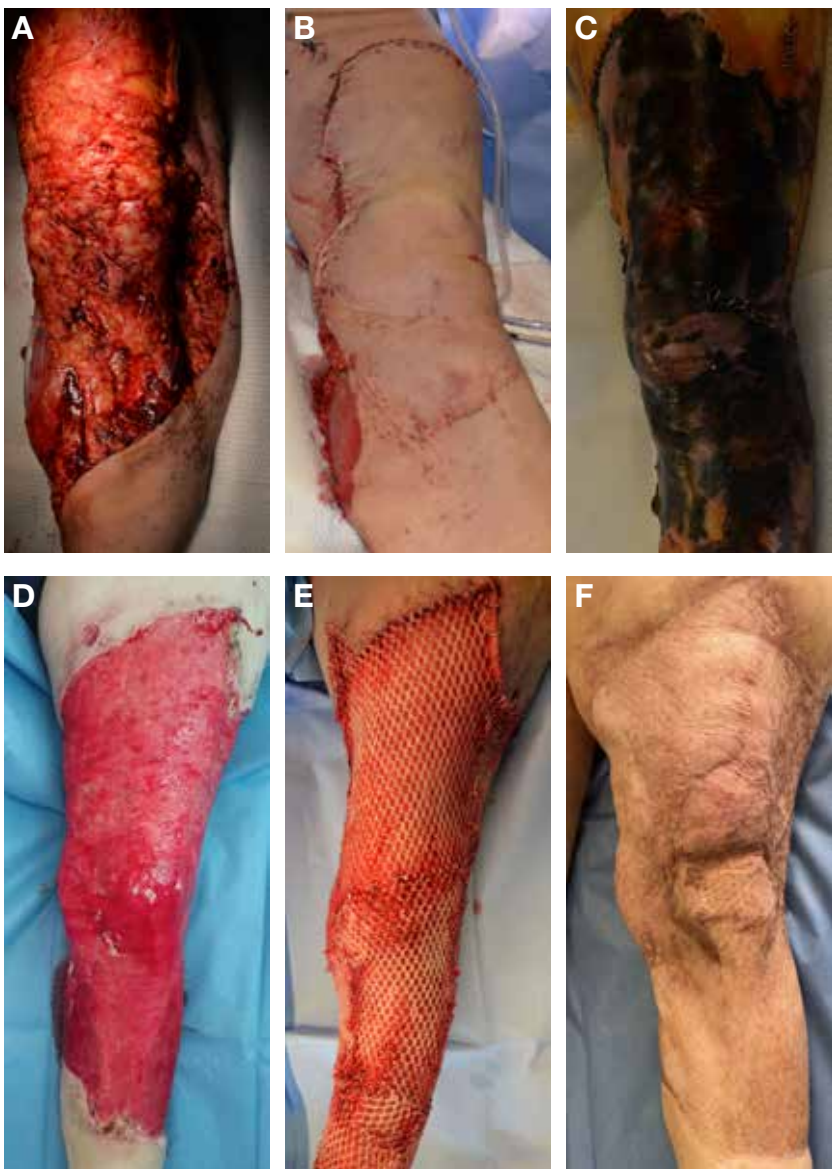

Figure 15. Kerecis case 2. a) Left leg degloving trauma in female patient. b) Immediate coverage with autologous injured flap as dressing. c) Necrosis of the skin after one week. d) Very good neovascularised tissue after debridement and 10 days of negative pressure wound therapy with instillation and dwell time; e) coverage with meshed Kerecis. f) One year after final skin graft.

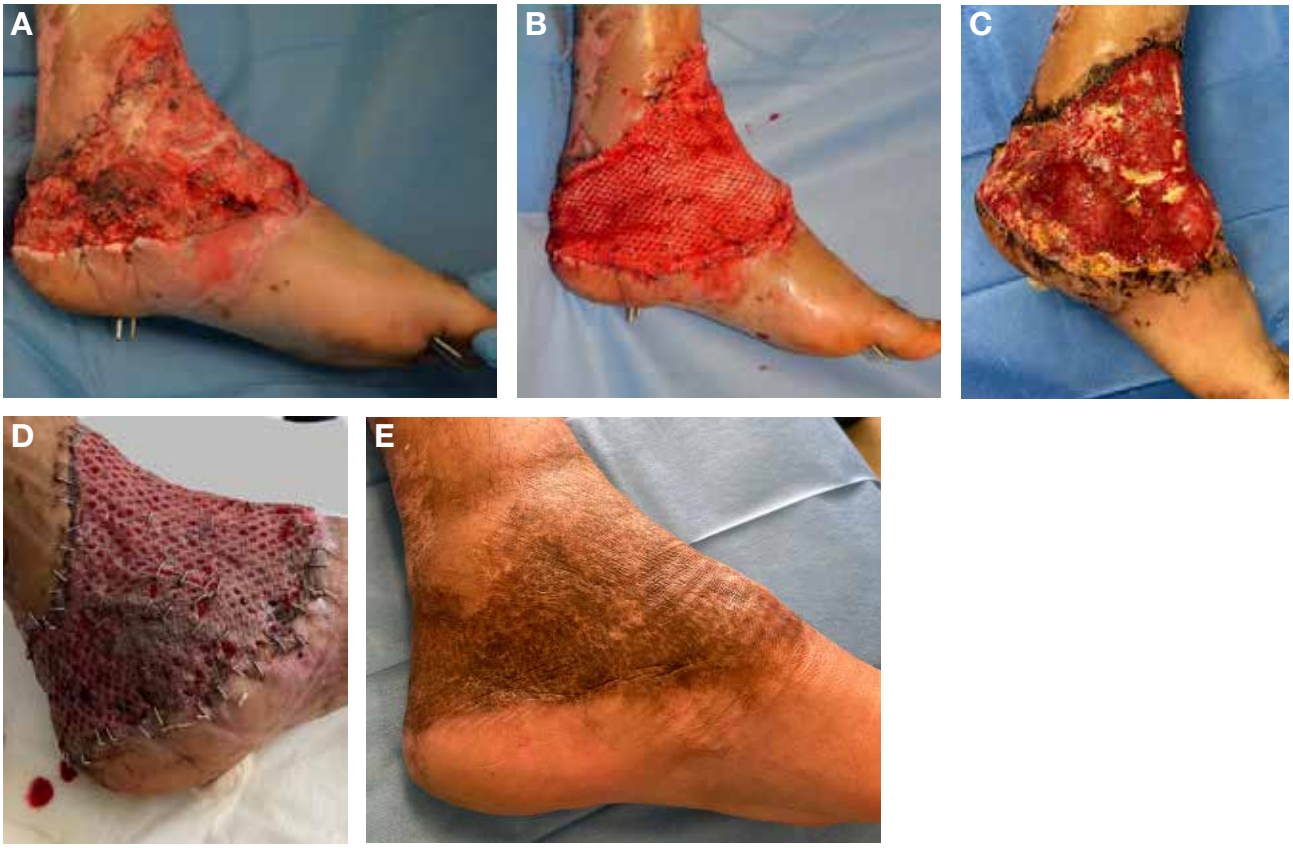

Figure 16. Kerecis case 3. Post-traumatic heel lesion. a) Preoperative. b) Intact fish skin and negative pressure wound therapy. c) Follow-up after 15 days. d) Skin graft. e) Follow-up after one year.

study on 8 postoperative diabetic feet, featuring 6 weeks of follow-up and a weekly dressing change. They noted a wound area reduction, mostly in recent (<3 months) lesions. Meanwhile, Badois et al[195] described faster healing, from 68 to 32 days, on 21 skin donor sites. Finally, in 2020, Kirsner et al[196] proposed a comparative, double-blind, prospective, randomised study on 170 wounds (85 per group) comparing amniotic membrane and acellular fish skin; also in this case, the group treated with acellular fish skin healed faster.

In 2022, Luze et al[197] published a systematic review and evidence-based process on burn wound management. The authors reported on 14 papers: 3 preclinical, 4 case report/series, 2 clinical pilots, 4 clinical cohorts, and 1 retrospective study. The analysis noted that acellular FSG may represent an effective, low-cost alternative for treating burns by accelerating wound healing, reducing pain and necessary dressing changes.

In 2023, Lantis et al[198] reported the results of a prospective, multicentre, randomised controlled trial evaluating the use of omega-3-rich acellular FSG on 102 patients affected by DFUs (n=51 FSG, n=51 standard of care). The authors noted that the diabetic foot wounds treated with FSG were significantly more likely to achieve closure than those managed with Collagen Alginate Therapy (CAT) (ITT: 56.9% vs 31.4%; P=0.0163). The mean percentage area reduction at 12 weeks was 86.3% for FSG vs 64% for CAT (P=0.0282), saving costs.

In 2024, Gao et al[199] published a meta-analysis on the efficacy of acellular FSG in the management of chronic ulcers. Out of 108 articles, only eight were eligible:

1. Lullove et al[104] published a randomised clinical trial on 49 patients affected by superficial diabetic foot ulcers treated with FSG or standard of care (SOC) using collagen alginate dressing. At 12 weeks, 16 of 24 patients (67%) in the fish skin arm were completely closed, compared with 32% in the SOC arm. At six weeks, the percentage area reduction was 41.2% in the SOC arm and 72.8% in the fish skin arm.

2. Yang et al[200] published a prospective evaluation on 18 patients affected by at least one "hard-to-heal" wound treated with five weekly FSG applications and three weeks of standard of care. A 40% decrease in wound surface area ($P<0.05$) and a 48% decrease in wound depth was observed with five weekly applications of the FSG and a secondary dressing.
3. Zehnder et al[201] published a randomised control trial reporting a reduction in 4–8 weeks (over 25% improvement in wound area vs standard of care).
4. Dorweiler et al[202] reported a multicentre case series on 25 wounds (vascular and diabetes) treated with acellular fish skin; in these patients, a reduction in analgesic intake was noted immediately after the treatment.
5. The authors also reported the papers by Michael et al, Lantis et al, Lullove et al and Woodrow et al, which were already reported earlier.[104,193,194,198]

In summary, while the strongest level of evidence currently supports the use of Kerecis in diabetic foot ulcers, the available clinical data suggest a broader potential role as a regenerative platform in the management of complex wounds. As with other dermal matrices, further prospective studies are needed to better define its indications across different wound aetiologies and clinical scenarios.

Matriderm

Matriderm is a bovine-derived dermal regeneration template composed of 97% native, non-crosslinked collagen type I, III and V and 2% elastin hydrolysate. This composition closely resembles human dermis both in ultrastructure and amino acid sequence. The native collagen fibres provide a natural scaffold for fibroblast ingrowth and matrix deposition, while elastin enhances angiogenesis and supports rapid neovascularisation. Compared with cross-linked or synthetic matrices, Matriderm demonstrates higher biocompatibility and cell affinity, minimising prolonged inflammation and enabling timely transition to proliferation.[129,203]

Matriderm is available in 1mm, 2mm and 3mm thickness and various sizes, the largest A4 and smallest A9 sheets as non-fenestrated (flex) or fenestrated forms. For smaller defects it can be used as a 'no-step' technique where epithelialisation occurs from the wound edge and avoids the need for a skin graft and subsequent morbidity (Figure 17). For larger defects it can be used as 'two-step' (skin graft undertaken at a later stage) to fill contour defects and as 'one-step' (skin graft undertaken at the same time) to bridge over tendons and bone with and without their respective vascular layers of paratenon and periosteum (Figure 18).

The various thicknesses of Matriderm make it versatile, and there are more than 200 publications in peer-reviewed journals that support the evidence for its safety. There is long-term data and a 12-year follow-up.[204]

Some of the more recently published evidence is summarised below. For the sake of synthesis and readability, the findings are presented in bullet points according to the focus of the papers covered.

- Integration and angiogenesis: Schmidt et al demonstrated that vessel ingrowth in Matriderm at two weeks equalled or exceeded that seen at four weeks in cross-linked collagen/GAG matrices.[205] Building on this, more recent comparative studies confirmed superior integration kinetics, with the collagen elastin matrix Matriderm showing the highest integration rate at 95% within one week, versus polyurethane matrix BTM at only 23% after one week.[206]
- Inflammation and myofibroblast transition: Hong et al[129] showed that Matriderm balanced pro- and anti-inflammatory factors within four days, in contrast to persistent pro-inflammatory signalling in synthetic matrices. Dill & Mörgelin[203] further demonstrated a reduction in fibroblast–myofibroblast transition, mitigating contraction and scarring.
- New dermis quality: as shown in human punch biopsies, Matriderm promotes tissue regeneration at the level of normal skin, unlike split-thickness skin graft alone and other products.[207,208]
- Clinical outcomes — Hospitalisation: Krasteva et al showed that adding Matriderm to split-thickness skin graft reduced hospital stay in trauma and chronic wound patients by more than 50%.[209]
- Flap surgery avoidance: Alawi et al reported that, in a cohort of flap surgery candidates with exposed structures, 77.5% were successfully treated with Matriderm and split-thickness skin graft, thus avoiding flap reconstruction.[210]

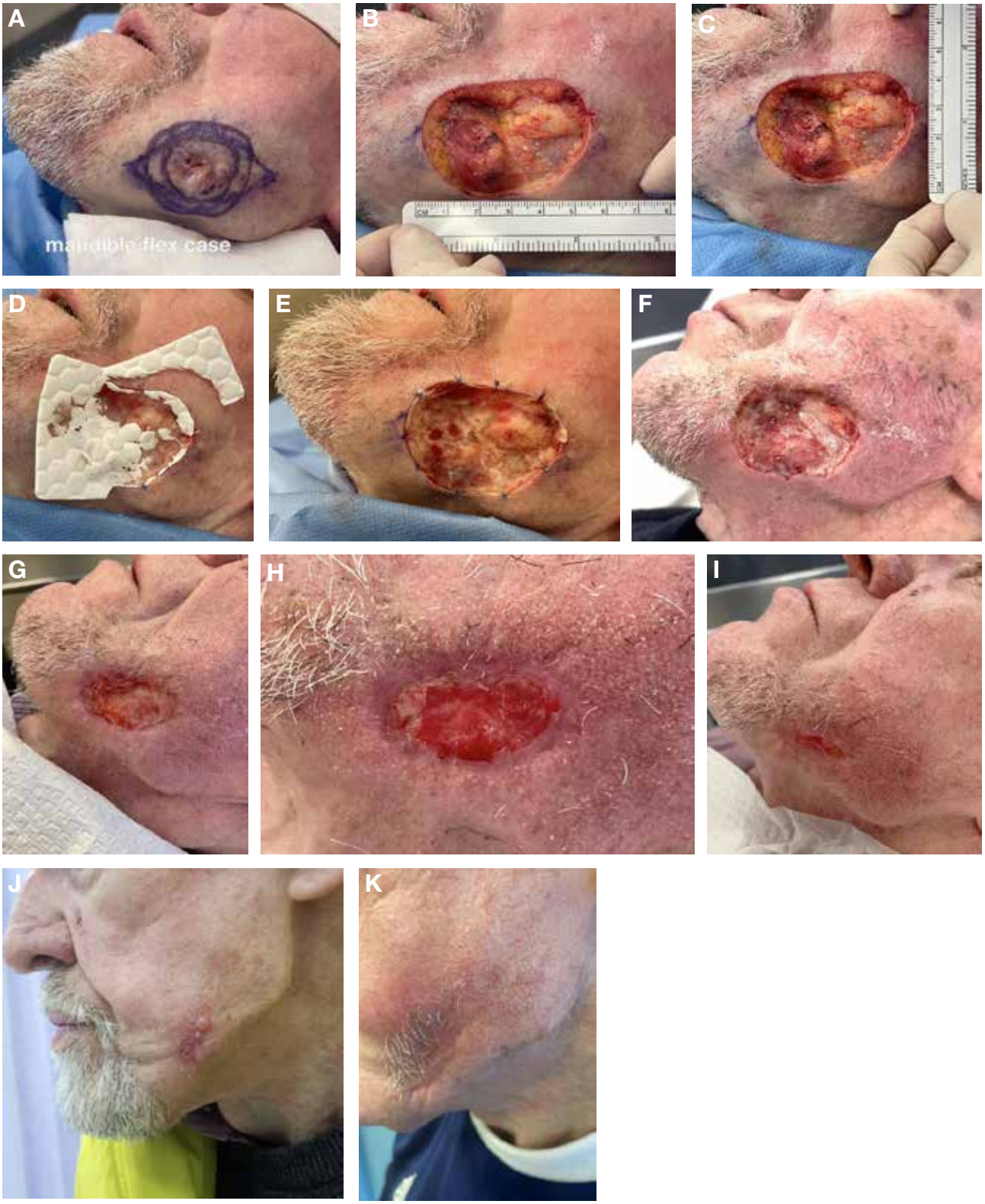

Figure 17. Matriderm case 1. a) Skin cancer marking. b,c) Post excision defect 6cm width, 5cm height. d) Matriderm 2mm template application. e) Template secured. f) Complete reabsorption after 2 weeks. g,h) After 3 and 4 weeks, the defect is epithelialising; i,j) After 6-8 weeks, re-epithelialisation is ongoing. k) Fully re-epithelialised with no contracture. No skin graft required, spontaneous re-epithelialisation.

