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REVIEW

Extracellular matrix-based scaffolding technologies for periodontal and peri-implant soft tissue regeneration

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Abstract

The present article focuses on the properties and indications of scaffold-based extracellular matrix (ECM) technologies as alternatives to autogenous soft tissue grafts for periodontal and peri-implant plastic surgical reconstruction. The different processing methods for the creation of cell-free constructs resulting in preservation of the extracellular matrices influence the characteristics and behavior of scaffolding biomaterials. The aim of this review is to discuss the properties, clinical application, and limitations of ECM-based scaffold technologies in periodontal and peri-implant soft tissue augmentation when used as alternatives to autogenous soft tissue grafts.

KEYWORDS

acellular dermal graft, collagen matrix, dental implant, gingival recession, soft tissue augmentation, soft tissue volume

1 | SCAFFOLD CONSTRUCTS FOR SOFT TISSUE AUGMENTATION

Biomaterials have progressively gained popularity in periodontics due to their advantages compared with autogenous grafts, such as unrestricted availability, avoidance of a secondary surgical site, reduction of the surgical time, and patient's preference.[1] Indeed, the risk of developing moderate/severe postoperative swelling and pain increased at 3% and 4%, respectively, for each minute of the surgical procedure.[2] Ideally, biomaterials should be characterized by certain properties, including biocompatibility, ease in surgical site adaptation and positioning, space maintenance, clot stabilization, tissue integration, cell invasion/guidance, and promotion of cellular proliferation.[3] Based on their origin, scaffolds can be classified as allogenic, xenogeneic, alloplastic, and living constructs (when they include cells). This review aims to present the characteristics, clinical application, and limitations of extracellular matrix (ECM)-based technologies in periodontal and peri-implant soft tissue augmentation.

2 | NATURAL AND CADAVERIC SCAFFOLDS

2.1 | Decellularized human dermis

Acellular dermal matrix (ADM) is a soft tissue graft obtained from human skin that has undergone a decellularization process.[4,5] Devoid of epithelium and cellular components, the preserved ECM serves as a scaffold that promotes cellular migration and revascularization from the surrounding host tissues.[4–7]

First introduced for the treatment of burn wounds,[8] the ADM has been extensively used in several other indications, such as facial augmentation, dural replacement, breast reconstruction, and esthetic plastic surgery.[4,9,10] In dentistry, ADM was firstly evaluated for increasing attached and/or keratinized gingivae.[11] However, the ADM clinical outcomes are inferior to the free gingival graft (FGG).[12,13] In particular, the ADM seems to be more prone to shrinkage, which may also explain the reduced tissue thickness observed.[5,13] Histological data of sites treated with ADM show a "scar" tissue appearance,[6] although better esthetic and color match with the surrounding tissue has been described, when compared with a FGG.[5,6,13]

Currently, the ADM is more routinely used for root coverage procedures (Fig. 1) and soft tissue augmentation at tooth or implant sites (Fig. 2),[14–19] particularly when avoiding a second surgical site and minimizing patient morbidity is the primary concern.[17,20,21] Although ADM is considered to be the graft substitute with the most similar outcomes to the connective tissue graft (CTG),[22] a recent network meta-analysis evaluating the changes in root coverage outcomes over time showed that only CTG-treated sites had a trend towards the stability of the gingival margin among the other root coverage techniques.[19] Similarly, a 12-year follow-up study reported a significant relapse of the gingival margin in multiple gingival recessions treated with ADM.[17] A possible mechanism may be that the ADM may not have the capability of inducing keratinization of the overlying epithelia,[5,7,13] which seems to be a positive predictor for the stability of the gingival margin.[17,19,23,24] It can be suggested that with the treatment of ADM, similar root coverage outcomes to CTG can be obtained in the presence of a distinct amount of keratinized tissue width at baseline ($\geq$2 mm[17]).

