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Soft Tissue Substitutes: Current Biomaterials and Indications at Teeth and Implant Sites

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ABSTRACT

Soft tissue augmentation around teeth and dental implants is a central aspect of periodontal and peri-implant plastic surgery. Autogenous soft tissue grafts are generally regarded as the gold standard for increasing keratinized mucosa, mucosal thickness, and soft tissue height, supported by extensive long-term evidence. However, limitations such as restricted tissue availability, increased surgical time, and donor-site morbidity have encouraged the development of soft tissue graft substitutes, including xenogeneic and allogeneic matrices, and collagen derivatives, among other biomaterials. Over the past two decades, these alternatives have shown promising results, particularly in sites with favorable anatomical conditions, including optimal bone support, tall and wide papillae, and adequate hard and soft tissue phenotype; although their predictability remains variable across the literature and is often lower than that of autogenous grafts in complex defects and esthetically demanding areas. Nevertheless, the growing emphasis on patient-reported outcomes has led several authors to explore the use of graft substitutes in different clinical scenarios, sometimes in combination with smaller autogenous grafts. This manuscript aims to summarize the current state-of-the-art on soft tissue graft substitutes for managing deficiencies at both teeth and implant sites. A comprehensive literature review is provided, together with clinical decision trees designed to guide clinicians in selecting autogenous grafts versus substitutes across different scenarios. These tools highlight the main factors influencing treatment selection, including baseline keratinized mucosa, buccal bone conditions, site anatomy, esthetic requirements, and patient preference. By integrating current evidence with practical algorithms, this review seeks to support clinicians in making informed, patient-centered decisions regarding soft tissue augmentation at teeth and implants.

1 | Clinical Context: Soft-Tissue Deficiencies Around Teeth and Implants

Soft tissues play a crucial role in the health, esthetics, and comfort of both teeth and implant sites [1–4]. Nevertheless, deficiencies in the quality and quantity of soft tissue are commonly observed. These conditions are relatively heterogeneous, not only in their clinical presentation but also in their etiological factors, the concerns expressed by patients, and the treatment strategies applied.

Gingival recession (GR) is defined as the apical shift of the gingival margin relative to the cemento-enamel junction (CEJ) [5]. A large portion of the population is affected by this condition [6–10], which is often associated with hypersensitivity, esthetic concerns, and carious or non-carious lesions [3, 5, 11]. More than 85% of untreated GRs tend to progress over a four-year period, while over 30% of teeth that did not previously exhibit this condition may develop midfacial GR overtime [12]. The high incidence and progression of GRs have been attributed to several factors, including traumatic tooth brushing, plaque-induced inflammation, periodontitis, orthodontic treatment, lack of or inadequate keratinized gingiva (KG) width, insufficient gingival thickness (GT), buccal bone dehiscence, and tooth malpositioning, among others [11, 13–17]. The current classification of GRs is based on the interproximal clinical attachment level [5, 18], which strongly affects the amount of root coverage that can be achieved [16, 18, 19].

Other soft tissue deformities or deficiencies that may be present at healthy natural teeth include missing papillae and black triangles, absence of KG and attached gingiva, reduced GT, high frenum pull without a band of KG and attached gingiva, and pseudo-pocket following soft tissue grafting [5, 14, 15, 20–22]. Some of these conditions may also occur simultaneously (Figure 1). The importance of an adequate gingival phenotype—characterized by sufficient KG, attached gingiva, and GT—lies in its positive effects on the long-term stability of the gingival margin, reduced likelihood of GRs development or progression, improved patient comfort during brushing, and decreased dental hypersensitivity [5, 11, 23–26].

Similarly, dental implants are often affected by soft tissue deficiencies in both quality and quantity [2, 27–29]. Clinically healthy implants—defined by the absence of bleeding on probing and bone loss [27, 30–33]–can still result in poor esthetic outcomes and patient dissatisfaction (Figure 2). Peri-implant soft tissue dehiscences/deficiencies (PSTDs) are common at anterior implant sites [29, 34, 35] and are an increasing concern in the dental community. These conditions are associated with implant malpositioning, absence of adjacent teeth, inadequate or absent keratinized mucosa (KM) width, reduced mucosal thickness (MT), buccal bone dehiscence, reduced vestibular depth, and suboptimal prosthetic design [29, 34–42]. PSTDs in the anterior zone have been shown to negatively impact patients' confidence and quality of life [43–45].