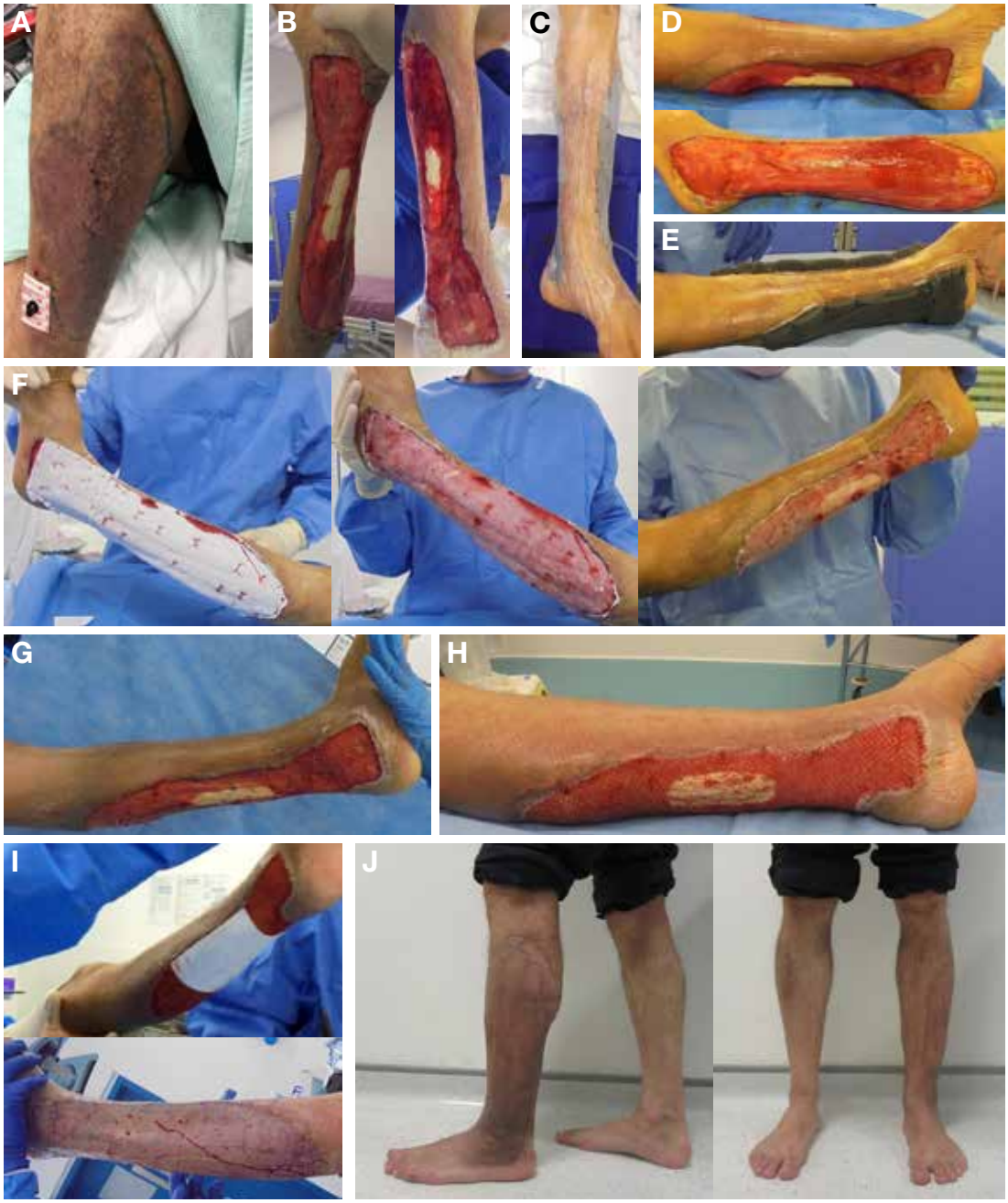

Figure 18. Matriderm case 2. Necrotising fasciitis of the lower leg showing two-step and one-step procedures in a 45-year-old man with type 1 diabetes. a) Emergency debridement for necrotising fasciitis of the lower leg. b) Near circumferential 5mm deep defect of skin, soft tissue and fascia including vascular layer (paratenon) of gastrocnemius tendons. c) Negative pressure wound therapy with instillation-dwell (NPWTi-d) applied. d) Further cleansing of the wound and granulation tissue for a more even (smoother) wound bed over the contours of the musculature. e) Two-Step procedure: bolstering with two A4 size 2mm thickness Matriderm dermal matrix sheets with NPWT. f) a non-adherent silicone layer was also applied. g) Seven-day NPWT dressing change showed good integration of Matriderm dermal matrix. h) Filling and obliteration of the soft tissue defect was achieved after several changes of NPWT and the areas of exposed tendons without paratenon reduced. i) One-step and interval stacking procedure: to bridge the remaining area of avascular tendons with application of 1mm Matriderm dermal matrix and Split-Thickness Skin Graft at the same time bolstered with NPWT. j) Two years postoperatively, the reconstruction of lower leg with two-step procedure with 2mm and one-step procedure 1mm Matriderm dermal matrix shows no soft tissue contour defect with intact and stable skin over the tendons, and full function.

- Infection and complications: Clinical data report low infection rates with Matriderm, typically 0–5%[211–213] compared with 16–42% for other biological and synthetic matrices.[214–216]
- Expanded indications: Recent reports extend its use beyond classical full-thickness skin defects. Applications include coverage of exposed bone, tendon and nerve, as well as mucosal repair, such as cleft palate;[217,218] and adhesion prevention by tendon/nerve wrapping.
- Clinical relevance: The ability to apply Matriderm immediately, or within the first 5–7 days post-injury, is crucial as it precedes the peak of myofibroblast activity (~day 7–14), thereby reducing pathological contraction and scar formation. This early grafting flexibility distinguishes Matriderm from matrices requiring longer pre-vascularisation periods.[219]

In summary, recent evidence positions Matriderm as a reliable, versatile dermal regeneration template. Its biomimetic composition supports rapid angiogenesis and dermal regeneration, while limiting inflammation, infection and contraction. Clinically, this translates into reduced hospital stay, decreased need for flap procedures, and improved functional and aesthetic outcomes. With expanding indications into mucosal and adhesion prevention surgery, Matriderm complements—rather than replaces—the reconstructive ladder, offering surgeons a flexible, evidence-based tool in the treatment of complex wounds.

Micromatrix/Cytal — Urinary Bladder Matrix (UBM)

The Urinary Bladder Matrix (UBM) is an acellular biological matrix derived from animal bladder mucosa—typically bovine or porcine—and is primarily used in regenerative surgery for the repair of damaged tissues or complex wounds. UBM is an acellular matrix that preserves the ECM and structural components derived from animal bladder tissue, particularly collagen (types I, III, IV, V), fibronectin, laminin and glycosaminoglycans. Its three-dimensional

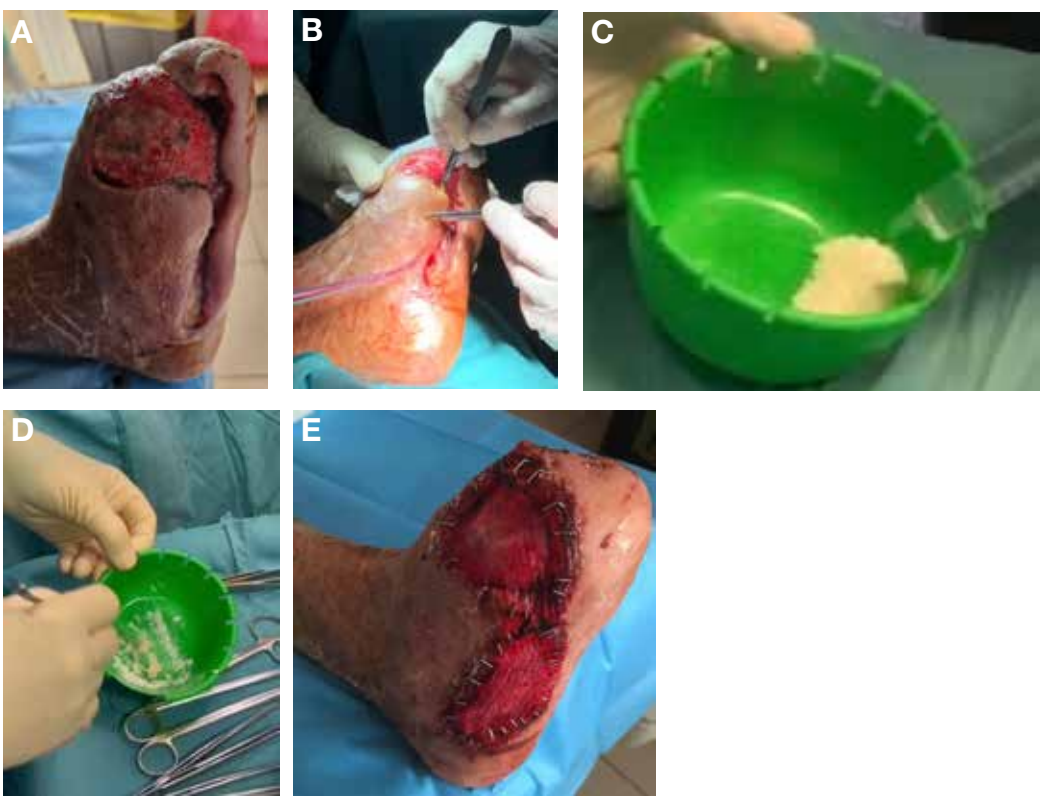

Figure 19. Micromatrix/Cytal case 1. a) This lesion resulted from a transmetatarsal amputation and plantar drainage in a neuro-ischaemic patient with forefoot gangrene and plantar access, following endovascular revascularisation. b) The lesion was surgically debrided, and its extension reduced by remarginating and suturing where possible without tension. c) Micromatrix was mixed with saline and d) mixed to obtain a paste that was applied to fill any voids within the lesion, which was then covered with Cytal and e) applied with staples.

porous structure promotes vascularisation and cellular infiltration by fibroblasts, endothelial cells and mast cells, which are essential for tissue regeneration.

With regard to recent literature, Daneshfar et al.[220] published a case report in 2021 describing the use of UBM for resurfacing 80% of the palm following postoperative necrosis after a table saw injury to the right volar palm at the distal crease. The authors also reported intact sensation and almost normal functional outcomes following treatment with the UBM.

In 2023, Baum et al[221] published a systematic review demonstrating that UBM may reduce time to definitive wound closure, recurrence of wound, infection and/or complication rates and immunogenic transplant rejection.

Meanwhile, Bormann et al[222] reported a UBM-based reconstruction of a split-thickness skin graft donor site, noting satisfactory healing, absence of pain, and excellent cosmetic and functional outcomes.

In 2024–2025, Kim et al[223,224] reviewed 56 lower extremity wounds treated with Integra and skin graft, Integra alone or UBM. The authors reported that patients in the UBM group were younger than those in the Dermal Regeneration Template group, with no significant difference in primary wound coverage failure (36.4% versus 41.2%; p=1.0).

Grussu et al[225] reported the reconstruction of large full-thickness scalp injury in children, describing high-quality outcomes.

In parallel, Alenizi[226] investigated the use of UBM in the management of postoperative infection by methicillin-sensitive *Staphylococcus aureus* following orthopaedic surgery. UBM promoted wound healing, controlling infection, and preventing further invasive procedures.

Based on our experience, UBM has been very useful in patients with infected wounds, such as infected vascular ulcers on lower extremities, and also as a filler in those with tri-dimensional lesions or tunnelling, where tissue repair requires more than simple coverage.

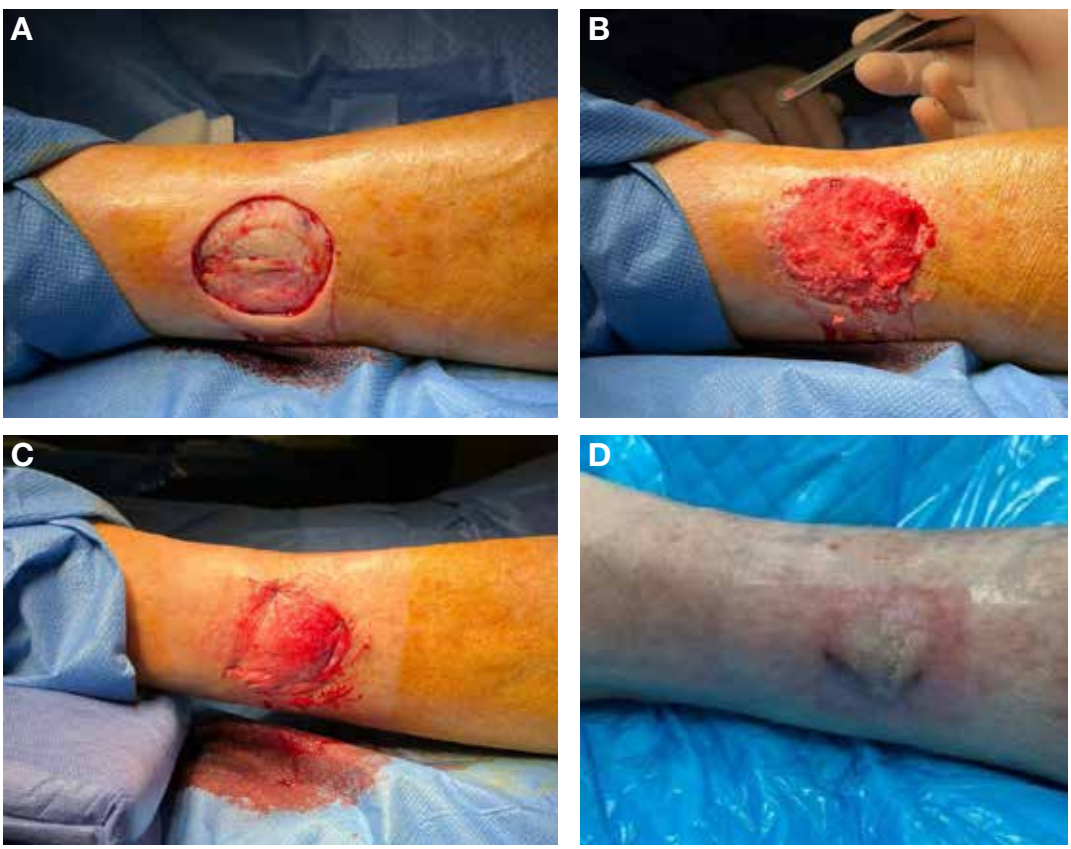

Figure 20. Micromatrix/Cytal case 2. a) post-skin cancer excision defect. b,c) Immediate coverage with particulate and sheet porcine urinary bladder matrix. d) Complete re-epithelialisation with no skin graft after 10 weeks.

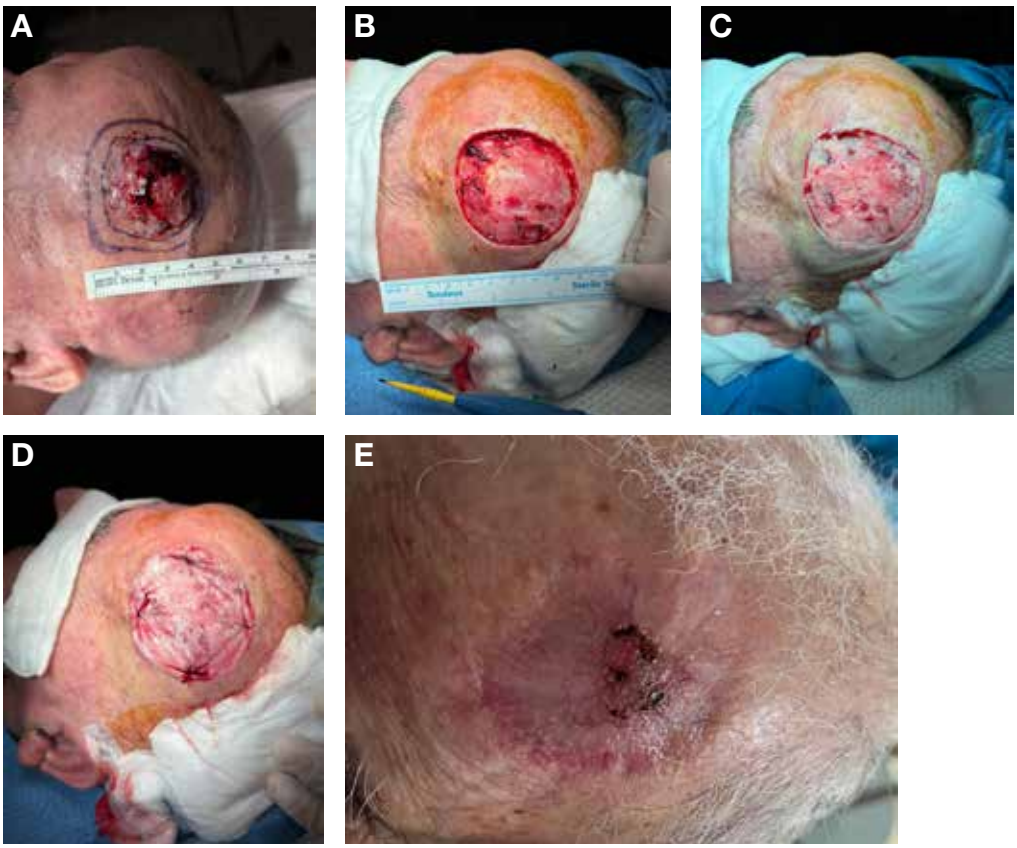

Figure 21. Micromatrix/Cytal case 3. a) post-skin cancer excision defect. b–d) Immediate coverage with particulate and sheet porcine urinary bladder matrix. e) Complete re-epithelialisation with no skin graft after seven weeks.