Various human-derived ADMs are currently available, including AlloDerm,* Puros Dermis,† and Allopatch‡. Allopatch is derived from the human fascia lata from the American Association of Tissue Banks. This allograft is minimally processed, which may better preserve the biomechanical and biochemical properties of the allograft. It has been suggested that several properties should be considered when choosing the graft, including tissue origin, processing methods, cross-linking, and biomechanical properties,[25] and that the different procedures to obtain human allografts may influence scaffold characteristics, such as cell penetration and proliferation.[26,27] Kuo et al. compared AlloDerm with Allopatch as scaffolds supporting cellular ingrowth in fabricating tissue-engineered grafts (TEGs).[27] They observed different properties between the allografts, suggesting that decellularization protocols can affect the scaffold's biological and physical characteristics.[27] Increased vascular invasion into the constructs were found for TEGs based on Allopatch compared with those including AlloDerm. However, AlloDerm-based TEGs showed more rapid cellular migration.[27]

2.2 | Human amniotic membrane

Human amniotic membrane (HAM) is the innermost fetal membrane lining the amniotic cavity (0.02 to 0.05 mm in thickness), which is derived from healthy maternal donors during an elective caesarian section.[28] All donors' serum samples are tested to ensure the absence of viruses and all serologic tests are also repeated 6 months later.[29] HAM undergoes a process of preparation and preservation, such as cryopreservation and glycerol preservation or lyophilization and gamma irradiation,[30] resulting in the elimination of the cellular component while preserving the matrix.[31,32] HAM is composed by a single epithelial layer, a thick basement membrane, and an avascular collagen layer.[28,30] The avascular stroma contains several growth factors, including epidermal growth factor, transforming growth factors alpha and beta (TGF-α, TGF-β), fibroblast growth factor-2, and keratinocyte growth factor.[29,33] These growth factors contribute to the anti-inflammatory, immunomodulatory, antimicrobial, antiviral, anti-scarring, and analgesic properties.[28,30,34,35] In addition, it has been reported that HAM promotes epithelial wound healing, angiogenesis, and ECM deposition.[28,30,34,35] Because of these properties, HAM has been used in several fields for the promotion of wound repair and regeneration.[30,36] In periodontics, it has been investigated for application in guided tissue regeneration[36] and in the treatment of gingival recession.[28] In a randomized controlled study, it was confirmed that cryopreserved amniotic membrane was effective in enhancing cicatrization, wound healing, and reducing pain in patients undergoing implant placement.[29] Disadvantages of this allograft includes difficulty in handling, rapid degradation, and the lack of adherence in full-thickness burns where HAM acts as a temporary wound dressing.[37] HAM is commercially available as BioXclude.§

* BioHorizons, Birmingham, AL.

† Zimmer Dental, Carlsbad, CA.

‡ Musculoskeletal Transplant Foundation, Edison, NJ.

§ Snoasis Medical, Golden, CO.