Other soft tissue deformities affecting clinically healthy dental implants include missing or deficient papillae, inadequate KM, lack of adherent and firm KM, insufficient MT, and a thin or reduced supracrestal tissue height (STH) [46–48] (Figure 2). These deficiencies have been associated with an increased risk of peri-implant diseases [38, 49–53], hard and soft tissue loss [2, 54, 55], esthetic complications [34, 38, 56, 57], discoloration of the peri-implant mucosa [58, 59], and patient discomfort [50, 60].

After reviewing the evolution of soft-tissue grafting procedures and the limitations of autogenous grafts, this manuscript aims to summarize the state-of-the-art on soft tissue graft substitutes for managing soft tissue deficiencies at both tooth and implant sites.

2 | Evolution of Soft Tissue Grafting Procedures and Minimally Invasive Augmentation Techniques

According to Zuhr et al., the introduction of the connective tissue graft (CTG) [61] and the increasing transition from the conventional free gingival graft (FGG) to CTG can be identified as the turning point from traditional mucogingival surgery to modern periodontal plastic surgery [62]. Traditional mucogingival surgery included vestibuloplasty, pedicle flaps, gingivectomy, and frenectomy. The introduction of FGG [63, 64] revolutionized the field, providing clinicians with new strategies for treating soft tissue deformities [3]. Nevertheless, FGG also has limitations, including post-operative pain at the donor site, color and texture mismatch with adjacent tissues, limited predictability in root coverage procedures, and suboptimal esthetic outcomes [14, 15, 22, 65–67].

In contrast, CTG has enabled clinicians to achieve improved clinical and esthetic outcomes in root coverage procedures compared to FGG or pedicle flaps without a graft [3, 14, 15, 68]. The evolution of surgical flap designs, techniques, microsurgical instruments, and scientific understanding has significantly increased the predictability of root coverage using CTG, with studies reporting mean root coverage (mRC) values approaching 100% [68–71]. Multiple systematic reviews have confirmed CTG to be the treatment option associated with the highest mRC and the greatest likelihood of achieving complete root coverage (CRC) [23, 68, 72, 73] As a result, CTG is widely regarded as the "gold standard" for the treatment of GRs [3, 73].

This concept, however, is probably valid if only clinicians' perspective and clinical "raw" numbers are considered. When the patient's perspective and surgical experience are also considered, the notion of a so-called gold standard may differ [25, 74–78]. Over the past decades, patient-centered outcomes such as perceived discomfort, postoperative pain, and satisfaction have gained increasing importance in clinical research and daily practice—not only in periodontology, but across all dental disciplines [25, 74, 79–82].

Therefore, contemporary periodontology has progressively focused on developing new strategies that optimize both clinical and patient-centered outcomes. Current minimally invasive, patient-centered surgical approaches to treating soft tissue deformities around teeth and implants should ideally follow these principles: (i) adopt minimally invasive flap designs; (ii) reserve autogenous grafts for cases where maximal efficacy is necessary, ideally using them through a selective, site-specific approach; (iii) consider soft tissue graft substitutes–either as alternatives to or in combination with autogenous grafts–depending on case selection.

FIGURE 1 | Gingival recessions and mucogingival deformities in natural dentition.

Today, the most commonly employed flap designs for the treatment of GRs and PSTDs include the coronally advanced flap (CAF) with conventional or modified designs, tunnel techniques (TUN) and their evolutions such as the modified coronal advanced tunnel (MCAT) and the vestibular incision subperiosteal tunnel access (VISTA), and the combination of CAF and TUN (Tunneled Coronally Advanced Flap [TCAF]) [15, 25, 83–87]. These flaps have been used in combination with various graft materials, including autogenous CTG, allogeneic and xenogeneic acellular dermal matrices, xenogeneic collagen matrices, and living cellular constructs [44, 88–94]. Additionally, biological agents–such as enamel matrix derivatives, recombinant human platelet-derived growth factor (rhPDGF), fibroblasts growth factors, and autologous blood –have also been used with different scaffolds to support these procedures [95–98].