Myriad

Myriad Matrix is an engineered ECM scaffold derived from ovine forestomach matrix (OFM), isolated from the submucosal layer of ovine gastric tissue. The decellularisation process preserves the native ultrastructure and essential bioactive molecules while eliminating cellular antigens, thereby minimising immunogenicity and maintaining a biologically functional scaffold conducive to tissue repair and regeneration. The biomaterial exhibits a multilaminar, perforated and highly porous architecture, facilitating rapid host cell infiltration, nutrient diffusion and neovascularisation. These structural features optimise integration within the host tissue and accelerate the early phases of wound healing.

The scaffold rapidly absorbs blood and cellular components, generating a bioactive provisional matrix that supports haemostasis and the initiation of reparative cellular processes within the wound microenvironment. Proteomic characterisation confirms the retention of more than 150 native ECM proteins, including multiple collagen isoforms, glycosaminoglycans and signalling molecules. These components modulate key cellular behaviours such as migration, proliferation and differentiation, thus promoting a regenerative, rather than a fibrotic, healing response. Residual vascular channels within the scaffold act as conduits for endothelial cell migration and alignment, thereby promoting angioconduction and facilitating the development of a functional microvascular network critical for tissue viability and remodelling. Following implantation, fibroblasts, endothelial cells and immune effector cells infiltrate the scaffold, depositing autologous ECM proteins and progressively remodelling the biomaterial into functional host-derived tissue. Over time, this process results in the formation of a structurally and biologically integrated autologous tissue construct.

In 2020, Bohn & Chaffin[227] published a pilot case series on the use of Myriad for complex soft tissue defects with exposed vital structures where skin grafting or flap surgery was unsuitable. Six defects in five patients were

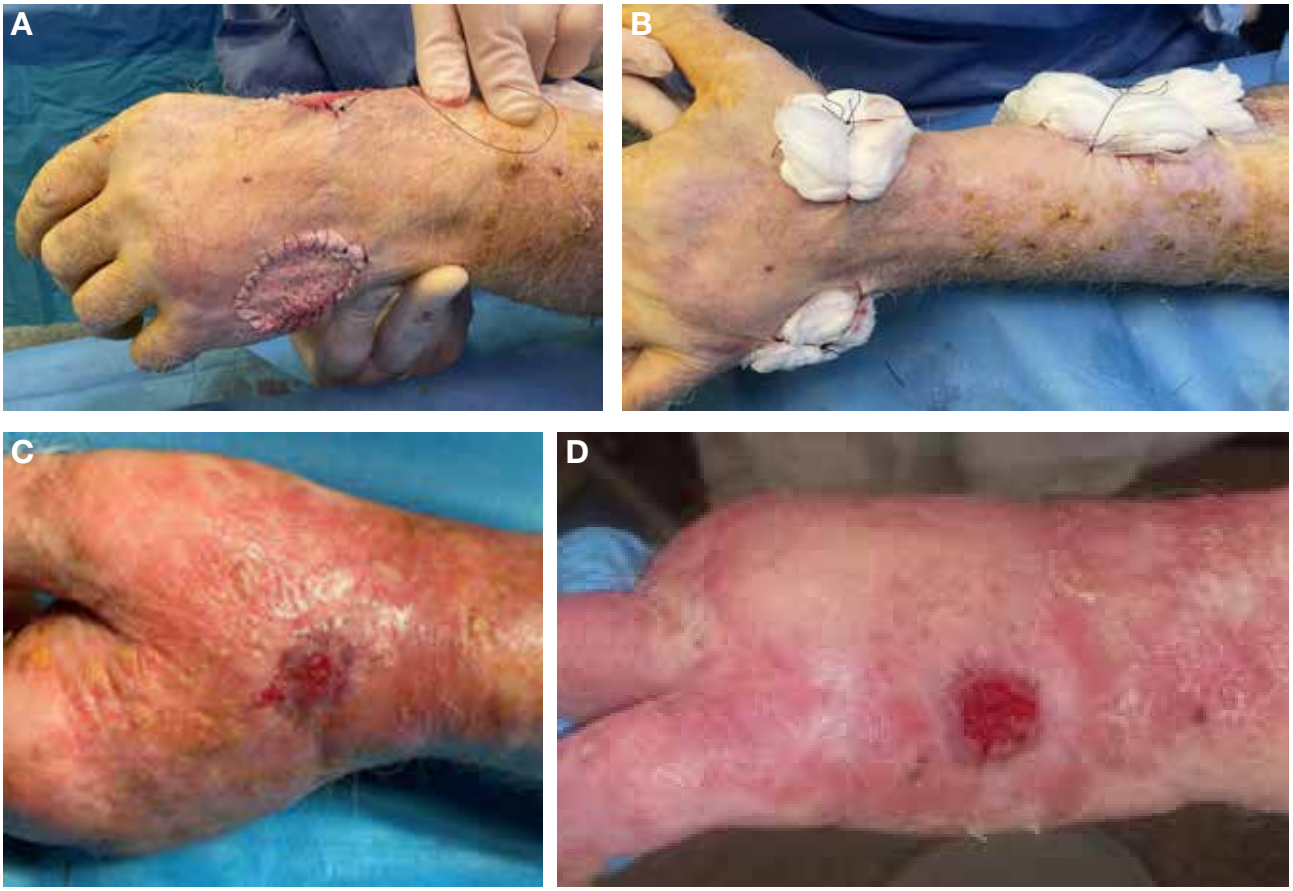

Figure 22. Myriad case. a) Following skin cancer excisions and immediate coverage with Myriad. b) Compressive moulage to improve adhesion on wound bed. c,d) Almost complete re-epithelialisation after 1 month, no skin graft required.

reconstructed using the Myriad Soft Tissue Matrix. The authors reported complete granulation in 1–6 weeks. Skin grafts achieved 100% take. No infections or major complications were reported.

In 2023, Cormican et al[228] performed a retrospective pilot case series describing 10 patients with 13 complex contaminated defects treated with Myriad combined with negative pressure wound therapy (NPWT). Granulation was achieved in 23.4±9.2 days. Definitive closure with skin grafts was achieved in 54% of wounds, while the remainder healed by secondary intention. No major infections or adverse events were reported.

During the same year, Bosque[229] published a retrospective case series evaluating the use of OFM products in the surgical reconstruction of 50 challenging lower extremity cases (n=50). A single application of OFM products was effective in regenerating well-vascularised neodermis, often in the presence of exposed structures, with a mean time of 26.0±22.2 days to 100% granulation.

In 2024, Lawlor et al[230] published a prospective observational study on 130 complex lower extremity reconstructions, reporting full coverage by granulation tissue in 30 days; no postoperative infections or major amputations were observed.

In summary, Myriad can be useful in complex or complicated wounds, including when skin grafting or flap surgery are unsuitable or refused.

Novosorb Biodegradable Temporising Matrix (BTM)

Novosorb BTM is a fully synthetic dermal matrix made of a 2mm-thick open-cell polyurethane foam, which is completely degradable, and covered by a non-degradable sealing membrane.

The development of this technology began in 2004 in Adelaide, Australia, with the identification of a distinct variety of polyurethane, which was tested and selected among other isoforms for its structure, an open-cell foam

with interconnecting micro-pores of 150micron in size, covered by a non-degradable polyurethane membrane.[231]

This distinct construct allows easy infiltration by host fibroblasts, endothelial cells and keratinocytes, while at the same time protecting the wound from fluid loss and external contamination.[232]

The porous foam acts as a temporary scaffold for the repairing cells and is completely degraded via hydrolysis in 12–18 months. After 4 to 6 weeks, the cellular infiltration and the formation of a healthy neodermis ready for grafting, is achieved, allowing removal of the external membrane.[233]

Novosorb BTM has been shown to elicit a strong response in the host, with the secretion of pro-inflammatory cytokines, which promotes fast and effective angiogenesis and fibrogenesis.[234]

Despite the intense inflammatory response, the quality of the neodermis generated with Novosorb BTM is characterised by reduced contraction and limited hypergranulation. This is attributed to the biophysical structure of the open-cell foam, which compartmentalises the wound into multiple micro-wounds, thereby attenuating biochemical signalling that would otherwise promote scarring and contraction. As a consequence, fibroblast transdifferentiation into myofibroblasts is limited.[235]

For these reasons, the quality of the neodermis formed with BTM has been described as being closer to that formed in the fetal environment, leading some authors to distinguish regenerative wound healing from reparative wound healing.[236]

Novosorb BTM has other interesting characteristics that can make a difference when compared to “biologic” matrices and which extend its potential indications in the management of chronic wounds.

The completely synthetic structure lowers its exposure to colonisation and infection from any kind of pathogen, from bacteria to fungi, making it possible to use it in contaminated wounds, or in contexts in which the risk of infection is particularly high, such as neuro-ischaemic or post-surgical wounds.

For the same reason, the production of Novosorb BTM does not require complex steps to ensure sterility in the manufacturing and maintenance until application. In

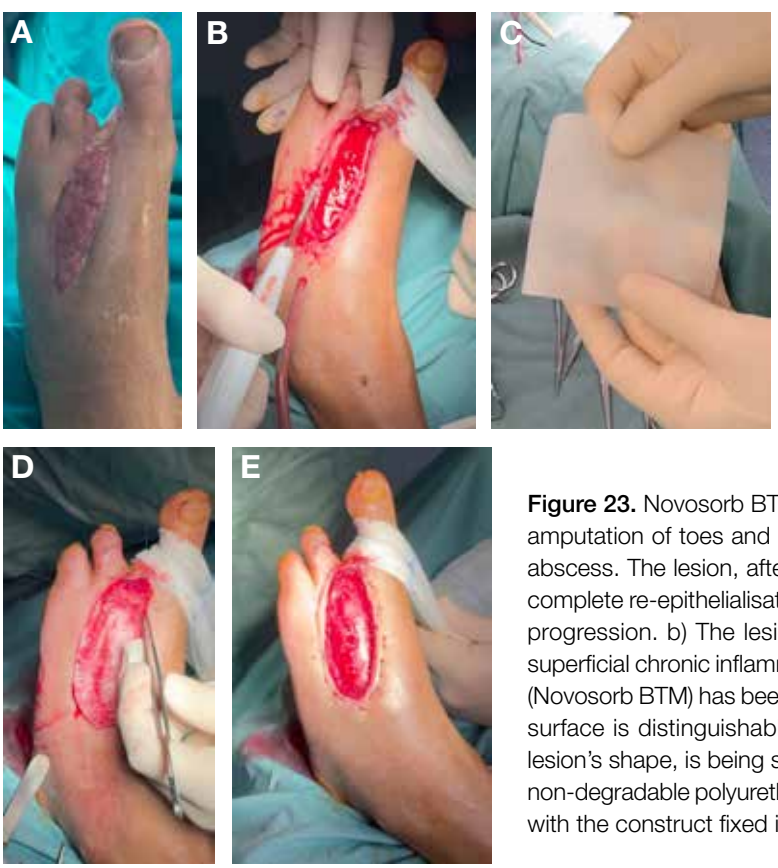

Figure 23. Novosorb BTM case 1. a) Dorsal lesion in a patient undergoing amputation of toes and drainage because of gangrene and medial dorsal abscess. The lesion, after an initial progress, stopped its evolution toward complete re-epithelialisation and remained stalled for 9 months without any progression. b) The lesion is debrided with hydrosurgery to remove the superficial chronic inflammatory tissue. c) The synthetic polyurethane matrix (Novosorb BTM) has been unfolded and is ready for application. The porous surface is distinguishable in the picture. d) The matrix, tailored to fit the lesion’s shape, is being secured with nylon 3/0 monofilament stitches. The non-degradable polyurethane sealing membrane is now visible. e) The lesion with the construct fixed in place at the end of the procedure.

Figure 24. Novosorb BTM case 2. a) "Chronic" burn of the forehead in Gaza patient. b,c) At 2 and 3 weeks after application of Novosorb BTM. d) Coverage with meshed skin graft at week 4. e) Result after two months.

addition, its availability is not dependent on access to biological source materials, unlike the biological matrices.

Both these factors have an impact on the costs of production of BTM, which are substantially lower when compared to the biologic competitors and allow a better accessibility of the device, extending the number of patients potentially treatable and the number of applications per patient.[237]

From a clinical perspective, Novosorb BTM, despite its relatively recent introduction, has been used in a variety of different settings on pathologies ranging from burns to post-traumatic and complex wounds, to chronic ulceration. More than 50 studies have been published so far in the peer-reviewed literature.

In burns, which currently represent the most frequently published area of application of BTM, the possibility of covering large areas avoiding fluid loss,[238,239] resistance to infection,[232,240,241], facilitation of graft take,[238–240,242,243] and the reduced tendency to retraction and contracture,[244,245] all represent positive features of BTM.

Post-traumatic and "non-graftable" wounds, such as those in which exposed tendons or joints or even bone do not allow grafting and eventually need complex free-flap reconstruction, have also been successfully managed with Novosorb BTM. Damkat-Thomas et al and Jou et al demonstrated that exposed tendons, that were primarily repaired or reconstructed with a tendon transfer, could be covered by soft tissue facilitated by BTM.[246,247] Furthermore, as reported by Concannon et al, patients with "un-graftable" wounds could be effectively treated with BTM and skin grafting in 92% of cases, thereby sparing these patients from flap surgery.[245]

BTM has also proven effective in extremely unfavourable indications, such as large defects after debridement for necrotising fasciitis[248] or cancer ulceration[249,250], where BTM was shown effective in repairing defects and promoting neodermis formation.

Chronic diabetic and vascular ulcers are difficult-to-reconstruct wounds, as diabetic and vasculopathic patients have impaired macro- and microvascular circulation, which compromises the ability of the biochemical and cellular factors involved in wound healing to reach the wound. Beyond this, the cellular environment of the chronic wound is fundamentally altered to impede effective wound healing.[251] Fibroblasts and keratinocytes are made senescent, and chronic inflammation prevents progression from the inflammatory to the proliferative phase of wound healing.[251]

Guerriero et al demonstrated, across 22 diabetic patients with concurrent peripheral vascular disease, that BTM successfully integrated and reconstructed 65% of chronic foot ulcers.[252]

In conclusion, Novosorb BTM is a novel synthetic degradable matrix with indications for a number of pathologies and conditions, ranging from chronic difficult-to-heal ulceration to cancer, post-traumatic wounds and contaminated wounds. Its characteristics include resistance to infection, complete degradability, easy accessibility and availability, all of which are related to its non-biologic synthetic origin, which also allows it to contain production costs.

Pelnac

Mostly used in Asia, Pelnac has recently been cleared for clinical use in Europe as well. It is a Porcine Origin Matrix composed of a biodegradable scaffold of porcine tendon-derived atelocollagen sponge layer (~3mm thick), the absence of telopeptides decreases antigenicity), and a reinforced silicone film layer that acts as a temporary external barrier to protect the wound and help control moisture. Once applied to a full-thickness or deep dermal wound, the silicone layer protects the wound from external contamination and helps maintain optimal moisture levels, while the collagen sponge conforms closely to the wound bed. Within approximately 2–3 weeks, host fibroblasts and capillaries migrate into the porous atelocollagen matrix, gradually replacing it with a dermis-like tissue rich in newly synthesised collagen and vasculature. Once sufficient neodermal tissue has formed (usually between 14–28 days, although timing may vary depending on patient and clinical factors), the silicone layer can be peeled off. At this point, the revascularised wound bed can either be covered with a thin split-thickness skin graft or left to heal on its own (secondary intention).