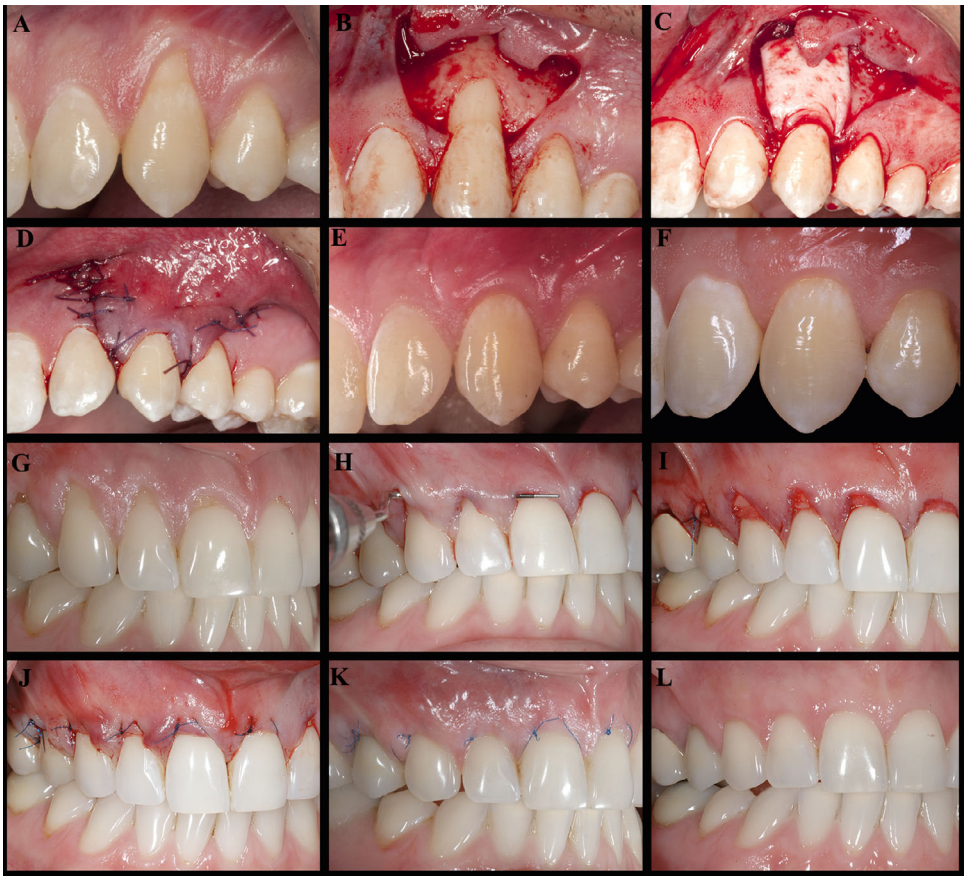

FIGURE 1 **A through F)** Coronally advanced flap and acellular dermal matrix for the treatment of an isolated gingival recession. **A**) Preoperative gingival recession on the left maxillary canine; **B**) flap design and elevation; **C**) acellular dermal matrix adapted and sutured over the root; **D**) flap coronally advanced and sutured; **E**) 6 month result; **F**) the complete root coverage is maintained also at the 10-year recall. **G through L**) Tunnel technique and acellular dermal matrix used for the treatment of multiple adjacent gingival recessions. **G**) clinical scenario at baseline; **H**) tunnel flap is performed; **I**) acellular dermal matrix is inserted in the flap; **J**) the flap is sutured together with the graft material in a coronally advanced position; **K**) 2-week postoperative; **L**) 6 month result showing the complete root coverage of the recession defects (adapted with permission from Ref. 17 from *Journal of Clinical Periodontology*)

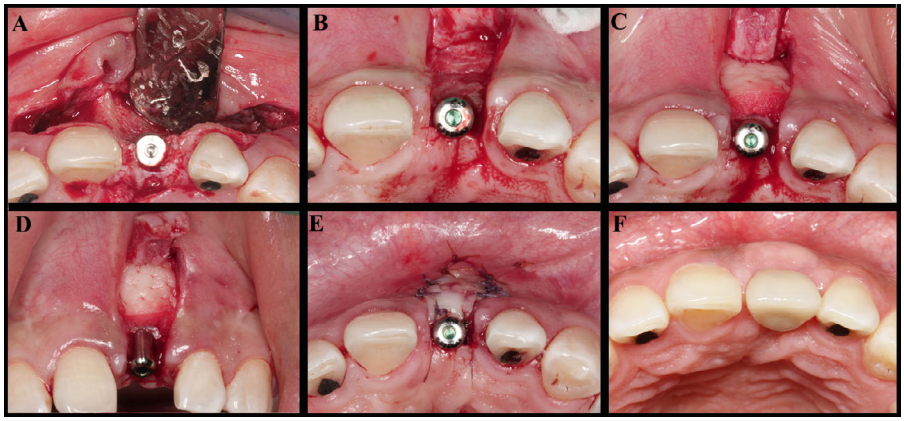

FIGURE 2 Acellular dermal matrix used for soft tissue augmentation in a maxillary dental implant lacking buccal bone. **A**) Clinical scenario before bone augmentation; **B**) 6 months after guided bone regeneration; **C and D)** soft tissue augmentation by using an acellular dermal matrix; **E**) flap closure; **F**) 5 year recall showing the stability of the obtained soft tissue volume