3 | Limitations of Autogenous Grafts and Patients' Perspectives on Palatal Harvesting

There is no doubt that autogenous soft tissue grafts, as a part of periodontal plastic surgical treatment, can provide excellent clinical outcomes across a wide range of clinical indications and scenarios [3]. Nevertheless, these procedures require palatal soft tissue harvesting, which not only extends the duration of the surgery, but also increases invasiveness and post-operative morbidity from the patient's perspective [22, 66].

The palatal donor site is often the primary source of postoperative pain, discomfort, and disruption of daily activities and eating habits [22, 66, 99]. As a result, regardless of the improved clinical outcomes, the need for palatal harvesting may negatively impact

FIGURE 2 | Soft tissue deficiencies and deformities at implant sites.

patients' perceptions and satisfaction with the overall treatment. Moreover, several potential complications related to palatal soft tissue harvesting have been reported, including injury to branches of the greater palatine artery, excessive intraoperative bleeding, primary flap laceration, postoperative pain, necrosis or sloughing of the flap, changes in feeding habits, and sensory disturbances, among others [22, 66, 99–101]. A cross-sectional study showed that patients could recall their experience with palatal harvesting and autogenous soft tissue grafting even 10–15 years after the procedure, with their willingness to undergo the same treatment again strongly influenced by the pain they had perceived [65].

Another limitation of autogenous grafts is the restricted quantity and quality of donor tissue available at the palatal or retromolar area, which often precludes harvesting grafts of sufficient dimensions for full-arch or full-mouth reconstructions [22]. In addition, patients' esthetic concerns, motivations, and expectations should also be considered when choosing between autogenous grafts or soft tissue substitutes. For some patients, gaining an additional 0.5 to 1 mm of root coverage may not justify a more invasive surgical approach, while for others even a half-millimeter gain may be considered critically important. Therefore, striking a balance between clinical efficacy and patient morbidity is crucial [102]. Bearing this in mind, clinicians should be fully aware of both the superior efficacy of autogenous grafts and their associated patient-related drawbacks and should tailor the surgical strategy based on clinical needs and patient preferences [25, 56, 65, 74, 82, 103].

4 | Classification and Characteristics of Soft-Tissue Substitutes

Soft tissue graft substitutes have become increasingly popular among clinicians due to several advantages over autogenous

grafts, including unlimited availability, elimination of the need for a secondary surgical site, reduced surgical time, lower morbidity, and–often–patient preference [74]. As noted by Griffin et al., shortening the surgical time can significantly reduce the risk of substantial postoperative swelling and pain [104].

Modern clinical practice increasingly emphasizes the simplification of surgical protocols through quick and minimally invasive interventions. These factors help explain the growing acceptance of soft tissue substitutes by both clinicians and patients as viable alternatives to autogenous grafts. Soft tissue graft substitutes can be classified in two main ways (Figure 3):

1. By origin:
   a. Allogenic (human-derived);
   b. Xenogeneic (animal-derived);
   c. Synthetic (laboratory-manufactured).
2. By composition:
   a. Dermal matrices
   b. Collagen matrices.

Soft tissue graft substitutes can also be classified based on their cellular content into:

- Living cellular constructs, which are seeded with autogenous or allogeneic viable cells, and represent an "active" tissue engineering approach,
- Non-living constructs, which do not contain living cells and function as scaffolds that support host cell migration and integration at the recipient site, representing a "passive" tissue engineering approach.

4.1 | Allogeneic Dermal Matrices

Human acellular dermal matrix (hADM) has been extensively and safely used in various applications, including treatment of burn wounds [105], facial augmentation, breast reconstruction, and esthetic plastic surgery procedures [106–108]. Derived from human cadaver skin, hADM undergoes a decellularization process–varying by manufacturer–to remove cellular components while preserving the structural integrity of the extracellular matrix, thereby rendering the material immunologically inert. Upon implantation, hADM acts as a scaffold that promotes cellular migration and revascularization from surrounding host tissues [106, 109–111]. In dentistry, hADM was the first soft tissue graft substitute introduced for soft tissue augmentation around natural teeth. Early reports described its use as an alternative to autogenous free gingival grafts to increase the width of attached and keratinized gingiva [110, 112, 113].