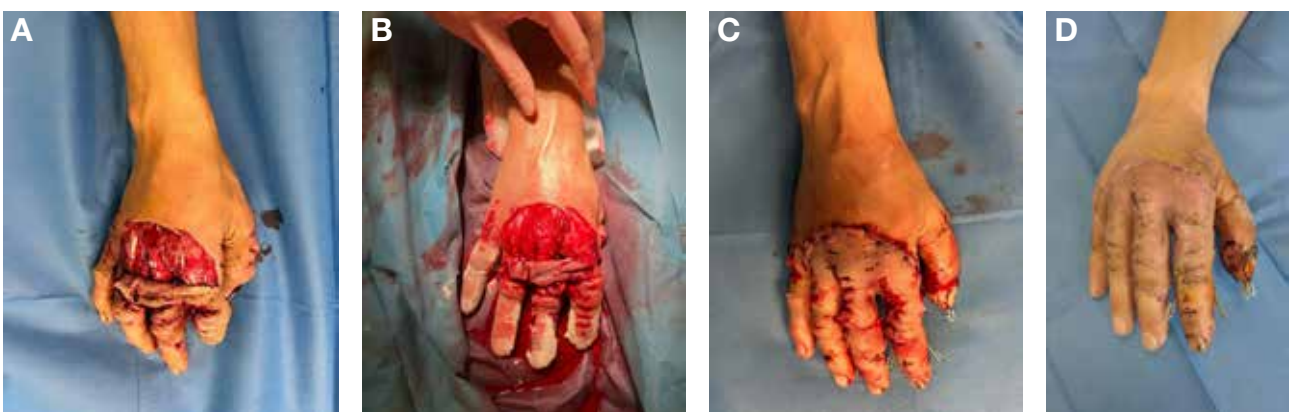

Figure 25. Pelnac case 1. a) Severe trauma of the right hand with degloving of the dorsum. b) Immediate coverage with Pelnac single layer and autologous injured flap. c) Immediate postoperative. d) After 40 days.

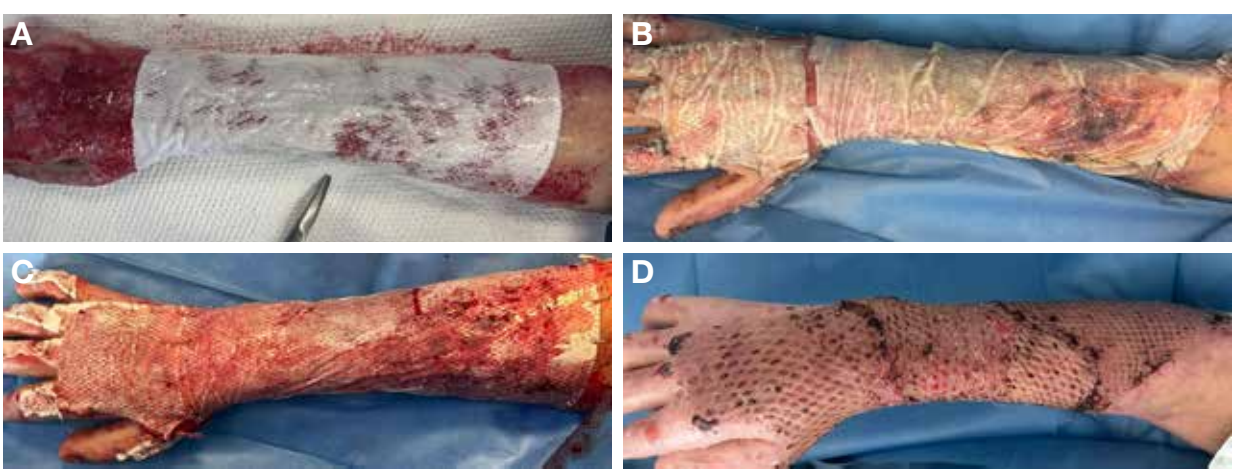

Figure 26. Pelnac case 2. a) Severe burn of the right arm: covered with Pelnac dual layer after necrectomy. b) After 1 week. c) After 2 weeks: change in 'colour' indicating that the wound bed is ready. d) 40 days after meshed skin graft: showing the complete grafting.

In 2020, Lisa et al[114] reported a retrospective study on 12 patients (9 tumour resections and 3 chronic ulcers) demonstrating complete intake after 21.3 days in 11 of the 12 patients (91.6%). Meanwhile, De Francesco et al[253] conducted a comparison between Pelnac and Integra on 71 patients in a randomised prospective observational paired study. Pelnac demonstrated better epidermal proliferation at 2 weeks and less contracture at 2 and 4 weeks; Integra was suitable for wounds deeper than 1.5cm. Finally, Lv et al[254] in the same year, demonstrated 100% graft take after 16.5 months in 16 patients affected by wounds with underlying bone and/or tendon exposure.

In 2021, Corrêa et al[255] published a randomised clinical trial on contraction of the split-thickness skin graft in 39 patients: 10 patients treated with Pelnac, 10 with Integra, 9 with Matriderm and 10 controls without matrix. They noted that twelve months after surgery, the control group presented lower rates of skin graft contraction than the Integra ($p<0.01$), Matriderm ($p=0.01$) and Pelnac ($p<0.01$) groups. Pelnac resulted in greater skin graft contraction than Matriderm ($p<0.01$) and Integra ($p=0.02$), while differences between Integra and Matriderm were not significant ($p=0.16$). The comparison between intraoperative and 12 months after surgery showed that the worst mean rates of skin graft contraction were observed with Pelnac (51.79%) and Matriderm (59.17%).

During the same year, as mentioned earlier, Cottone et al[116] published a retrospective cohort study comparing Integra, Nevelia and Pelnac in management of critical lower-limb wounds in 122 patients. In this study, the authors noted that Integra had the highest rates of skin graft take and viability; Nevelia showed a low secondary healing induction rate, but its graft take was superior compared with Pelnac, while Pelnac was the quickest in acute wounds.

In 2022, Salloum et al[256] conducted a systematic review comparing the application of different types of dermal matrices in various skin defects. The authors analysed 14 articles on porcine dermal matrix applied in 1511 patients and noted the major application area in burn injury (n=1038, 68.7%), tumour excision (n=221, 14.6%), other (trauma, compartmental syndrome, not reported) (n=232, 15.4%), necrotising fasciitis (n=8,0.5%), ulcers (n=6, 0.4%), and pretibial lacerations (n=6, 0.4%). Almost all wounds (97.6%) dressed with porcine graft healed spontaneously without additional surgical intervention. The mean discharge date or length of stay was on the 6th day (6.35 days). The mean time of graft healing was reported for 33.7% (n=510) of patients included in the article. In these patients, a significant improvement was achieved, where the lesion had healed by the 4th week (29 days) following porcine dermal matrix application. Infections were the most common adverse event reported, with wound colonisation observed in 3.7% of patients (n=57).

Meanwhile, Li et al[257] reported their experience in 7 patients affected by lower-extremity full-thickness skin defect with exposed bone or tendon. The patients were treated with a one-stage application of Pelnac in order to promote wound healing, and after a maximum of 20 weeks, all wounds were completely healed.

Many studies were published in 2024. The first, by Ali et al[258], was a prospective study on 26 patients with acute isolated tendon injuries distal to the wrist joint. The patients were initially treated with Pelnac and later covered with a split-thickness graft. The authors reported an integration rate of 100% of cases, with complete graft take in 22 of 26 patients. The mean QuickDASH score was 20.5±15.7, and the mean Vancouver Scar Scale score was 3.53±3.2. Full range of motion returned in 22 of 26 patients.

During the same year, Nocini et al[259] published a prospective study on 21 patients who underwent radial forearm and fibula flaps harvest for reconstruction of head and neck defects following oncological surgery. The patients were divided into two groups: 13 patients treated by one-stage Pelnac reconstruction of the donor-site defect, and eight patients who underwent full-thickness skin grafting. Scar quality was evaluated using the Vancouver Scar Scale. The authors reported that most patients treated with one-stage Pelnac reconstruction showed good healing of the flap donor site, with minor complications, good scar quality and overall satisfaction.

Meanwhile, Kang[260] published a single-centre prospective study on 31 patients affected by fingertip injuries involving volar pulp defects treated with Pelnac and a semi-occlusive dressing (IV 3000). The reported mean treatment duration was 45.29 days (SD=17.53). Interestingly, the authors noted a considerable regeneration of fingertip (mean score=2.58, SD=0.67) with a high cosmetic and patient satisfaction and minimal sensory disturbance and pain.

Zhang et al[261] published a retrospective case-control study

analysing clinical data from 45 cases of skin and soft-tissue defects featured by bone or tendon exposure. The authors reported the safety and effectiveness of Pelnac in patients who cannot undergo autologous skin flap transplantation. Elkholy et al[262] reported a prospective observational cross-sectional study on 53 patients affected by traumatic injuries of the leg and ankle region, reporting a complete coverage of exposed structures following the use of Pelnac.

Finally in 2025, Rady et al[263] conducted a randomised control trial evaluating 46 patients affected by acute deep dermal burns of the upper limb. The patients were divided into two groups: a graft-only group (23 patients), treated with traditional split-thickness skin grafts, and a Pelnac group (23 patients) followed by delayed grafting. After initial failure in 17 patients due to insufficient debridement, the Pelnac group showed significantly better scar outcomes, and no significant differences in functional recovery.

In summary Pelnac offers several clinical advantages:

- High vascular ingrowth ("take rate" of 95–100%), which supports effective grafting.
- Reduced scar contraction, better aesthetic outcomes, and lower risk of hypertrophic scarring compared with traditional methods.
- Effectiveness in challenging wound types, such as deep burns, exposed bone or tendons, traumatic defects, post-oncologic resections, nevi removal, donor sites, and chronic ulcers.

Hy-Tissue Micrograft Technology

Although it cannot be considered in the strictest sense to be a matrix, Hy-Tissue Micrograft Technology deserves a place among medical devices identified with this term because of its characteristics and indications.

This represents a typical example of how combining different technological approaches in this case, mechanical fragmentation and autologous tissue processing—can lead to a result that effectively extends the potential of the two individual options.

Hy-Tissue Micrograft Technology (Fidia, Abano Terme, Italy) is a polyether-ether-ketone-made, single-use medical device for the fragmentation of tissue biopsies. It is composed of a chamber in which the harvested tissue is placed and a rotating engine that mechanically fragments the tissue. The medical device is sterile and intended for single use under sterile conditions, according to the Meek et al technique of skin micrograft, modified by Kreis et al and Trovato et al. From a skin epidermal biopsy, it produces, after processing in a dedicated area of the device, particles named Fragmented Dermo-Epidermal Units (FdeU), which are placed onto the wound bed and injected into the margins.[264–266]

FdeU have been shown to be composed of keratinocytes respecting physiological stratification, with the presence of cutaneous adnexa and fibroblasts, embedded within a well-organised collagen fibre net.[267]

The FdeU have been intensively studied and characterised not only in their three-dimensional organisation and structure by means of electron microscopy, but also for their viability, which has been demonstrated to be preserved over a three-week period, and for their vitality, by measuring the production of growth factors (adiponectin, VEGF, FGF, TNF) and interleukins (IL2, IL6, IL7, IL8, IL10).[267]

From a practical point of view, the procedure requires harvesting a 2x0.5cm tissue lozenge from thigh, inguinal or low abdominal areas, including skin and dermis while avoiding subcutaneous fat, considering that 1mm squared of dermal micrografts is expected to heal a wound with a maximum size of 2cm squared. After dividing the biopsy into four pieces, these are processed simultaneously, one for each quadrant of the grid.

Tissue processing is conducted (with a rotation speed of 150rpm) through the addition of 15mL of sterile physiological solution. Once fragmentation is complete, the saline solution containing the micrografts is aspirated from the lower chamber using a 20mL sterile syringe without a needle (Figure 27).

Approximately 50% of the suspension can be seeded into a collagen or hyaluronic acid scaffold to create the bioconstruct. Approximately 50% of the suspension from 2 punches of 6mm, resuspended in 15mL of saline, can be seeded onto a 5× 5cm squared dressing. The remaining suspension is injected into the lesion site of injury, with placement of the bioconstructs over the ulcer and a secondary moist dressing with paraffin gauze and moist gauze on top with a final moderate compressive dressing.[267]

Although the approach of micrografting boasts a long tradition, with thousands of cases successfully performed over the years since the 1960s,[268–271] it is only following the technological refinements introduced in more recent years[266,272] that clinically sound experiences on chronic ulcers have been published, especially on the lower extremities.

De Francesco et al showed, in a group of 30 patients with ulcers of mixed aetiology treated with FdeU, improved healing of venous, diabetic, pressure and post-traumatic ulcers after a few weeks of treatment, generally accomplished with improved quality of life for the patients. In vitro results showed that these micrografts expressed mesenchymal stem cell markers such as CD34, CD73,

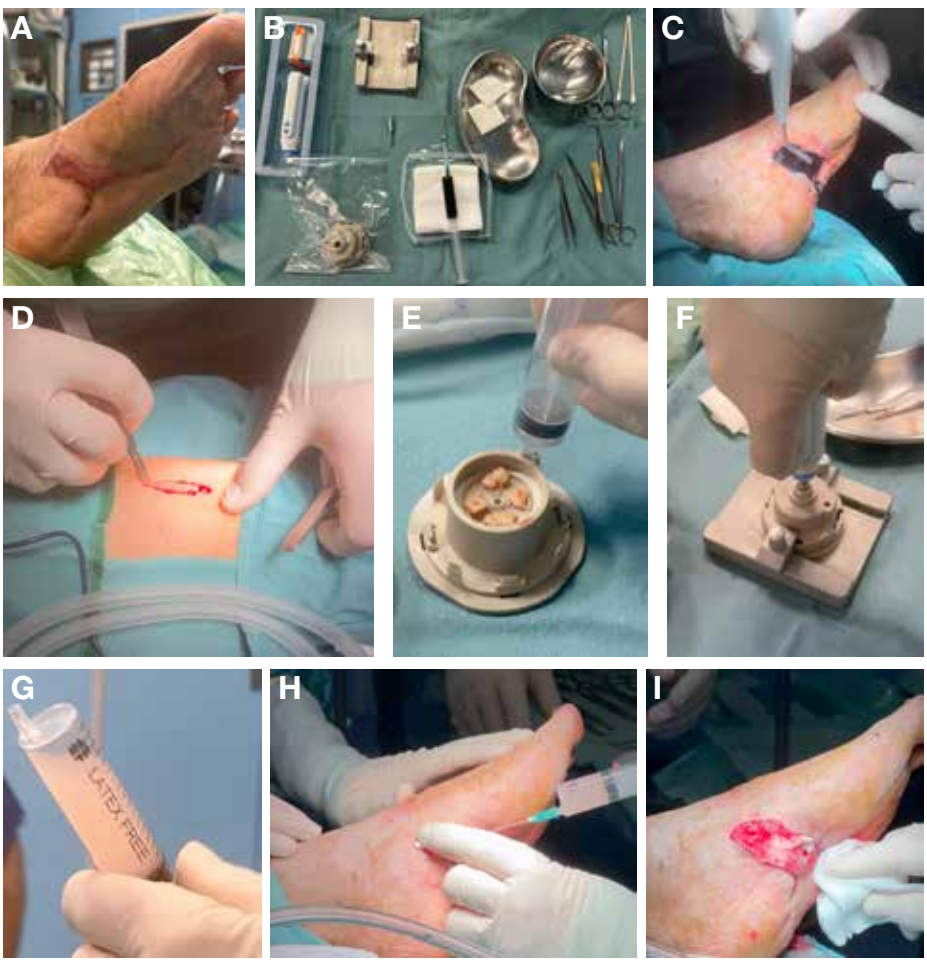

Figure 27. Hy-Tissue Micrograft Technology. a) Diabetic foot patient with a post-surgical lesion following plantar drainage. The lesion shown had been present and non-evolving for 18 months. b) Operative set. On the left, the micro-engine and the batteries, the rotating tissue processor, the base for securing the processor. On the right, the collagen sponge the micro-fragmented tissue is placed on. In the centre, on the gauze pad, the syringe with methylene blue used to paint the bottom of the lesion prior to debridement. c) Debriding the lesion with hydrosurgery, after painting it with methylene blue for better definition and precision. d) Harvesting full-thickness biopsy 0.5x2x0.2cm from the homolateral thigh. e) The biopsy, already divided into four small pieces is placed into the processor. f) Processing the tissue with the engine connected to the processor, rotating 60 seconds clockwise and 60 seconds anticlockwise. g) Collecting the micro-fragmented tissue into a 15ml saline syringe. h) Injecting half of the suspension into the wound margins. i) Injecting the remaining suspension into the collagen sponge. j) Securing the construct with paraffin gauze and polyurethane film.