2.3 | Xenogeneic collagen matrices

2.3.1 | Bilayered collagen matrix

Mucograft* is a non-cross-linked, resorbable, porcine bilayered collagen matrix (CM) composed of collagen types I and III.[38,39] CM presents an occlusive compact layer of dense collagen and smooth texture aiming at promoting cell adhesion and a porous structure facing the host tissue that enhances tissue integration and angiogenesis.[39–41] The compact layer, made from porcine peritoneum, acts as a barrier and provides stability, while the porous layer, obtained from the porcine skin, is designed for supporting blood clot stabilization and the promotion of cellular ingrowth.[39]

These properties demonstrate the potential clinical applications of the biomaterial in periodontal plastic surgical procedures, where CM has been used to increase keratinized tissue, cover single and multiple gingival recession(s), and augment soft tissue thickness.[41–43] Among its main advantages are the reduced surgical time and patient morbidity compared with autogenous soft tissue grafts.[41,42] Clinical trials have shown that CM is able to increase the keratinized tissue width,[41,44] but some have questioned this potential because it lacks the cellular component needed for keratinized tissue formation.[45] Furthermore, root coverage procedures may also benefit from the addition of xenogeneic allografts.[46] However, a recent randomized clinical trial did not meet the non-inferiority end point of CM compared with the "gold standard" CTG in the treatment of multiple gingival recessions. These findings examined odds of achieving complete root coverage, although CM was related to a shortened surgical and recovery time.[42]

An excellent color match with the surrounding tissue was reported when CM was used in soft tissue augmentation.[39,40] This result may be due to the properties of CM that acts as a scaffold matrix, accelerating migration of cells from adjacent tissues and at the same time as a protective dressing when left exposed.[41,47]

Histological data have confirmed the good integration of CM in the host tissues without signs of adverse tissue reaction, or evidence of a significant inflammatory response.[38,40,48] Therefore, collagen matrices have also been proposed as scaffolds for supporting the proliferation of fibroblasts and keratinocytes in TEGs.[49,50]

2.3.2 | Volume-stable collagen matrix

A new porcine, porous, CM (Fibrogide)[‖] has recently been introduced for soft tissue regeneration. This graft has also been called volume-stable collagen matrix (VCMX) since one of its main advantages is the ability to maintain a good volume stability.[51,52] VCMX is made of collagen and undergoes a cross-linking providing volume stability and some elasticity at the same time.[51–53] VCMX has only one porous layer that promotes angiogenesis, ingrowth of fibroblasts, matrix biosynthesis, and tissue integration.[51,52,54] In contrast to CM that has been used also in an open environment, VCMX requires a submerged healing.[52,55] Several preclinical and clinical studies investigating VMCX showed promising results in terms of volume gain, without any significant adverse reactions noted[52,55–57] (Fig. 3). Further studies with longer follow-up are needed to confirm these early findings of VCMX (especially compared with CTG) in increasing mucosal thickness at implant sites.

2.3.3 | Xenogeneic acellular dermal matrix

Porcine-derived acellular dermal matrix (PADM: Mucoderm)[†] is a CM obtained from porcine dermis after a multi-step process aimed at removing all the antigenic components.[58,59] Therefore, PADM serves as a three-dimensional (3D) matrix, promoting the proliferation of fibroblasts and endothelial cells and supporting a fast revascularization of its structure.[58,60] The use of PADM has been suggested as a carrier for enamel matrix derivatives in the treatment of gingival recessions,[59] where histological evidence of periodontal regeneration was observed.[59] Figure 4 showed two clinical cases in which PADM was used for the treatment of soft tissue deficiencies at tooth and implant sites.