Scarano et al. conducted a histological and ultrastructural analysis of hADM before implantation and at various time points following treatment with an apically positioned flap (APF) combined with hADM [109]. Initially, the matrix was composed of fibrous reticular connective tissue rich in collagen bundles but devoid of cells and epithelium. After 4 min post-implantation, erythrocytes were noted between the collagen fibers. During the first week, macrophages were seen phagocytosing existing collagen. By the end of the first week, fibroblasts and some peripheral epithelial cells were present. At 2 weeks, inflammatory cells had decreased, while fibroblasts and epithelial cells had increased. New small blood vessels were seen particularly at the graft–recipient bed interface. At 3 weeks, epithelial coverage increased and neovascularization extended to the outer matrix. By 4 weeks, many original collagen fibers were resorbed and replaced by newly formed ones, and the superficial layers resembled granulation tissue. By 6 weeks, re-epithelialization was complete, with a well-organized basement membrane. At 10 weeks, no inflammatory cells were detected, and complete re-epithelialization was evident [109].

Other histological studies have indicated that the tissue augmented with APF + hADM does not fully resemble native gingiva, often appearing more like scar tissue [110, 114]. Nevertheless, due to the risk of sloughing or necrosis when hADM is left exposed, it is now primarily used in bilaminar techniques for root coverage and soft tissue thickness augmentation at teeth and implant sites [109, 115, 116].

A study from Harris found that while CTGs resulted in greater probing pocket depth reduction and keratinized tissue gain compared to hADM, these differences were not clinically significant in terms of root coverage outcomes [117]. In a case requiring gingivoplasty 3 months after hADM-based root coverage, a punch biopsy revealed mostly normal histological features, except for elastin fibers–normally absent in oral mucosa but present in hADM–suggesting successful incorporation of the graft [117].

Clinicians should note that numerous commercial hADM products are currently available. Although no clinical evidence to date has shown significant differences in clinical outcomes among these products [116, 118], in vitro studies have suggested that processing factors such as decellularization methods, cross-linking, and biomechanical properties may influence cellular penetration and proliferation [119–121]. Therefore, differences in performance across various hADM brands in the clinical setting cannot be entirely ruled out.

4.2 | Xenogeneic Dermal Matrices

Porcine-derived acellular dermal matrices (pADMs) are obtained from porcine dermis through a multi-step process aimed at removing all the antigenic components [122, 123]. These matrices retain a three-dimensional extracellular structure composed primarily of collagen types I and III, along with elastin, which supports the proliferation of fibroblasts and endothelial cells [122, 124]. Scanning electron microscopy has revealed a porous collagen architecture that facilitates vascularization and provides a scaffold for host cell migration [93, 125, 126].

Like hADM, pADMs undergo disinfection procedures to eliminate non-collagenous proteins, cells, bacteria, viruses, and other immunogenic constituents [122, 127]. Preclinical data suggest that pADM effectively supports fibroblast migration and rapid revascularization while eliciting a limited inflammatory response [128, 129]. A canine study by Suarez Lopez del Amo et al. provided histological evidence of pADM integration when stabilized underneath a flap for root coverage procedures [130]. At 2 weeks post-surgery, the graft appeared well integrated within

FIGURE 3 | Soft tissue graft substitutes and respective classification based on their source.

healthy surrounding tissue, with no signs of irritation such as multinucleated giant cells or lymphocyte infiltration. Mild degradation of the matrix was noted at this stage. By 6 weeks, moderate degradation was observed, but the matrix remained well integrated and inflammation-free. After 10 weeks, these favorable histological findings persisted, with no evidence of necrosis or foreign body reaction, leading the authors to conclude that pADM is safe and well tolerated [130]. Notably, compared to sites augmented with a collagen matrix, tissues receiving pADM showed a higher concentration of elastic fibers at all time points [130].

pADMs have become popular in specific countries, partly because they are subject to fewer regulatory restrictions than hADMs [85, 127]. Furthermore, pADM offers greater availability and can be obtained in larger quantities [127].

4.3 | Xenogeneic Collagen Matrices

The first generation of porcine-derived collagen matrices included a bilayered collagen matrix (CMX), composed of collagen types I and III, manufactured through a standardized and controlled proprietary process [131, 132]. One layer of CMX is formed from dense collagen derived from porcine peritoneum, designed to serve as an occlusive and compact barrier providing graft stability. This layer has a smooth texture to facilitate cell adhesion [132–134]. The other layer, intended to face the host tissue, features a porous structure that promotes blood clot stabilization, cellular ingrowth, and angiogenesis [132–134].