CD90 and CD105, and were able to form a viable and proliferative biocomplex with collagen sponge. Finally, ulcer sites displayed a different expression of epidermal growth factors, insulin-like growth factors, platelet-derived growth factors and their receptors, as well as tumour necrosis factor-β, compared with healthy skin samples.[273]

Miranda et al showed, in 15 patients with chronic mixed ulcers in the lower limb treated with FdeU, a healing rate of 86.7% a 16 months, with good quality of the regenerated tissue.[274]

Riccio et al demonstrated, in 70 patients with post-traumatic wounds of the upper and lower limbs, complete healing occurring between 35 and 84 days in 69 patients (98.6%), without any significant adverse events.[275]

Lázaro Martínez et al showed, in a case series of 10 patients with chronic DFU, a healing rate of 60% at 12 weeks and a reduction in wound area of 67.2±23.5% at 4 weeks and 87.5±24% at 12 weeks, respectively, with no complications and no severe adverse events.[276]

According to the clinical experience accumulated so far, the potential to stimulate the reparative processes through the secretion of growth factors and cytokines, while at the same time initiating re-epithelialisation coverage from the bottom of the cutaneous adnexa present in the FdeU, makes Hy-Tissue Micrograft Technology extremely useful in cases where grafting is problematic according to the traditional techniques, either because of the large surface to be covered, as in extensive burns, or because of limited availability of skin for grafting, as in children.

Moreover, due to its dual nature, this is a one-step technology that combines pro-regenerative and resurfacing phases in chronic wound management, results in a net saving in resource consumption.

Conclusion

Normal wound healing follows a highly regulated cascade of haemostasis, inflammation, proliferation, and remodelling. However, in complex wounds—such as deep defects, exposed structures including tendons and bone, or in patients with comorbidities—this sequence is often

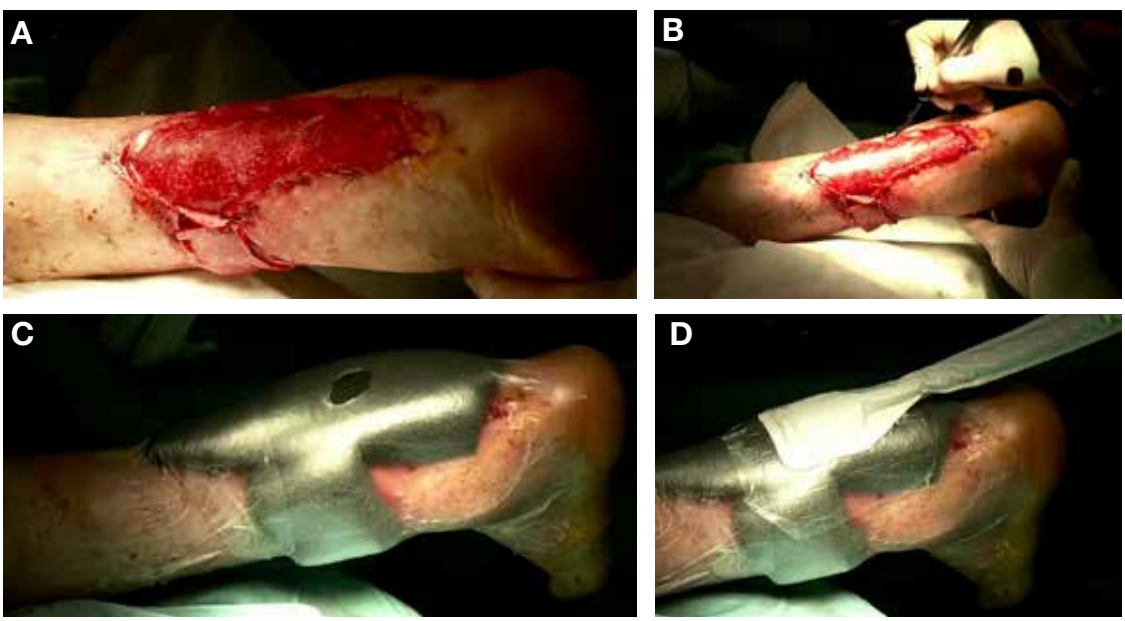

Figure 28. A case of combination of two different technologies, negative pressure wound therapy (NPWT) and dermal matrices, as complementary approaches to a difficult-to-heal chronic wound. a) A lesion on the Achilles tendon caused by inadequate bed positioning during intensive care unit admission has already been debrided and a dermal matrix has been positioned. b) The matrix is being fenestrated to help drainage and secure the transmission of negative pressure, that will increase the contact of the graft on the wound bed. c) The polyurethane foam is being applied and secured with polyurethane film on the construct, with the interpolation of a neutral secondary dressing, in this case paraffin gauze. d) The tubing is being applied to the construct, connecting it to the machine producing a controlled vacuum, not exceeding 60mmHg, to avoid damaging the matrix and its taking.

disrupted. Prolonged inflammation delays proliferation, impairs angiogenesis, and leads to disorganised remodelling with inevitable contraction and scarring. The reconstructive ladder offers various surgical solutions, but each step carries specific limitations and morbidity of the surgical and/or donor site. Dermal matrices—sometimes used in combination with other approaches, such as negative pressure (Figure 28)—complement split-thickness skin grafts by supporting dermal regeneration and enhancing both functional and aesthetic outcomes.

Table 3. Studies on dermal matrices for skin damage repair

Authors, year [reference]	**Type of study**	**Acellular matrix/ technology tested**	**Number of cases**	**Results**
Yang et al, 2016[200]	Prospective	Kerecis	18 patients (5 weekly applications and 3 weeks of standard of care)	40% decrease in wound surface area ($p<0.05$) and a 48% decrease in wound depth
De Francesco et al, 2017[273]	Case series and in vitro	Hy-Tissue Micrograft	30 ulcers with mixed aetiology	Improved healing and better quality of life. In vitro
Miranda et al, 2018[274]	Case series	Hy-Tissue Micrograft	15 chronic mixed ulcers in lower limb	Healing rate of 86.7% at 16 months
Dorweiler et al, 2018[202]	Multicentre case series	Kerecis	25 wounds (VLU and DFU)	Reduction of analgesics intake immediately after the treatment
Greenwood et al, 2018[232]	Prospective	Novosorb BTM	5 burned patients (20–50% TBSA)	Replacement of 9% TBSA with fresh BTM, with complete subsequent integration. The scar results at 12 months, using POSAS and MAPS scar scales, were very good
Wagstaff et al, 2018[248]	Case series	Novosorb BTM + secondary skin graft	7 necrotising fasciitis	Loss of BTM over 'mobile cavities' and no graft was lost over BTM
Riccio et al, 2019[275]	Case series	Hy-Tissue Micrograft	70 post traumatic wounds of upper and lower limbs	98.6% complete healing between 35 and 84 days
Alam et al, 2019[192]	Case series	Kerecis	10 split-thickness donor site on burned patient	Analgesic effect plus a 100% re-epithelialisation
Michael et al, 2019[193]	Retrospective case series	Kerecis	58 DFU	Surface reduction in 87.57% and complete healing in 60.34%
Woodrow et al, 2019[194]	Prospective	Kerecis	8 postoperative diabetic feet (6 weeks follow up and dressing changed weekly)	Wound area reduction mostly in recent (<3 months) lesions
Badois et al, 2019[195]	Case series	Kerecis	21 skin donor site	Faster healing from 68 to 32 days on 21 skin donor sites
Damkat-Thomas et al, 2019[246]	Case report	Novosorb BTM + split-thickness skin graft	Dorsal foot degloving	The paratenon-denuded tendons glided under the neo-dermis without tethering to the overlying integrated matrix, allowing a full range of digital movement

Authors, year [reference]	Type of study	Acellular matrix/ technology tested	Number of cases	Results
Kirsner et al, 2020[196]	Comparative double blind, prospective, randomised study	Kerecis	170 wounds (85 treated with Kerecis versus 85 treated with amniotic membrane)	Group treated with Kerecis healed faster
Raizman et al, 2020[98]	Multicentre case series	Endoform	27 patients (VLU, DFU, PU, surgical wounds, traumatic, sinus pilonidalis, necrotising fasciitis, radiation-induced injury)	Average time wound closure 8.2 weeks (2.7–19.7 weeks); 64% reduced wounds at 4th week, average area reduction 66%; 73% complete closure at 12 weeks
Hicks et al, 2020[173]	Prospective case series	Integra	107 DFU	After 18 months 93+/-3.3% of patients were healed
Dalla Paola L et al, 2020[174]	Retrospective case control	Integra	13 cases (critical limb ischaemia) and 13 controls	Integra promoted a faster healing (83 days versus 139 in the control group)
Scalise et al, 2020[175]	Retrospective case series	Integra	111 patients divided into two groups according to complications	No difference in complications. No skin graft, only matrices if elderly and multiple comorbidities
Bernstein et al, 2020[177]	Case series	Integra + skin graft	14 extremely elderly patients affected by scalp defects	Complete healing in 86%
Choughri et al, 2020[178]	Case series	Integra	14 traumatic soft tissue defects on dorsal hand, fingers and thumb	After 36 months, Integra demonstrated to be a good alternative to flap reconstruction
Shakir et al, 2020[179]	Retrospective Case-control	Integra	191 wounds	70% healed cases after 180 days
Rudnicki et al, 2020[180]	Retrospective case series	Integra + skin graft	13 burned patients	Good results when applied immediately after escharectomy
Chaiyasate et al, 2020[181]	Retrospective case series	Integra	13 scalp defects	Good scalp reconstruction after 3 months of follow up
Gonzalez et al, 2020[183]	Systematic review	Integra	602 patients and 1254 treated areas	212 infections (16,9%): application not suitable for sites at risk of infections
Vana et al, 2020[184]	Prospective	Integra versus Matriderm	24 patients (12 Integra versus 12 Matriderm)	Integra has lower retraction, better skin quality, and it's still present after 12 months
Phillips et al, 2020[213]	Retrospective Case series	Integra versus Matriderm	59 burned patients treated with Integra and 35 with Matriderm	Matriderm group has lower rate of infection and contractures
Bohn et al, 2020[227]	Pilot case series	Myriad	6 complex wounds	Complete granulation in 1–6 weeks. Skin grafts achieved 100% take

Authors, year [reference]	Type of study	Acellular matrix/ technology tested	Number of cases	Results
Greenwood et al, 2020[238]	Case report	Novosorb BTM + Autologous bilayer composite cultured skin	95% burned patient	Possibility of covering large areas avoiding fluid loss
Larson et al, 2020[243]	Case series	Novosorb BTM + Recell	3 burned patients (35-60% TBSA)	BTM used in conjunction with Recell ASCS successfully achieved definitive closure of full-thickness burn wounds and demonstrated acceptable outcomes
Lisa et al, 2020[114]	Retrospective case study	Pelnac	12 patients (9 tumour resection and 3 chronic ulcers)	Complete intake after 21.3 days in 11 on 12 patients (91.6%)
De Francesco et al, 2020[253]	Randomised prospective observational paired study	Pelnac versus Integra	71 patients	Pelnac demonstrated a better epidermal proliferation at 2 weeks and less contracture at 2 and 4 weeks; Integra was suitable for wounds deeper than 1.5cm
Lv et al, 2020[254]	Retrospective case series	Pelnac + skin graft	16 patients with underlying bone and/or tendon exposure (average follow up 16.5 months)	100% graft take
Romano et al, 2021[182]	Retrospective case series	Integra	20 scalp lesions (patients also affected by comorbidities, aggressive or relapse tumours)	Good results after 68 days of follow up
Lullove et al, 2021[104]	Randomised clinical trial	Kerecis	49 DFU treated with Kerecis or collagen alginate dressing	67% treated with Kerecis were completely closed versus 32% in collagen group at 6 weeks, the area reduction was 41.2% in the collagen group versus 72.8% in Kerecis group
Daneshfar et al, 2021[220]	Case Report	Micromatrix/ Cytal	1 post traumatic injury of the right volar palm at the distal crease	Resurfacing 80%, intact sensation and almost normal functional outcomes
Kelly et al, 2021[239]	Case Report	Novosorb BTM	86% TBSA	Novosorb BTM can stay in place for 3 months and can be used to stabilise the patient
Concanoon et al, 2021[245]	Case report	Novosorb BTM + split-thickness skin graft	42% full-thickness burns	Good reconstruction option for complex extensive perineal wounds in frail elderly patients
Sun et al, 2021[250]	Case report	Novosorb BTM + split-thickness skin graft	Large carcinoma of the back	BTM used to cover defect promoting neodermis formation

Authors, year [reference]	Type of study	Acellular matrix/ technology tested	Number of cases	Results
Corrêa et al, 2021[255]	Randomised Clinical Trial	Pelnac vs Integra versus Matriderm versus control	39 split-thickness skin graft (10 treated with Pelnac, 10 with Integra, 9 with Matriderm, 10 controls)	At 12 months the control group presented lower rated of skin graft contracture that the treatment groups. the worst mean rates of skin graft contraction were from the Pelnac (51.79%) and Matriderm (59.17%)
Cottone et al, 2021[116]	Retrospective cohort study	Integra vs Pelnac versus Nevelia	122 critical lower limb wounds	Integra had the highest rate both of skin graft take and viability, Nevelia had a low secondary healing induction rate, but its graft take was superior comparing with Pelnac, but Pelnac was the quickest in acute wounds
Prezzavento et al, 2022[185]	Two-year retrospective review	Integra + skin graft after 20 days	13 cutaneous oncologic excision	Mean graft take rate was approximately 92%, with an average grafting time of 20 days, yielding optimal aesthetic and functional outcomes and no significant infectious complications
Bosque et al, 2022[172]	Retrospective pragmatic real-world data (case-control)	Endoform	1150 DFU treated with matrix vs 1072 DFU treated with collagen/oxidised regenerated cellulose	DFU treated with OFM healed up to 5.3 weeks faster. Cox proportional hazards analysis showed that treated wounds had an 18%–21% greater probability of healing
Abla et al, 2022[240]	Case series	Novosorb BTM + regenerative epidermal suspension concerning cell harvesting	3 burned patients	Using them in conjunction allowed to shorten the length of stay in patients with severe partial and full-thickness burns
Schlottmann et al, 2022[241]	Single-centre retrospective analysis	Novosorb BTM	20 complex wounds	BTM showed to be a reliable and versatile reconstructive option, especially for patients with multiple co-morbidities and microbiologically colonised wounds
Gładysz et al, 2022[244]	Case report	Novosorb BTM	15% TBSA burned patient with persisting Pseudomonas aeruginosa infection	The application of Novosorb BTM over a contaminated field can win extra time for topical infection treatment and additionally provide an excellent skin grafting ground
Salloum et al, 2022[256]	Systematic review	Pelnac and others	14 articles about Pelnac with 1511 patients	97.6% of the wounds treated with Pelnac healed spontaneously
Lantis et al, 2023[198]	Prospective, multicentre, randomised controlled trial	Kerecis	102 DFU (51 treated with Kerecis versus 51 treated with collagen alginate therapy)	56.9% closure in Kerecis group vs 31.4% in control group; the mean percentage area reduction at 12 weeks was 86.3% for Kerecis versus 64.0% for controls

Authors, year [reference]	Type of study	Acellular matrix/ technology tested	Number of cases	Results
Krasteva et al, 2023[209]	Case series	Matriderm + skin graft	22 patients (11 patients treated with skin graft and 11 treated with Matriderm and skin graft (chronic wounds and post-traumatic))	Reduced hospital stay in trauma and chronic wound patients more than 50%
Baum et al, 2023[221]	Systematic review	Micromatrix/ Cytal	94 articles on complex wounds	UBM may reduce time to definitive wound closure, recurrence of wound, infection and/or complication rates, and immunogenic transplant rejection
Bormann et al, 2023[222]	Case report	Micromatrix/ Cytal	Split-thickness skin graft donor site	Satisfactory healing, no pain
Cormican et al, 2023[228]	Retrospective pilot case series	Myriad + NPWT	13 complex contaminated defects	Granulation was achieved in 23.4±9.2 days. 54% of the wounds were definitely closed with skin grafts and others healed by secondary intention
Bosque et al, 2023[229]	Retrospective case series	Myriad	50 surgical reconstructions	One application of OFM products was effective in regenerating well-vascularised neodermis, with a mean time to 100% granulation of 26.0±22.2 days
Granick et al, 2023[231]	Case series	Novosorb BTM	27 complex wounds	Wide range of applications for this product well beyond burn care. Its safety record, resistance to infection and ease of use facilitate surgery
Heard et al, 2023[242]	Case series	Novosorb BTM + Culture epithelial autograft	10 burned patients (average TBSA 81%)	Five patients had complications related to the BTM requiring removal or replacement including three fungal infections, one bacterial infection, and one with bleeding and a large clot burden
Guerriero et al, 2023[252]	Case series	Novosorb BTM	22 diabetic patients with peripheral vascular disease	BTM successfully integrated and reconstructed 65% of chronic foot ulcers
Li et al, 2023[257]	Case series	Pelnac	7 lower extremity full-thickness skin defects with exposed bone or tendon	100% healing after 20 weeks
Boschetti et al, 2024[186]	Retrospective case series	Integra single layer + split-thickness skin graft (one stage procedure)	18 scalp full-thickness defect after carcinoma excision	Complete graft take rate of 77%, a reduced healing time (<60 days) with consequent possibility of early radiotherapy
Turton et al, 2024[187]	Case series	Integra	101 scalp reconstructions	95% success rate using Integra alone. Postoperative infections in 21% of cases, managed with topical and oral antibiotics