2.3.4 | Extracellular matrix

DynaMatrix[‡] is a 3D structure porcine-derived matrix from the submucosa of the small intestine in a cell-free procurement, while the natural composition of the matrix molecules is preserved.[61,62] The matrix provides a scaffold that promotes the repopulation of fibroblasts, blood vessels, and epithelium from the adjacent tissues.[62] In vitro studies showed its favorable properties in stimulating cellular adhesion, differentiation, and proliferation[63,64] as well as in facilitating angiogenesis.[65] These characteristics may explain the clinical outcomes of this matrix that was found to be effective and predictable in keratinized gingiva augmentation and in resembling the surrounding tissue.[62]

Although these ECM-based scaffolds have been proposed as alternatives to an autogenous graft, clinical considerations regarding their handling characteristics and stabilization compared with free gingival graft– and CTG are lacking in the literature. The clinical experience of the authors suggests that the use of these graft substitutes poses additional challenges for suturing the material on the recipient bed or for inserting it into a tunnel flap. It has been reported that one of the

* Geistlich Pharma, Wolhusen, Switzerland.

† Botiss Dental, Berlin, Germany.

‡ Keystone Dental, Burlington, MA.

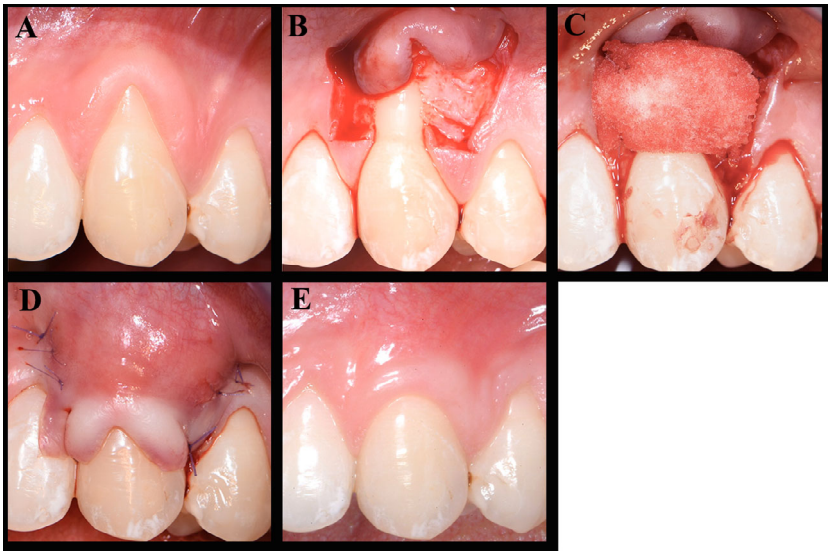

FIGURE 3 Volume-stable collagen matrix around teeth used for root coverage purposes. **A**) Gingival recession defect on a maxillary canine; **B**) a split-full-split flap limited to the canine was performed; **C**) after the de-epithelialization of the anatomical papillae, a volume-stable collagen matrix was applied on the root surface and sutured to the de-epithelialized papillae; **D**) the flap was coronally advanced and sutured; **E**) 1-year outcomes