CMX has been employed as a substitute for FGGs in keratinized tissue augmentation around teeth and implants, and as an alternative to CTGs for root coverage procedures [134–136]. One notable advantage of CMX is its capacity for healing by secondary intention, which has led to its use in alveolar ridge preservation and immediate implant therapy [137–139]. Histological studies confirmed the safety, biocompatibility, and complete integration of CMX within the host tissues, with no signs of adverse reactions or significant inflammatory response at 3 months [131, 133, 140–142].

More recently, a second generation of porcine-derived collagen matrices has been introduced: the "volume-stable" collagen matrix (VCMX). This graft substitute was named for its stability during surgery, regardless of compression or contact with blood and saliva [143, 144]. VCMX is characterized by a thick layer of cross-linked collagen organized in a trabecular structure with large honeycomb-like pores [143–146]. This design facilitates angiogenesis and the ingrowth of host cells, along with matrix biosynthesis and tissue integration [143, 144, 147].

An in vitro study demonstrated that VCMX had the highest resistance to degradation when compared to CMX and a pADM, likely due to its unique "smart-linked" collagen cross-linking and the addition of elastin, which enhances elasticity, strength, and volume stability [148]. Unlike the first generation of collagen matrices, which may also be used in open healing conditions, VCMX requires submerged healing [144, 149]. However, accidental exposure of VCMX during initial healing—for example, due to flap sloughing—does not lead to significant complications, though clinical outcomes may be inferior to those expected with primary closure [88, 96].

Several preclinical studies have investigated the initial healing and tissue integration of VCMX [146, 150–156]. In a canine model, Ferrantino et al. used VCMX to augment peri-implant soft tissue, placing it over the periosteum using a split-thickness envelope flap [156]. The graft was stabilized with a horizontal mattress suture and submerged via primary closure. Immediately after placement, the matrix was infiltrated with erythrocytes and plasma. By Day 4, leukocytes were found around the graft, and a few mesenchymal cells appeared at its margins. At 1 week, additional mesenchymal cells, leukocytes, and vessels had penetrated further into the graft. The central portion contained a fibrin network with erythrocytes, multinucleated giant cells, and mesenchymal cells. By 2 weeks, vascularization was evident throughout the matrix, with reduced leukocytes and increased mesenchymal cells and fibroblast-like cells. By Day 30, fibroblasts predominated, multinucleated giant cells were absent, and numerous blood vessels were seen within the newly formed matrix. At 90 days, the graft was fully integrated within the connective tissue, with collagen fibers enclosing the residual VCMX, infiltrated by new collagen and blood vessels [156].

Another animal study by Caballé-Serrano further detailed the tissue response and cell behavior within VCMX [146]. Blood rapidly filled the matrix pores, followed by a brief inflammatory phase and rapid ingrowth of vessels and fibroblasts, leading to successful integration. The matrix retained sufficient volume during early healing, enabling the proliferation of mesenchymal cells producing collagen type I before degradation.

Other preclinical investigations have corroborated the safety, biocompatibility, and volume stability of VCMX during healing, along with substantial tissue volume gain [150–155]. Its high porosity, interconnected structure, and cross-linked collagen support its use as a scaffold for progenitor cell migration and the delivery of biologic agents [25, 96, 145, 150, 151, 157, 158]. An in vitro study revealed enhanced cellular populations and metabolic activity within VCMX when employed as a scaffold for recombinant human platelet-derived growth factor-BB (rh-PDGF) [145].

5 | Diagnostic Tools and Clinical Methods to Assess the Treatment Outcomes Following Soft Tissue Augmentation with Substitute Grafts

The outcomes of periodontal and peri-implant plastic surgeries have traditionally been assessed using clinical measurements, radiographic parameters, esthetic indices, and both clinician- and patient-reported outcome measures [15, 82, 159, 160]. More recently, advancements in diagnostic technologies have enabled the evaluation of additional outcomes, including changes in the hard and soft tissue phenotype, profilometric and volumetric alterations, and tissue perfusion in the treated area [11, 161–165].

The periodontal probe remains the most widely used tool to evaluate clinical parameters before and after the surgical intervention. These include gingival recession or PSTD depth, KT width, probing pocket depth, and bleeding/suppuration on probing [15, 27]. Probes—either standard or color-coded—can also be used to assess soft tissue phenotype. Using a conventional probe, the phenotype is classified as thin or thick based on probe visibility through the tissue [166, 167], while with color-coded probes the phenotype is categorized as thin, medium, thick, or very thick [166, 167] (Figure 4).