Authors, year [reference]	Type of study	Acellular matrix/ technology tested	Number of cases	Results
Dardari et al, 2024[190]	Randomised clinical trial	Kerecis	255 DFU (129 Kerecis and 126 standard of care)	Higher rate of healing at 16 weeks (44% versus 26%) and shorter time (17.3±0.69 versus 19.4±0.66 weeks, respectively) in the Kerecis group
Alawi et al, 2024[210]	Single-centre, retrospective follow-up study	Matriderm + split-thickness skin graft	49 complex wounds	77.5% were successfully treated with Matriderm and split-thickness skin graft
Kim et al, 2024[223]	Retrospective case series	Integra + skin graft vs Integra alone vs UBM	56 lower extremities wounds	UBM group vs integra group had no difference in primary wound coverage failure (36.4% versus 41.2%; p=1.0)
Grussu et al, 2024[225]	Case report	Integra + Micromatrix (UBM)	Large full-thickness scalp injury in child	Integra DRT and Integra Micromatrix can be used together for the management of full-thickness complex wounds
Alenizi et al, 2024[226]	Case report	Cytal (UBM)	Ankle fracture wound	Application of UBM over the wound showed significant improvement, with tissue remodelling observed within two weeks
Lawlor et al, 2024[230]	Prospective observational study	Myriad	130 complex lower extremity reconstruction	A full coverage by granulation tissue in 30 days
Jou et al,. 2024[247]	Case series	Novosorb BTM + late split-thickness skin graft	2 patients: 1) dorsal hand injury with exposed tendons, 2) forearm injury with exposed tendon	Excellent tendon gliding and functional outcomes
Buick et al, 2024[249]	Case report	Novosorb BTM + split-thickness skin graft	Large basal cell carcinoma of the face	Good skin colour match with minimal contour deformity
Ali et al, 2024[258]	Prospective study	Pelnac and late split-thickness skin graft	26 patients with acute isolated tendon injuries distal to the wrist joint	Integration rate of 100% of cases, with complete grafts taken in 22 of 26 patients; full range of motion returned in 22 of 26 patients
Nocini et al, 2024[259]	Prospective study	Pelnac vs skin graft	21 patients (13 treated with one stage Pelnac vs 8 with full-thickness skin graft)	Most patients treated with one-stage Pelnac reconstruction showed good healing with minor complications, scar quality and overall satisfaction
Kang et al, 2024[260]	Single centre prospective study	Pelnac + semiocclusive dressing (IV 3000)	31 fingertip injuries involving pulpar defects	Mean treatment duration: 45.29 days. Considerable regeneration of fingertip (mean score=2.58, SD=0.67)
Zhang et al, 2024[261]	Retrospective case control study	Pelnac	45 skin and soft tissue defects with bone or tendon exposure	Safety and effectiveness in patients who cannot undergo autologous skin flap transplantation

Authors, year [reference]	Type of study	Acellular matrix/ technology tested	Number of cases	Results
Elkholy, 2024[262]	Prospective observational cross-sectional study	Pelnac	53 traumatic injuries on the leg and ankle region	Complete coverage of exposed structures
Lázaro-Martínez et al, 2025[276]	Case series	Hy-Tissue Micrograft	10 chronic DFU	Healing rate 60% at 12 weeks; reduction of wound area of 67.2±23.5% at 4 weeks and 87.5±24% at 12 weeks
Jović et al, 2025[188]	Systematic review	Integra	202 defects with exposed bone (evaluation of 40 studies)	Reported average success rate was 87.54% (±25.9), and the average graft take was up to 98.8%
Zehnder et al, 2025[201]	Randomised control trial	Kerecis	17 treated with Kerecis and 26 with standard of care	Reduction of the area at 4–8 weeks (over 25% improvement in wound area versus standard of care)
Adnan et al, 2025[218]	Retrospective case series	Matriderm	20 cleft palate	Over 50% epithelialisation was observed at 1 week, and over 75% by 2 weeks, with no scarring or arch collapse
Rady et al, 2025[263]	Randomised controlled trial	Pelnac + delayed skin graft vs skin graft	46 acute deep dermal burns of the upper limb (23 treated only with skin graft and 23 with Pelnac + delayed skin graft)	After 17 failures in the Pelnac group due to insufficient debridement, the Pelnac group had better scar quality

Table 4. Evaluation of evidence levels: dermal matrices for skin damage repair

Acellular matrix/ technology	Level of evidence	Comments
Endoform	4	Positive results from case series and 1 retrospective case control.
Hy-Tissue Micrograft	4	Positive results from case series.
Integra	1b	Positive results from case series and retrospective studies. Prospective and/ or randomised controlled trials.
Kerecis	1b	Positive results from case series and retrospective studies. Prospective and/ or randomised controlled trials.
Matriderm	3b	Positive results from case series and retrospective studies.
Micromatrix/Cytal	4	Positive results essentially from case reports.
Myriad	4	Positive results essentially from case series.
Novosorb	4	Positive results essentially from case series and case reports.
Pelnac	1b	Positive results from case series and retrospective studies. Prospective and/ or randomised controlled trials.

5. Regulatory aspects of the technologies for tissue repair

Regulation: can it conquer an epidemic?

In 2010, the World Health Organization (WHO) concluded in their report *Wound and Lymphoedema Management* that chronic wounds are to be considered a global epidemic.[277] Optimistically though, WHO also stated in the same document that, with wound care intervention education, it was apparent that a new era was about to revolutionise global wound care.

Almost two decades later, with the wisdom of hindsight, it seems that this expectation of WHO might have been optimistic. As Gould and Herman wrote in their report of the May 2024 Annual Conference of the Wound Healing Society (WHS), hard-to-heal, chronic wounds still represent a silent pandemic, which seems to be in lock step with the ever-growing prevalence and incidence of diabetes and obesity.[278] The scale of this increase was put into numbers recently in *The Lancet*, where study results from 1108 population-representative studies with a total 141 million participants aged 18 years and older show that in 2022, an estimated 828 million adults had diabetes, a more than quadruple increase from the 198 million in 1990.[279] Furthermore, the 948 authors also observed in relation with this massive increase, that in most countries, especially in low-income and middle-income countries, diabetes treatment has not increased at all, or increased insufficiently in comparison with the rise in prevalence.[279] Although DFUs are just one category of chronic, hard-to-heal wounds, they do illustrate the severity of the unmet need with regard to chronic wounds. Clinical epidemiology shows that between 10% and 15% of those with diabetes can expect to develop a foot ulcer at some point in their lives, and approximately 20% of diabetic patients with foot ulcers will suffer from inadequate arterial blood flow to their lower extremities.[280] Furthermore, individuals with diabetes are over ten times more likely to have a non-traumatic amputation than those not affected by diabetes.[280] Given the 828 million adults reported in *The Lancet,* this would equate to a population of approximately 124 million patients with hard-to-heal DFUs.[279,281]

Given such numbers, dynamics and prospects, it is not surprising that the cost of chronic wounds concerns politicians, health strategists, insurers and, indeed, regulators. In their 2022 publication on the unmet medical need of chronic wounds in the United States, FDA calculated the cost in excess of 25 billion US dollars spent on treatment annually, while Freedman et al, one year later in *Science* adjusted this amount for the US upwards to $30 billion.[84,282] In Europe, similar epidemiology and health economic conclusions are found. Guest et al, for example, show in the *BMJ* that the British National Health Service (NHS) spent 5.3 billion pounds per year to manage chronic wounds and associated comorbidities.[283–286] No doubt, with the increasing pressure on healthcare budgets in mind, the FDA announced its renewed focus on non-healing chronic wounds in its 2022 perspective paper.[282] In it, Verma and colleagues wrote that FDA understood that innovative product development was critical for addressing the significantly increasing wound healing pathology prevalence and incidence. Due to its high unmet medical need, and relatively limited research and funding, FDA therefore identified non-healing chronic wounds as an area of priority, and said it intended to help advance product development for the ultimate betterment of patients.[282]

Can regulators help conquer chronic, hard to heal wounds?

What piqued the interest of wound therapy innovators and manufacturers was the proffered help mentioned by the FDA in its perspective paper, sparking discussions on what such help would encompass. After all, in order to become a new, useful tool at the bedside of patients instead of vapourware, new wound healing solutions must obtain their regulatory and market access approval expeditiously. Without a proper regulatory approval, a therapy can be truly innovative, life and world changing, but will never reach the patients it is supposed to help. Fuelled by past practical experiences, many ruminate on whether the current regulatory frameworks are receptive, flexible, and adaptive enough to facilitate such new and innovative therapeutic wound care solutions, which are

supposed to relieve both patient and healthcare budget burdens.[287,288] Illustratively, Chen et al asked themselves in 2023 why there are so few FDA-approved therapeutics for wound healing.[289] Ever since the FDA approval of human recombinant PDGF-BB, becaplermin in 1997 for the treatment of diabetic neuropathic foot ulcers, no new therapeutic for any type of wound healing has advanced to clinical applications, apart from a plethora of physical therapies, medical devices, dressings, (alleged) anti-microbial agents, and other preventive treatments.[290] During the same period of time however, FDA did approve an additional 250 new drugs for various human tumours, which Chen and colleagues found to be labelled as "wounds that do not heal".[289]

Although European regulators do not seem to share the FDA wound care focussed attention, insight and urgency, the base principles of regulatory evaluation of new wound healing therapies are surprisingly similar between the United States of America and Europe.[291] Some might opine that the EU regulatory approach holds an inherent rigidity, which does not facilitate the introduction and availability of new and innovative wound healing therapies. By the same token, others will argue rightly that regulatory frameworks and authorities first and foremost should safeguard a stable, albeit less flexible base, where new products should just comply with the already defined and applicable generic standards and policies.[292] Contemplating this delicate balancing act, and the overarching (legal) obligation to supply citizens with the best therapeutic care possible, it nevertheless seems imperative and self-explanatory that regulatory frameworks should also adapt and adjust continuously, albeit vigilantly, to welcome never before encountered therapeutic approaches.[288]

What is the product to regulate?

By definition, a regulatory evaluation for eventual approval and market access attempts to fit a new innovative wound product into predefined categories, summarised crudely as a determination of what it is, what it does, and how it does it. For most wound care products, this evaluation will mean the determination of whether it should be regarded a medical device, a pharmaceutical product, a combination product, or something else entirely.[292] Medical devices in the European Union and European Free Trade Association (EFTA) countries are regulated by the Medical Device Regulation EU 2017/745 (MDR), which came into force in May 2021, replacing the previous 1992 Medical Device Directive 92/42/EEC.[293–296] The supervision and continued compliance of such medical devices has been assigned to the Notified Bodies, guided by scientific consultation from the European Medicine Agency when needed.[293,297] Pharmaceutical products however, also called medicinal products officially, are regulated by different legislation: Regulation (EC) 726/2004 and Directive 2001/83/EC.[298,299] These are not governed by the Notified Bodies, but by the European Medicine Agency and the Competent Authorities of the European Union Member States direct.[300] On 10 April 2024, the European Parliament adopted its position on the European Commission proposal of November 2020 to reform the core EU pharmaceutical legislation, which will replace Directive 2001/83/EC and Regulation 726/2004, and also strengthen the orphan and paediatric medicines regulations.[301,302]

Whether a product is a medical device or a pharmaceutical product can be found in the first articles of the respective directives.[293,299] Article 2 of the Medical Device Regulation defines a medical device as "*any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, [...] and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means*".[293] Article 1 of Directive 2001/83/EC in turn defines a medicinal product as "*(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or (b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis*".[299]

From these two seemingly mutually exclusive definitions, one might conclude that the distinction is unambiguous. The earlier mentioned combination products are however, as the name indicates, a combination of a medical device and "*a substance which, if used separately, can be considered to be a medicinal product, as defined in point 2 of Article of Directive 2001/83/EC*".[293] Since such a combination

product holds components that individually are regulated by different pieces of legislation, it becomes critical to determine and classify which component performs the "primary", and which the "secondary" or "supportive" action of the product. For example, a wound dressing containing an antimicrobial agent will be regarded a medical device if its primary action is described and regarded to be wound coverage, protection and absorption, while the ancillary antimicrobial action is seen as, for example, a preservative. However, if its primary action is judged to be the delivery of antimicrobial agents for the treatment of wound infection, the dressing as a whole will be considered a medicinal product, and thus will be regulated accordingly.[303] This ratiocination becomes even more opaque when more novel therapeutic designs are implemented.

By definition, innovative products tend to explore the borders of previously unknown therapeutic territories and approaches. This can be through, for example, a revolutionary, never before applied approach, or creating synergy by combining previously known, but separate, individual, not earlier brought together concepts. One such example are matrices used in reconstructive and regenerative medicine.[304] Although oral or published testimony of encouraging clinical results might condone immediate application to help patients in need, regulators will (need to) question first the safety of use of the product, an aspect for which they are publicly and legally responsible unequivocally.[305] With this default, but critical consideration in mind, the first question no doubt should be: what actually is a matrix? When exploring this question, one will find immediately that no uniform naming or definitions exist. Broadly similar products are dubbed differently, for example: matrix, scaffold, skin substitute, or substrate. Although the latter is used widely, the term substrate might be less appropriate, since it is commonly used mainly in relation to cells and (biological) cell cultures. In its 2010 Technical Report 978, the WHO Expert Committee on Biological Standardisation recommends to national regulatory authorities that "*Cell substrates are cells used to manufacture biological products. It is well established that both cell substrates themselves and events linked to cell growth can affect the characteristics and safety of the resultant biological products. Therefore, a thorough understanding of the characteristics of the cell substrate is essential, in order to identify points of concern and to develop a quality-control system that addresses these points*".[306]

Another befuddling exemplification might be the description of the US Agency for Healthcare Research and Quality (AHRQ) in their Evidence-based Practice Center Technical Brief Protocol, *Skin Substitutes for Treating Chronic Wounds*. It states that: "*The skin substitutes included in the earlier evidence report are a broad collection of various combinations of cellular and acellular components, both human and animal derived, intended to stimulate the host to regenerate lost tissue and replace the wound with functional skin. Cellular therapies, also called bioengineered cellular therapies provide skin cells (fibroblasts, keratinocytes or both) to create a source of growth factors, cytokines and enzymes that promote tissue regeneration. Natural and synthetic material, such as collagen and polyglactin, respectively, may be used to create the extracellular matrix for tissue ingrowth. Acellular products provide an extracellular matrix devoid of cells and composed of a collagen substrate or other material into which cells can migrate and initiate tissue regeneration. Beyond being merely a scaffold, the extracellular matrix may also have an active role in stimulating tissue growth. The broad category of skin substitutes may have the potential to stimulate chronic wound healing and reduce the medical burden these wounds create*".[307] It will not escape the careful reader that in this description the terms skin substitute, matrix, substrate and scaffold are all used simultaneously. It is, therefore, perhaps not surprising that in the Technical Brief's Table 1, the first question listed for the AHRQs Clinical Experts is: "*Is there any accepted definition of skin substitutes?*"[307]

This very relevant question was also identified some years earlier by Snyder et al, in their Health Technology Assessment report *Skin Substitutes for Treating Chronic Wounds*.[308] At that time, the authors concluded that their study would include all products "*commonly referred to as skin substitutes and on the regulatory pathways required for the different types of products*". More relevant to the regulation of such products, however, they stated "*that FDA does not refer to any product or class of products as 'skin substitutes,' and we are not proposing an official classification system*".[308] In 2020, in the next updated iteration of their Health Technology Assessment report, the authors again mention that they will not suggest any definition for skin substitutes, but do note that "*several investigators have proposed definitions and outlined what skin substitutes should accomplish*".[309] One of the more

commonly accepted definitions was published in 2024 by Mulder et al in their excellent international consensus document.[310] Here, the authors also concluded that the term skin substitutes should be regarded an umbrella term for the wide range of biological dressings and matrices, which facilitate the repair and/or regeneration of the skin through various mechanisms.[310]

How to classify the product to regulate?