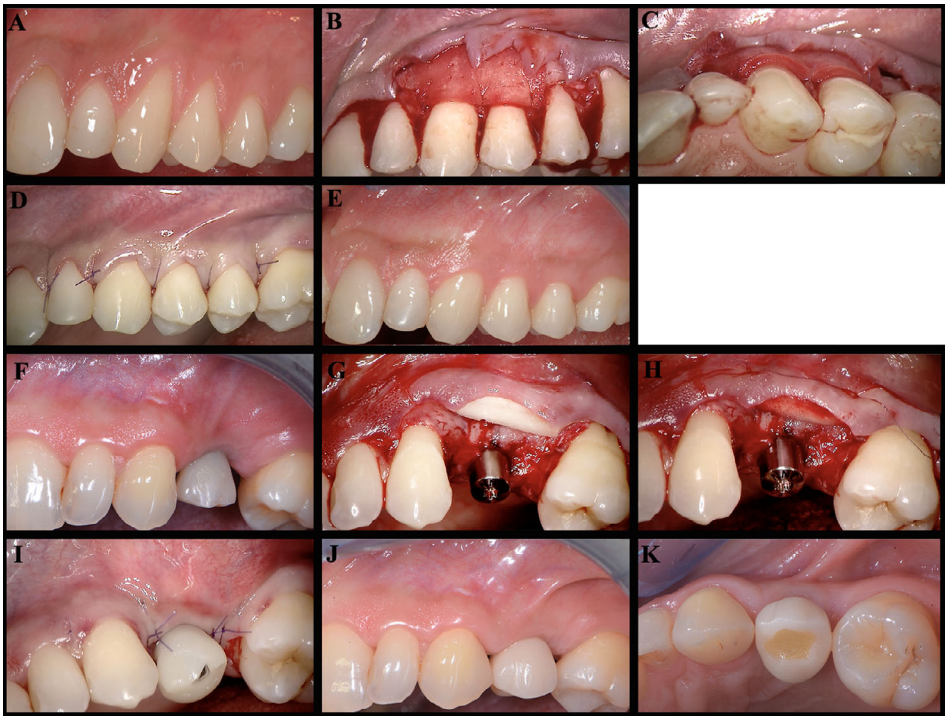

FIGURE 4 Xenogeneic acellular dermal matrix used for the treatment of multiple adjacent gingival recessions (**A through E**) and for soft tissue augmentation at a single implant site (**F through K**). **A**) Multiple adjacent maxillary gingival recessions; **B and C**) after the split-full-split envelope flap preparation, a xenogeneic acellular dermal matrix was inserted and stabilized over the roots; **D**) flap closure; **E**) 1-year outcomes; **F**) dental implant presenting with inadequate soft tissue thickness and poor esthetics; **G and H**) xenogeneic acellular dermal matrix sutured around the implant; **I**) flap closure; **J and K**) 1-year outcomes showing improved peri-implant soft tissue thickness, contour, and esthetics

advantages of the VCMX compared with CM is the property of regaining its initial volume within few minutes, due to its high elasticity.[52] Nevertheless, also VCMX seems to be less resistant to compression than CTG which can be easily stabilized to the de-epithelialized papilla or inserted into the tunnel flap with sutures. In the future, there should be greater studies on the material handling characteristics to optimize placement during surgery.

3 | POLYMERIC MATRICES

Polymeric matrices have been widely used as biomaterials in tissue engineering for fabricating scaffolds and medical devices. Natural polymers can be derived from 1) proteins, including collagen, silk, gelatin, and fibrin glue; 2) polysaccharides, such as hyaluronic acid and chitosan; and 3) polynucleotides.[66] Additionally, the manufacturing

TABLE 1 Summary of the extracellular matrix-based scaffolds used in periodontal and peri-implant soft tissue reconstruction

Scaffold	Origin	Main advantages	Primary indications	Secondary indications	Level of evidence (SORT)	Reference(s)
Decellularized human dermis	Human acellular dermis	Promotes cellular migration and revascularization from the host tissues Minimal patient morbidity	Root coverage Increasing tissue thickness	Increasing keratinized tissue in combination with apically positioned flap	A	Scarano et al.[5]; Wang et al.[15]; Hutton et al.[14]
Human amniotic membrane	Innermost fetal membrane lining the amniotic cavity	Contains several growth factors Anti-inflammatory, immunomodulatory, antimicrobial, antiviral, anti-scarring, and analgesic properties Promotes epithelial wound healing, angiogenesis, and extracellular matrix deposition	Root coverage	Adjunctive to surgery for enhancing wound healing	C	Velez et al.[29]; Kiany et al.[36]; Jain et al.[28]
Bilayer collagen matrix	Porcine	One layer promotes cell adhesion, and enhances tissue integration and angiogenesis, while the other acts as a barrier and provides stability Excellent color match with the adjacent tissue Lower morbidity then autogenous grafts	Root coverage Increasing tissue thickness	Increasing keratinized tissue in combination with apically positioned flap	A	Sanz et al.[41]; Lorenzo et al.[44]; Cairo et al.[43]; Tonetti et al. 2018[42]
Volume-stable collagen matrix	Porcine	Maintenance of a good volume stability Promotes angiogenesis and ingrowth of fibroblasts	Root coverage Increasing tissue thickness	Increasing keratinized tissue in combination with apically positioned flap	B	Thoma et al.[52,55]; Zeltner et al.[56]
Xenogeneic acellular dermal matrix	Porcine dermis	It promotes the proliferations of fibroblasts and endothelial cells	Root coverage Increasing tissue thickness		B	Shirakata et al.[59]
Extracellular matrix (as stand-alone technology)	Porcine small intestine submucosa	Promotes the repopulation of fibroblasts, blood vessels, and epithelium from the adjacent tissues Stimulates cellular adhesion, differentiation, and proliferation	Increasing keratinized tissue in combination with apically positioned flap		C	Nevins et al. [62]