Gingival thickness (GT) and MT have been commonly measured 1.5 mm and/or 3 mm apical to the soft tissue margin using the transgingival/transmucosal probing method. This involves piercing the soft tissue with an anesthesia needle or endodontic file and marking the tissue surface with a silicon stopper, allowing measurement with a digital caliper [26, 167]. Although this method is simple and cost-effective, concerns have been raised about its accuracy and reproducibility. Limitations include potential bending of the instrument within the tissue (leading to

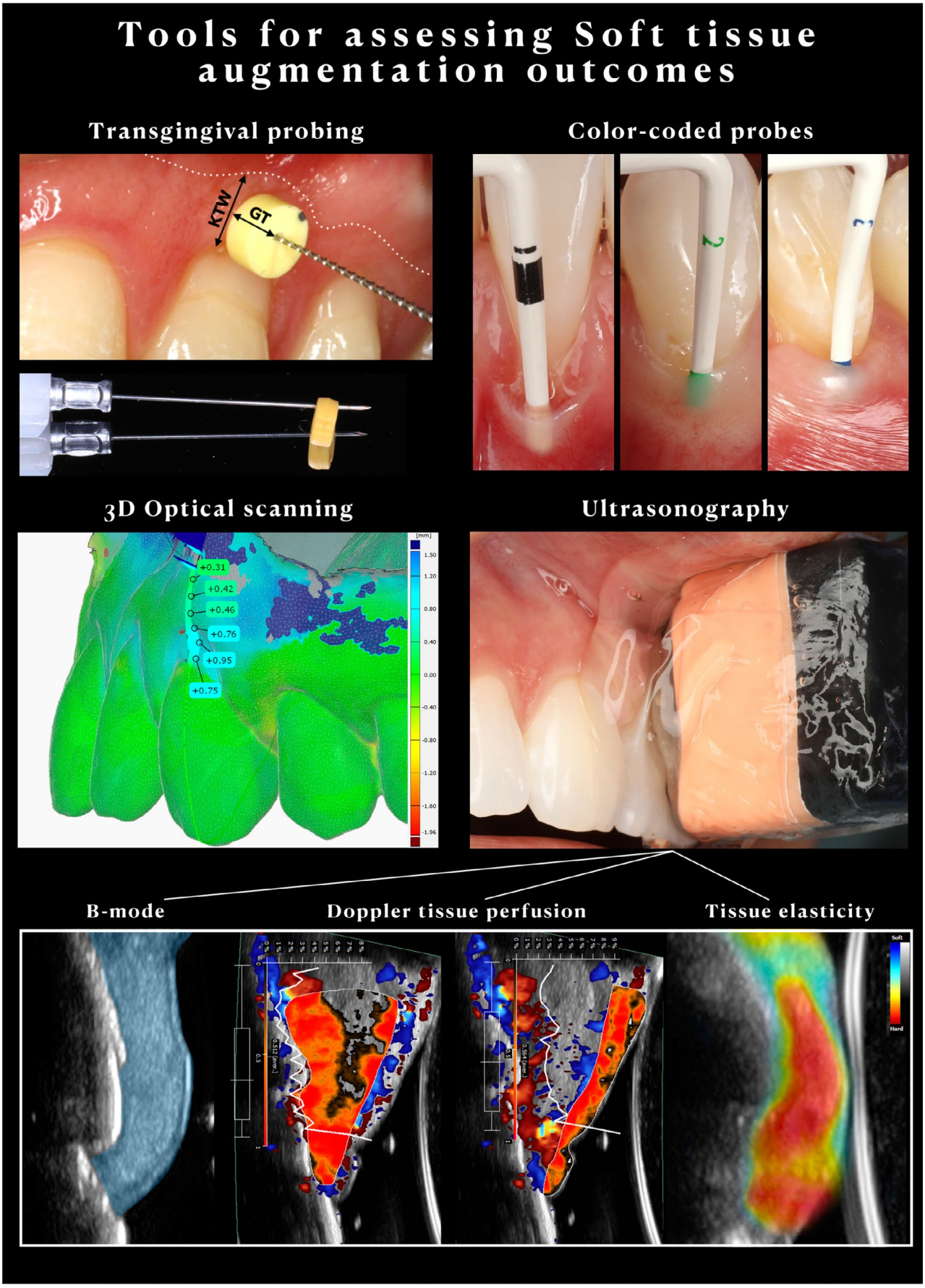

FIGURE 4 | Tools for assessing the outcomes of soft tissue augmentation at teeth and implant sites.

overestimated values), movement of the silicon stopper during removal, and patient discomfort due to the need for local anesthesia [34, 167].