If one, however, searches specifically for a "classification system for skin substitutes", a process step which represents the core of any regulatory review process, one will find different interpretations of the same query. Kumar and Gupta for example describe a three tier classification system for skin substitutes, which later was extended by Kondej et al to also encapsulate the more recent innovative 3D bio-printed skin substitutes.[311,312] Although these are extremely useful, highly informative, and do identify and characterise skin substitutes, the classification suggested is not an official classification system in a regulatory sense. Taking a different approach to the same issue, Belsky and Smiel reversed the direction of their analysis, and looked at approved skin substitutes in the United States and subsequently reviewed their specific classification. They note that FDA regulates skin substitutes under several categories, depending on the product's origin, composition, and intended use.[313] So are HCT/Ps human cells, tissues, and cellular and tissue-based products, human-derived products that are minimally manipulated and intended for homologous use. Premarket Approval (PMA) and humanitarian use device (HUD) products are human- and human/animal-derived products, while the 510(k) pathway is applied for animal-derived and synthetic products. Furthermore, FDA recommends the Biologics License Application (BLA) pathway when human tissues and cells are used to produce cellular-derived material for a specific therapeutic claim of action like "enhanced wound healing", or when the product undergoes more than minimal manipulation during production.[313] As might be expected, each of these pathways varies in submission and clinical requirements, as well as the review and decision timelines.

In Europe, the classification of therapeutic products is based on the risk that that product poses to the patient, thus also determining the extent of regulatory control required to demonstrate its safety and effectiveness.[291,295,314,315] Despite the similarities with regard to risk-based classification of products, it is also vital to note the significant differences in the European regulation of cell-based products, including those derived from pluripotent stem cells. Contrary to the US, these are regulated as Advanced Therapeutic Medicinal Products (ATMPs) in Europe and are classified based on the principle of their primary mode of action. Since the principal therapeutic actions of ATMPs are, according to European regulators, "*restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action"*, and their function is "*structural*" or "*physical*", their authorisation and commercialisation are regulated currently by Directive 2001/83/EC and Regulation (EC) No. 726/2004, amended by Regulation (EU) No. 12 35/2010.[294,298,299,301,302,316] In practice, this means that ATMPs have to fulfil the same high regulatory standards as other pharmaceuticals, overseen by the European Medicine Agency (EMA).[298,299,317] With regard to acellular matrices, the European situation is not necessarily more accommodating. As reported earlier by Piaggesi et al, many US approved acellular advanced wound products are not available to European patients.[2]

A look inside: matrices according to EUDAMED and FDA

When returning to the original question, and (re)viewing it through regulatory eyes specifically, one can ask oneself whether there is a unified, generally used regulatory nomenclature with regard to cell matrices. A good approach for such an analysis would be to, as mentioned earlier, review the regulatory summary of product characteristics documentation of various products dubbed matrices in everyday clinical practice.[313] However, when attempting to do this for products approved in Europe, one will find that this information is not readily available. On 30 October 2019, the European Commission confirmed the creation and implementation of the new European Database on Medical Devices (EUDAMED) as described in article 44 of the Medical Device Regulation EU 2017/745, which should *"improve transparency and coordination of information regarding medical devices available on the EU market, and contain information on manufacturers and actors, Unique Device Identifiers (UDI) and devices, Notified Bodies and certificates, vigilance, clinical investigations, performance studies, and market surveillance*".[293,318] Unfortunately, the European Commission announced the same month at the Certificates Working Group, that the deployment of

EUDAMED would be delayed by two years, deployment most likely to take place in 2022, with a subsequent transition period up to 2024.[318] On 23 January 2024, the European Commission extended the full roll-out of EUDAMED and the corresponding information obligation for manufacturers even further.[319] Hence, the objective to collate and process information about medical devices made available in the EU, in order to "*enhance overall transparency through better access to information for the public and healthcare professionals*", had not materialised at the time of writing, and could therefore not be consulted.[320]

The more mature FDA regulatory information database however, which has shared similar product information publicly since 2000, provides more insight in the matter, even though the guiding legislation, as mentioned previously, is not similar between the US and EU.[321,322] Reviewing the regulatory documentation of various approved matrices there, it becomes clear that there is a significant discrepancy between the "Name of the device" or "Trade Name" as given by the manufacturer, the "Common Name", and the "Classification Name" stored by FDA. As with trade and common names, various product designations such as "wound matrix", "extracellular matrix", "topical matrix", "reconstructive matrix", "bilayer matrix wound dressing", "antimicrobial wound dressing", "dermal repair scaffold", "surgical graft", "surgical mesh", "macroporous mesh, "anatomical mesh", "wound sheet", "dermal template", or "tissue repair biomaterial" can be found, the device classification name is a less exciting variation of either "dressing" or "mesh". Some examples of the most common classification codes found for wound matrix products can be found in Table 5.[323]

Reviewing the regulatory information in Table 5, it becomes clear that products, all labelled commonly as, for example, "matrix", either by their manufacturers, or by the health care professionals using them, are regarded and classified very differently regulatory-wise. As can be seen in Table 5, the FDA, similar to the EU, assigns a device class designation to a specific medical device, depending on its risk, invasiveness and potential impact on patient health. Class I represents devices with the lowest risk profile, while Class III devices pose the highest risk.[324,325] Wound products, that, through innovation and development, might have outgrown the classification methodology, can be seen with for example the FRO classed products. This category holds a large variety of products, including not only matrices in the "solid dressings" subcategory, but also gels, creams, ointments, and liquid wound wash solutions.[326] Knowing this, it is not difficult to recognise that this mode of operating might become even more of a regulatory predicament when, for example, innovative combination wound products are submitted for regulatory approval. An example of such a hypothetical dilemma could be so-called smart-dressings of coaxial electrospun nanofibres, not only used as a regeneration matrix exhibiting active cell contact and motility guidance promoting growth, but also as a well-suited drug delivery device for a large variety of bioactive factors.[327–335]

Table 5. Examples of FDA Classification Product Codes found for regulatory approved wound matrices

Product code	Device classification name	Regulation description	Device class	Review panel
FRO	Dressing, wound, drug	Unclassified	Unclassified	General & Plastic Surgery
FTL	Mesh, surgical, polymeric	Surgical mesh	2	General & Plastic Surgery
FTM	Mesh, surgical	Surgical mesh	2	General & Plastic Surgery
KGN	Wound dressing with animal-derived material(s)	Unclassified	Unclassified	General & Plastic Surgery
KGX	Tape and bandage, adhesive	Medical adhesive tape and adhesive bandage	1	General & Plastic Surgery
OHX	Mesh, surgical, collagen, plastic and reconstructive surgery	Surgical mesh	2	General & Plastic Surgery
QSZ	Absorbable synthetic wound dressing	Unclassified	Unclassified	General & Plastic Surgery

What does the regulatory future of regenerative therapies hold?

With research progressing steadily, new innovative regenerative therapies are becoming ever more versatile. When considering scaffolds and matrices, the interdisciplinary field of skin tissue bioengineering, as a whole, is an example of this. Therapies are being developed to reduce the time required to accomplish stable closure of wounds with minimal scars in patients with insufficient donor sites for autologous split-thickness skin grafts. Regarding the various compositions of these engineered skin tissues, which can include cells, biopolymer scaffolds, and medicinal (drug) products, it seems a paradigm of break-through innovative therapeutic solutions is being hampered by significant challenges in attaining regulatory market approval before, if ever, reaching the bedside of the patient.[336] This becomes even more palpable when considering the exciting and encouraging body 3D bioprinting research in skin wound healing.[337–346]

Having said this though, looking specifically at the wound healing therapies available to European health care professionals currently, some more practical questions come to mind: Are regulatory frameworks, and in particular the European one, flexible and adaptive enough to facilitate such new therapeutic solutions? This question was seemingly highlighted by the Heads of the Medicines Agencies to the Director General for Health and Food Safety (DG SANTE) of the European Commission,[347] in light of the increasing wound morbidity prevalence and incidence, and its corresponding pressures on healthcare budgets. The main objective must surely be to provide patients with optimal care, and thus enable their physicians to do so safely with the most effective tools possible. In order to achieve this, regulatory rules, regulation and frameworks should be updated continuously, although assiduously, to make new, innovative, more effective therapeutic approaches available.[348] In the United States, FDA has already declared non-healing chronic wounds as an area of priority, and committed publicly to help advance innovative wound healing therapy development.[282] If the regulatory authorities in the European member states would follow the example of their American counterparts, and also commit to ensure a “sound and flexible regulatory system”, as defined by the European Commission in their *Pharmaceutical Strategy for Europe*, it will not only recognise, but also address the unmet medical need of the chronic, non-healing wound epidemic, that WHO identified so many years ago.[277,297,349]

6. Dimensions of the market for dermal matrices

Global market: wound care

The growing elderly population around the world is a significant factor impacting healthcare systems, as older adults are more prone to chronic and non-healing wounds. Furthermore, the rise of diabetes, obesity and cardiovascular diseases contributes to an increased need for advanced wound care products. According to The International Diabetes Federation (IDF) Diabetes Atlas (accessed on 2 March 2026, https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/), 11.1% of the adult population (20–79 years) is living with diabetes globally with over four in 10 unaware that they have the condition, and estimates that approximately 853 million will be living with diabetes in 2050.

In 2022, 2.5 billion adults aged 18 years and older were overweight, including over 890 million adults who were living with obesity. About 16% of adults aged 18 years and older worldwide were obese in 2022 and the prevalence of obesity more than doubled between 1990 and 2022.

Medical devices for chronic and non-healing wounds have increased globally with many products used in chronic wounds, burns, trauma and reconstructive surgery tissue integration, revascularisation and resultant healing.

The wound care market in 2021 amounted to US $19,572.9 million and it is estimated to reach US $28,630 million in 2028. Table 6 presents the wound care market by product from 2021, forecast to 2028.

Among the players in the wound care market, 3M Company (US) accounted for the largest share. The business revenue of the top players increased over 2022 (Figure 29). These players dominated the market due to their extensive product portfolios and wide geographical presence, representing 40.6% of the total wound care market (Figure 30).

Global market: dermal matrices

Acellular dermal matrices (ADMs) are sourced globally from various origins, including human, animal, porcine and bovine dermis. Key components of ADMs include elastic fibres and collagen. They are a bioactive matrix, supporting cell repopulation, revascularisation and tissue remodelling.

The ADM market was valued at US $9.22 billion in 2024 and is projected to reach US $26.40 billion by 2032. The regions covered by the ADM market are: North America (USA, Canada), Europe (Germany, UK, France, Spain, Italy, rest of Europe), Asia-Pacific (China, India, Japan, Australia, South Korea, rest of Asia-Pacific), Latin America (Brazil, Mexico, Argentina, rest of Latin America) and Middle East and Africa (Saudi Arabia, UAE, South Africa, rest of Middle East and Africa).[351] North America represents the major market, followed by Europe (Figure 31).

The ADM market includes wound care, reconstructive surgery, dental applications, and peripheral nerve repair. Wound care represents the largest segment, accounting for approximately 35% of total market demand. Reconstructive surgery, driven primarily by breast reconstruction and hernia repair, accounts for an estimated 30% of the market.[352]

Table 6. Wound care market by product, 2021–2028 (US $ millions)[350]

Product	2021	2022	2023	2024	2025	2026	2027	2028	CAGR (2023–2022)
Advanced wound care	9,401.6	10,026.2	10,711.8	11,466,4	12,302.1	13,227.8	14,244.7	15,374.7	7.5%
Surgical wound care	5,656.0	5,845.0	6,055.2	6,290.7	6,554.0	6,848.2	7,171.0	7,530.8	4.5%
Traditional wound care	4,515.3	4,632.5	4,766.0	4,9171.1	5,087.9	5,280.7	5,492.8	5,730.5	3.8%
Total	19,572.9	20,503.7	21,533.0	22,674.2	23,944.0	25,356.7	26,908.5	28,636.0	5.9%

Table 7. Wound therapy devices market by country, 2021–2028 (US $ million)[350]

Country	2021	2022	2023	2024	2025	2026	2027	2028	CAGR (2023–2022)
US	743.2	755.2	768.6	783.5	800.1	818.5	838.2	859.9	2.3%
Canada	64.9	65.1	65.5	65.9	66.5	67.3	68.2	69.2	1.1%
Germany	166.4	171.4	176.9	183.0	189.7	197.1	205.1	213.8	3.9%
UK	142.1	145.5	149.3	153.6	158.4	163.7	169.6	176.0	3.3%
France	63.6	65.2	67.0	68.9	71.1	73.5	76.1	78.9	3.3%
Italy	61.7	62.9	64.3	65.8	67.6	69.5	71.6	73.9	2.8%
Spain	55.6	56.2	57.0	57.9	58.9	60.2	61.5	63.1	2.1%
Russia	40.2	41.6	43.1	44.7	46.6	48.6	50.7	53.1	4.3%
China	122.8	133.7	145.4	158.0	171.7	186.5	202.6	220.2	8.7%
Japan	119.0	124.4	130.2	136.7	143.7	151.5	159.9	169.1	5.4%
India	57.7	62.6	68.0	74.0	80.7	88.1	96.4	105.7	9.2%
Australia	38.4	40.0	41.7	43.6	45.6	47.9	50.4	53.1	4.9%
South Korea	27.1	28.2	29.3	30.5	31.9	33.4	35.0	36.7	4.7%
Singapore	18.7	19.4	20.2	21.1	22.1	23.2	24.4	25.6	4.9%
Brazil	43.2	46.8	50.5	54.6	58.9	63.6	68.6	74.1	8.0%
Mexico	23.0	24.8	26.6	28.6	30.7	33.0	35.4	38.0	7.4%
Middle East & Africa	77.5	80.6	83.9	87.6	91.5	95.9	100.5	105.6	4.7%
Rest of the world	241.5	258.2	276.1	295.5	316.4	339.2	363.8	390.7	7.2%
Total	2106.4	2181.7	2263.6	2353.4	2452.0	2560.5	2677.7	2806.7	4.4%

	2018	2019	2020	2021	2022
3M Company	2,192.5	2,150.4	2,144.0	2,316.0	2,290.5
Medtronic	1,718.6	1,753.2	1,653.9	1,631.4	1,818.0
Cardinal Health	1,198.4	1,274.8	1,544.4	1,668.7	1,588,7
Smith & Nephew plc	1,305.9	1,502.7	1,310.0	1,496.0	1,512.0
Mölnlycke Health Care AB	366.3	1,048.3	958.9	1,086.9	1,114.2

Figure 29. Revenue analysis of top players in the wound care market, 2018–2022 (US $ million).[350] Note: Segmental revenues for wound care products and services for the top five players have been considered. This is because segmental shares of wound care products and services may vary significantly from company to company, depending on individual company product portfolios.