SORT, strength-of-recommendation taxonomy; SORT A, consistent, good-quality patient-oriented evidence; SORT B, inconsistent or limited-quality patient-oriented evidence; SORT-C, consensus, disease-oriented evidence, usual practice, expert opinion or case series for studies of diagnosis, treatment, prevention, or screening.[74]

methods of natural and synthetic biomaterials include many processes, such as electrospinning, 3D printing, or the use of CAD/CAM. Natural polymers were among the first biomaterials investigated in dental tissue engineering and, among their main advantages, a greater biocompatibility and interaction with host cells compared with synthetic matrices have been described.[66] Because of its properties of promoting wound healing, silk has been widely used as a scaffold in soft and bone tissue engineering in combination with epidermal or mesenchymal stem cells or fibroblasts.[67,68] Collagen is the most abundant naturally-derived protein in the human body and it's the major protein of the ECM of the skin dermal layer.[67] Several collagen-based grafts have been proposed in wound healing and tissue engineering of skin,

including ADM, cellular epidermis/dermis, and bilayered skin equivalents.[67] The lack of biostability and frequent wound contracture are among the disadvantages of collagen-based scaffolds.[67] These limitations have been overcome by cross-linking the collagen matrices or by combining them with other ECM molecules.[67,69]

Synthetic materials have progressively become widely used in the biomedical field since they can be tailored for attaining different desired characteristics using various fabrication techniques.[66,67] Compared with natural polymers, synthetic scaffolds are produced in large quantities and have a longer shelf life. In addition, they show consistent properties, such as tensile strength, elastic modulus, and degradation rate.[66] However, lack of cellular recognition, biocompatibility, and biodegradability represent their main drawbacks that may limit its clinical application.[66] Given these shortcomings, synthetic biomaterials are usually used in combination with natural polymers.[67,70] Polycaprolactone (PCL), poly(lactic acid) or polylactic acid or polylactide (PLA), and poly(lactic-co-glycolic) acid (PLGA) are among the most used synthetic polymers in tissue engineering, specifically with bone regeneration.[66,71] PLGA is a versatile polymer that can be personalized to any shape and size while controlling its degradation time to match the rate of the tissue neogenesis or the desired drug release profile. This material has been used as a scaffold for tissue regeneration or as a drug delivery system, in particular as nanoparticles/microparticles of PLGA that are able to control the delivery of growth factors for tissue engineering applications.[72,73] Nevertheless, there is limited evidence available on the use of synthetic biomaterials for soft tissue reconstruction in humans. Table 1 summarizes the ECM-based scaffolds used in periodontal and peri-implant soft tissue reconstruction.

4 | CONCLUSIONS

Extracellular-based scaffolding technologies are effective in soft tissue augmentation at periodontal and peri-implant sites. Given that these materials are devoid of cells and usually cellular signaling molecules, they promote soft tissue volume, but not keratinized tissue neogenesis. Nevertheless, ECM scaffold constructs generally encourage the migration and the proliferation of fibroblasts and keratinocytes providing an excellent color match with the surrounding tissue. The reduced surgical time and morbidity compared with autogenous grafts are some of the main advantages of these materials as patient preferences indicate. The use of synthetic scaffolds made from polymeric biomaterials such as PCL, PLGA, and PLLA have shown good potential for combination drug delivery approaches; however, as stand-alone technologies they do not promote new tissue formation or stimulate cellular and vascular ingrowth critical for clinical success. Future research should examine combination of biologic and/or cell-based ECM constructs for clinical application to improve treatment outcomes.

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