Alternatively, GT and MT can be evaluated using cone-beam computed tomography (CBCT), either alone or by superimposition with the STL file obtained from a digital impression [11, 159, 168]. Intraoral scanning is increasingly employed to monitor volumetric changes following augmentation procedures [160, 165] (Figure 4). However, this method requires at least two digital impressions taken at different time points [160, 165]. As such, single digital impressions alone cannot assess soft tissue phenotype unless paired with CBCT data.

High-frequency Ultrasonography (HFUS) has emerged as a non-ionizing, reliable imaging modality for characterizing periodontal and peri-implant anatomy, disease status, tissue perfusion, and surgical outcomes over time [96, 161, 169–172]. HFUS allows real-time, non-invasive assessment of whether volumetric changes following soft tissue augmentation are confined to soft tissues or also involve the underlying bone. Given the limitations of transgingival/transmucosal probing (invasiveness and accuracy/reproducibility), intraoral scanners (need for multiple time points, unless combined with a CBCT [168]), and CBCT alone (radiation exposure and limited accuracy for soft tissues), several authors have recommended HFUS as the preferred tool for evaluating GT, MT, and buccal bone dimensions. HFUS can also assess tissue perfusion and elasticity (strain elastography) (Figure 4).

Perfusion imaging with HFUS is based on Doppler phase-shift effects, which visualize blood flow by detecting frequency shifts caused by moving red blood cells [173, 174]. Doppler ultrasound has proven effective in distinguishing healthy from diseased implant sites [161], and in characterizing flap and graft vascularization during healing after soft tissue augmentation at teeth and implants [163, 175].

Strain elastography, a well-established tool in medical imaging [176, 177], has recently been applied in dentistry [178, 179]. It involves compressing the target tissue with the ultrasound transducer, then analyzing tissue deformation to generate a color-coded elastogram that overlays the B-mode ultrasound image. This allows visualization of tissue elasticity gradients—from soft to stiff [174, 176, 177]. Our group recently described how ultrasound elastography can assess the elasticity of periodontal and peri-implant soft tissues. Tissue elasticity reflects the underlying composition and characteristics of soft tissue and is influenced by KT width and GT/MT. Notably, soft tissue augmentation at implant sites using CTGs led to a significant increase in tissue stiffness over a 12-month period, particularly in the coronal peri-implant region [178]. While further research is needed to validate this modality, it is reasonable to speculate that tissue elasticity reflects the integrated biomechanical behavior of the peri-implant phenotype, potentially correlating with soft tissue margin stability over time [178].

Table 1 summarizes the diagnostic tools and methods employed to assess primary, secondary, and exploratory outcomes in clinical studies evaluating soft tissue substitutes at teeth and implants [59].

6 | Methods

The present manuscript is structured as a narrative review on the use of soft tissue graft substitutes for the treatment of soft tissue deformities and deficiencies at both tooth and implant sites. The literature search and data extraction were based on previous systematic reviews [2, 4, 13, 23, 26, 27, 44, 54, 59, 82, 98, 180–184] and an updated manual search. When interpreting the raw data and the weighted averages for each treatment modality, readers should keep in mind that the aim of this manuscript was to provide a qualitative synthesis of the available evidence on soft tissue graft substitute–based augmentation procedures. The weighted averages are reported to support the general effectiveness of the various interventions, but no statistical comparisons or meta-analyses were performed. Therefore, the interpretation of these weighted averages, as well as any qualitative comparison across treatment modalities, should be approached with caution.

For root coverage procedures, given the large number of available studies, we included only randomized clinical trials (RCTs) reporting outcomes of soft tissue graft substitutes for the treatment of RT1 gingival recessions (Tables S1–S5). For keratinized tissue augmentation and other applications of soft tissue graft substitutes in natural dentition, both RCTs and non-RCTs were considered. Similarly, both RCTs and non-RCTs reporting outcomes of soft tissue graft substitutes at implant sites for PSTD treatment, and for the augmentation of KM, MT, and STH, as well as papilla augmentation and other indications, were taken into account (Tables S6–S8).