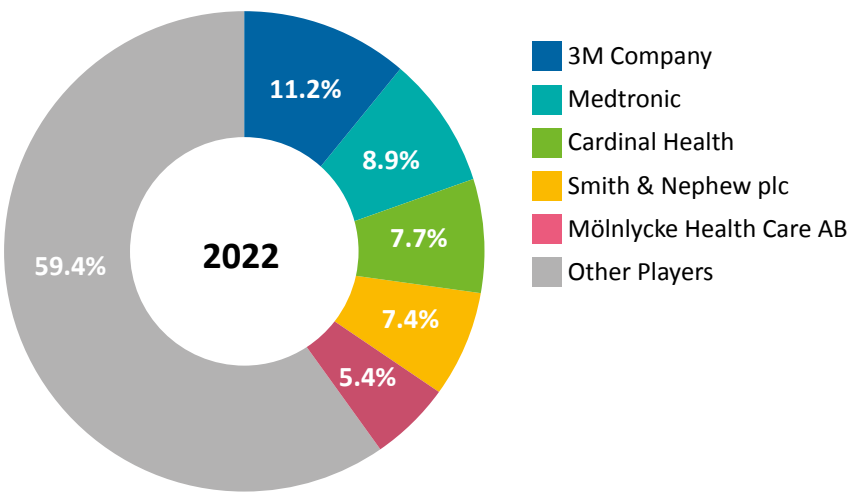

Figure 30. Wound care market share analysis by key players, 2022. Note: other players include Baxter International Inc (USA), B Braun Melsungen AG (Germany), Convatec Group plc (UK), Paul Hartmann AG (Germany), Coloplast A/S (Denmark), Organogenesis Inc (USA), MIMEDX Group Inc (USA), Integra LifeSciences Corporation (USA), Bioventus LLC (USA), Zimmer Biomet Holdings Inc (USA), Ethicon Inc (USA), DeRoyal Industries Inc (USA), Kerecis (Iceland), ACell Inc (USA), Lohmann & Rauscher GmbH & Co KG (Germany); Medela AG (Switzerland), Talley Group Ltd (UK), Welcare Industries SpA (Italy), Wuhan VSD Medical Science & Technology Co Ltd (China), Pensar Medical LLC (USA), Haromed BV (Belgium), DermaRite Industries LLC (USA), Medline Industries Inc (USA), Advancis Medical LLC (UK), and Mil Laboratories Pvt Ltd (India).[350]

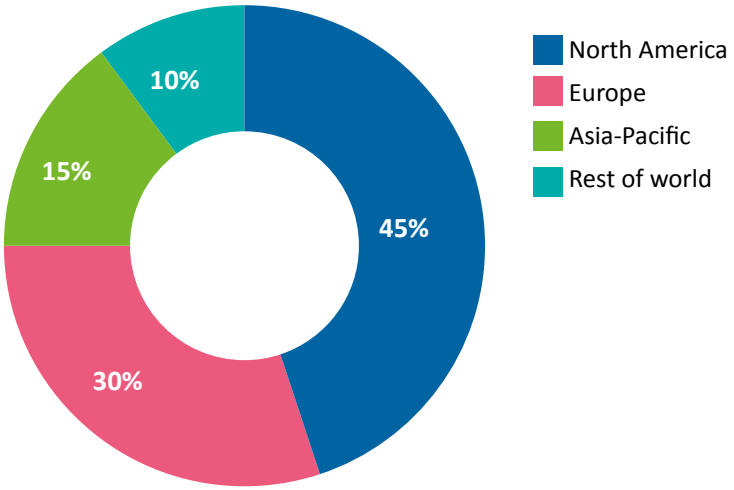

Figure 31. Acellular dermal matrix regional market share.[352]

Acellular animal-derived products are expected to increase from US $553.16 million (2021) to US $972.75 million in 2028. India, China, Brazil and Mexico show the highest increase (Table 8). This growth can be attributed to the increasing incidence of diabetic foot ulcers, venous leg ulcers and burn injuries.

Dermal regeneration involves various techniques for skin restoration, such as dermal substitutes, scaffolds, cellular matrices or acellular matrices. In 2024, the global dermal regeneration market was valued at US $1.01 billion. The market is projected to grow from US $1.1 billion in 2025 to US $2.1 billion in 2034.

This global market growth is primarily driven by increasing demand for non-invasive cosmetic procedures, a higher incidence of burn injuries, and a high incidence of chronic wounds, including diabetic foot ulcers, venous leg ulcers and pressure ulcers.

The use of dermal substitutes in chronic wounds, burns and surgical wound care enhances the healing process, reduces the risk of infection and scarring, compared to traditional grafts.[353]

Diabetic foot ulcers

The global diabetic foot ulcer treatment market size was valued at US $8.83 billion in 2024. The market is expected to grow from US $9.36 billion in 2025 to US $14.37 billion by 2032. North America reports a market share of 39.07% in 2024. Figure 32 shows that the segment with the largest market share was represented by wound care dressings, divided into antimicrobial dressings, foam dressings, film dressings, alginate dressings, hydrogel dressings and other dressings.

With respect to end users, the hospital segment dominated the global market in 2024. This segment's dominance is attributable to the facilities provided by hospitals and the patients' higher preference for hospital-based wound care. Furthermore, the increasing number of patient hospitalisations and the demand for advanced diabetic wound care provided by skilled professionals have boosted the segment's growth.[354]

Venous leg ulcers

The venous skin ulcer treatment market was valued at US $3,460.24 million in 2024. The size of this market is expected to increase to US $5,075.67 million by 2031. Figure 33 shows that compression therapy accounted for the highest percentage of the market.

European market

Chronic wounds require advanced treatments, including tissue-engineered products like skin substitutes and collagen-based scaffolds, to promote regeneration and restore tissue integrity.

Tissue-engineered solutions, such as skin grafts and bioactive wound dressings, offer promising alternatives to

Table 8. Acellular animal-derived products market, by country, 2021–2028 (US $ million)[350]

Country	2021	2022	2023	2024	2025	2026	2027	2028	CAGR (2023–2022)
US	209.38	221.00	233.62	247.36	262.39	278.82	296.59	316.03	6.2%
Canada	16.53	17.05	17.62	18.25	18.93	19.69	20.50	21.38	3.9%
Germany	44.28	47.65	51.37	55.50	60.08	65.19	70.84	77.15	8.5%
UK	36.37	38.90	41.69	44.79	48.23	52.07	56.32	61.07	7.9%
France	18.54	19.90	21.41	23.08	24.93	26.99	29.27	31.80	8.2%
Italy	16.68	17.77	18.96	20.27	21.73	23.35	25.12	27.10	7.4%
Spain	15.79	16.68	17.65	18.72	19.92	21.23	22.68	24.28	6.6%
Russia	11.51	12.44	13.47	14.61	15.88	17.30	18.87	20.63	8.9%
China	35.62	40.50	46.01	52.22	59.26	67.25	76.29	86.58	13.5%
Japan	32.73	35.74	39.09	42.84	47.05	51.79	57.09	63.07	10.0%
India	15.54	17.61	19.97	22.70	25.85	29.50	33.70	38.59	14.1%
Australia	10.29	11.18	12.18	13.29	14.54	15.95	17.51	19.27	9.6%
South Korea	7.20	7.81	8.48	9.23	10.07	11.01	12.05	18.23	9.3%
Singapore	2.33	2.51	2.71	2.94	3.19	3.47	3.78	4.12	8.7%
Brazil	12.48	14.11	15.93	17.98	20.28	22.88	25.80	29.11	12.8%
Mexico	6.39	7.18	8.05	9.02	10.10	11.31	12.67	14.20	12.0%
Middle East & Africa	19.27	21.00	22.92	25.05	27.43	30.09	33.06	36.38	9.7%
Rest of the World	42.23	46.87	52.01	57.76	64.19	71.42	79.49	88.58	11.2%
Total	553.16	595.90	643.14	695.61	754.05	819.31	891.63	972.57	8.6%

traditional wound care methods, providing faster healing, reduced scarring and improved patient outcomes.

The European tissue engineering for wound care market size is expected to be worth around US $8.38 billion by 2034 from US $2.09 billion in 2024, growing at a CAGR of 15.1% during the forecast period from 2024 to 2034. Table 9 shows the annual amounts (US $ million) for tissue engineering used in chronic and acute wounds.[356]

The demand for tissue engineering solutions for chronic wounds is growing, driven by the need for specialised and long-term treatment. Among these wounds, diabetic ulcers are particularly common, especially in individuals with poorly controlled diabetes. These ulcers develop because of neuropathy and impaired circulation, which significantly hinder the body's ability to regenerate tissue.

Table 10 highlights the growing trend for each application type.

Hospitals held the largest market share at 62.5%, as they serve as the primary end users and deliver comprehensive care for both acute and chronic wounds. With advanced infrastructure and specialised medical staff capable of managing complex cases, hospitals remain the leading consumers of tissue-engineered products.

Challenges for the dermal matrices market

The main challenges in the acellular matrices market are:

- Stringent regulatory requirements
- Ethical concerns regarding tissue sourcing
- High costs
- Potential risks of adverse reactions

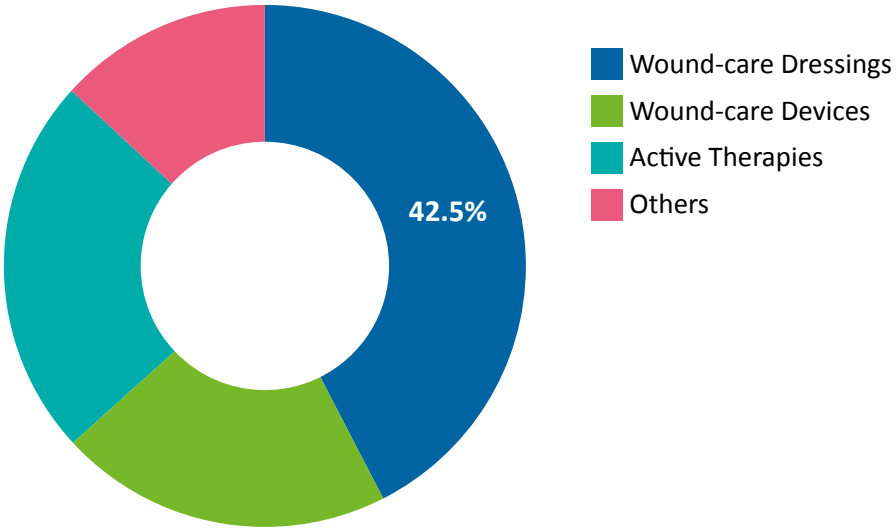

Figure 32. Global diabetic food ulcer treatment market share, by product, 2024.[354]

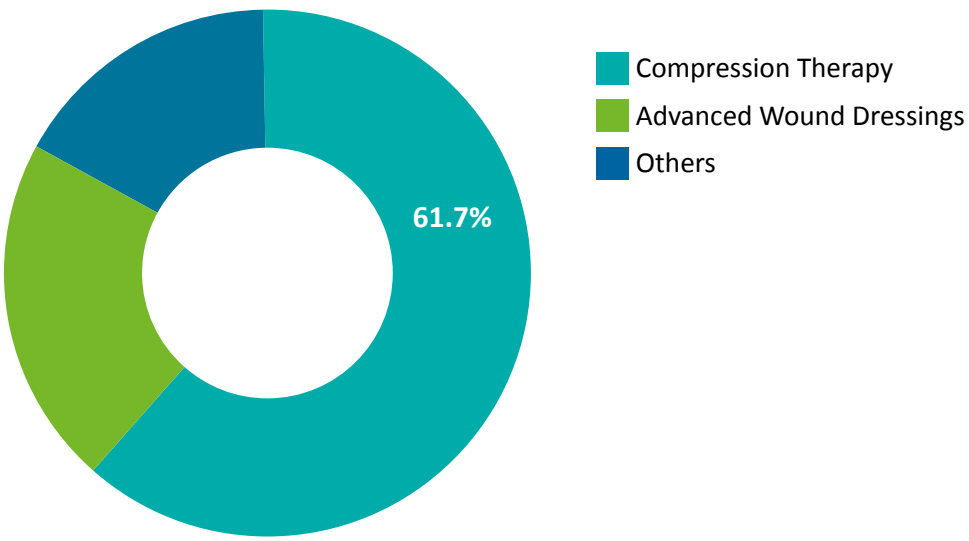

Figure 33. Global venous leg ulcer treatment market share, by product, 2018.[355]

The major challenges in the ADM market are the high set-up costs for product development. Furthermore, the shortage of skilled personnel in most countries and delays in the development of new products because of economic constraints negatively impact the diffusion of the products.

Europe's complex regulatory landscape poses a significant challenge to the growth of the tissue engineering market for wound care. Tissue-engineered products must meet rigorous standards and secure approvals from the European Medicines Agency (EMA) or national regulatory authorities—a process that is both lengthy and expensive.

Furthermore, many products are classified as Advanced Therapy Medicinal Products (ATMPs) and must comply with

stringent requirements applicable to both pharmaceutical and medical device regulations.

Approval of a tissue-engineered skin substitutes used in wound healing requires comprehensive clinical trials and detailed documentation of manufacturing protocols, often resulting in significant delays to market entry. The stringent approval requirements, coupled with ongoing post-market surveillance obligations, create an added regulatory burden, particularly for smaller companies with limited resources. Similar regulatory delays in wound care significantly hinder timely patient access to innovative treatments. Furthermore, variations in national regulatory requirements across the European Union add another layer of complexity, making market entry even more challenging.

Opportunities in the dermal matrices market

The shift toward personalised medicine is creating substantial opportunities for advancing tissue engineering, particularly in wound care. Personalised medicine is grounded in the recognition that each patient possesses distinct genetic, molecular and physiological characteristics that can significantly influence how they respond to treatment. These differences affect not only healing trajectories but also susceptibility to infection, inflammatory responses and overall tissue regeneration capacity.

In the context of tissue engineering, this paradigm enables the development of highly customised therapeutic solutions. By integrating patient-specific biological data—such as genomic markers, cellular behaviour, immune profiles and biomechanical properties—engineered tissues and wound-care products can be tailored to match individual anatomical and clinical parameters with far greater precision.

This approach enhances treatment effectiveness by promoting more predictable healing outcomes, reducing the risk of rejection or complications, and improving overall patient comfort and recovery times. Furthermore, the growing adoption of digital health tools such as AI-based diagnostic platforms, advanced imaging and data-driven predictive models, supports the personalisation of tissue-engineered wound-care interventions, enabling clinicians to design, monitor and adjust therapies in real time.

Economic impact of dermal matrices

Currently, the literature related to the economic evaluation of dermal matrices is very poor in diabetic foot ulcers and venous leg ulcers. According to our literature review, only two papers were identified.

A study by Khorasani et al from 2025[357] assessed the economic outcomes including cost-effectiveness and cost-benefit of an alloplastic polylactic acid (PLA) dermal matrix versus a collagen dressing for the closure of diabetic foot ulcers. Primary data were obtained from a clinical trial comparing the healing outcomes of standard of care (SOC) wound care plus either PLA matrices or collagen dressings over a 28-week period in a sample of 30 patients, with 15 patients per arm. In a scenario without wastage, PLA treatment costs decreased rapidly after 10 weeks, whereas the costs of the collagen group increased until week 28. The mean cost difference at 12 weeks between collagen versus PLA amounted to US $173.80 ($p<0.001$). In a scenario with wastage, the collagen group presented higher costs than the PLA group. The cost to achieve wound closure was US $5284 for the collagen group versus US $2989 for the PLA group($p<0.001$). The use of PLA was cost-effective compared with collagen-based dressings for treatment of diabetic foot ulcers, promoting faster wound closure, improving quality of life and reducing healthcare costs.

A multicentre, randomised controlled trial by Zelen et al from 2016[358] compared complete wound healing of diabetic foot ulcers at 6 weeks using acellular reticular allogenic human dermis matrix (HR-ADM) plus SOC versus SOC alone. A total of 40 patients were included, with 20 patients in each group. At 6 weeks, 65% of the HR-ADM group had healed compared with the SOC group ($p=0.00028$); at 12 weeks, 80% versus 20% ($p=0.00036$). Mean and median graft costs to closure per healed wound in the HR-ADM group were US $1475 and US $963, respectively. The trial demonstrated the clinical superiority of HR-ADM versus SOC at 6 weeks and 12 weeks in non-healing diabetic foot ulcers, indicating that HR-ADM may represent a cost-effective solution.

Table 9. Tissue engineering for wound care market, type of wound analysis, 2020–2024 (US $ million)[356]

Type/Year	2020	2021	2022	2023	2024
Chronic wound	628.4	778.0	981.1	1178.4	1360.0
Diabetic ulcers	304.6	377.9	477.7	575.1	665.3
Venous ulcers	184.5	228.6	288.6	346.9	400.7
Pressure ulcers	139.4	171.4	214.8	256.3	293.9
Acute wounds	347.7	427.1	534.4	636.9	729.3
Surgical wounds	172.9	211.9	264.7	314.8	359.8
Traumatic wounds	99.4	122.2	153.0	182.4	209.0
Burn care	75.4	93.0	116.8	139.7	160.6

Table 10. Tissue engineering for wound care market, application analysis, 2020–2024 (US $ million)[356]

Application/Year	2020	2021	2022	2023	2024
Skin regeneration	508.2	623.9	780.4	929.7	1064.1
Bone and cartilage regeneration	221.9	275.2	347.7	418.4	483.8
Soft tissue repair	157.2	193.7	243.1	290.5	333.7
Organ regeneration	88.9	112.3	144.4	176.6	207.0

Table 11. Tissue engineering for wound care market, end-user analysis, 2020–2024 (US $ million)[356]

End users	2020	2021	2022	2023	2024
Hospitals	617.4	759.2	951.1	1134.8	1301.0
Specialty centres and clinics	264.7	330.1	419.2	507.2	589.5
Ambulatory surgical centres	94.0	115.8	145.2	173.3	198.8

Final considerations

Economic growth, healthcare expenditure, and government investment in research and development are key drivers of the dermal matrix market. Regulatory environments and reimbursement policies vary across countries, shaping market accessibility and adoption rates. In regions with strong economies and well-developed healthcare systems, investment in innovative wound care solutions is higher, supporting rapid market expansion. Conversely, economic downturns or budget constraints can limit funding and slow the uptake of advanced technologies. Additionally, geopolitical factors—such as trade policies, tariffs and international collaborations—play a significant role in market dynamics. Economic downturns or budget limitations may disrupt the supply chain for essential materials, while favourable policies and strategic partnerships can enhance innovation and accelerate overall market growth.

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