7 | Clinical Indications for Soft Tissue Grafting Around Natural Teeth

Soft tissue grafting procedures around natural teeth are primarily indicated for the treatment of GRs that result in esthetic concerns and/or dentinal hypersensitivity [5, 14, 15]. The correction of a thin periodontal phenotype, in particular the absence of keratinized and attached gingiva, is also considered a possible indication for soft tissue grafting in specific clinical scenarios [5, 7, 12, 185]. Another potential indication includes patients undergoing orthodontic treatment, particularly when buccal tooth movement is planned. In these cases, if a tooth presents with a pre-existing buccal bone dehiscence, a thin soft tissue phenotype, and/or gingival recession, soft tissue grafting may be considered to reduce the risk of further recession. However, current scientific evidence does not yet support strong, evidence-based recommendations for this preventive indication. Further indications include the treatment of specific carious or non-carious cervical lesions, where a combined restorative and mucogingival approach may be beneficial [5, 186–188] (Figure 1).

7.1 | Soft-Tissue Substitutes in Root Coverage Procedures

hADM has been the first graft substitute that has been introduced and utilized for the treatment of mucogingival deformities around teeth [110, 112, 113, 189] (Figures 5 and 6). Therefore, it is not surprising that there is a large body of

TABLE 1 | Outcome measures and their respective tools for the assessment of the performance of autogenous grafts and substitutes when employed for soft tissue augmentation at teeth and implant sites.

Outcomes	Teeth	Dental implants	Tools
Clinical outcomes	mRC, CRC, Rec depth, Recession width, PD, BOP, SUP, KT width, AG width, AG (yes/no)	mean PSTD coverage, complete PSTD coverage, PSTD depth, MREC depth, PD, BOP, SUP, KM width, AM width, AM (yes/no)	Periodontal probe
Phenotype-related outcomes	KT width	KM width	Periodontal probe
	GT	MT	Transmucosal probing, CBCT, Superimposition of CBCT and 3D digital impression, or HFUS
	BBT	BBT	CBCT or HFUS
	BBD*	BBD[a]	CBCT or HFUS
		STH	Superimposition of CBCT and 3D digital impression, or HFUS
Volumetric outcomes	Profilometric and Volumetric changes (linear measures, ΔD, and Vol)	Profilometric and Volumetric changes (linear measures, ΔD, and Vol)	Superimposition of digital impressions
Professional Esthetic outcomes	RES, SES	PES, PES\WES, ICAI, IAS, IDES, etc.	Direct or photographic assessment
PROMs	EST, post-operative morbidity, SAT, OHIP-14, DH, discomfort during brushing/probing	EST, post-operative morbidity, SAT, OHIP-14, discomfort during brushing/probing	Surveys and questionnaires
Additional outcomes	Tissue perfusion	Tissue perfusion	Doppler HFUS or Laser Speckle Doppler
	Tissue elasticity	Tissue elasticity	HFUS
	Expression of certain biomarkers and their changes over time	Expression of certain biomarkers and their changes over time	Wound healing Biomarkers

Note: ΔD, volumetric changes, assessed as a distance between the two surfaces, calculated in mm.
Abbreviations: AG, attached gingiva; AM, adherent mucosa; BBD, buccal bone dehiscence/distance; BBT, buccal bone thickness; BOP, bleeding on probing; CBCT, cone beam computed tomography; CRC, complete root coverage; DH, dental hypersensitivity; EST, esthetic evaluation; GT, gingival thickness; HFUS, high frequency ultrasonography; IAS, implant esthetic index; ICAI, implant crown esthetic index; IDES, implant soft tissue dehiscence coverage esthetic score; KM, keratinized mucosa; KT, keratinized tissue; mRC, mean root coverage; MREC, mucosal recession; MT, mucosal thickness; OHIP-14, oral health impact profile-14; PD, probing depth; PES, pink esthetic score; PES/WES, combined pink and white esthetic score; PSTD, peri-implant soft tissue dehiscence/deficiency; Rec depth, recession depth; RES, root coverage esthetic score; SAT, satisfaction; SES, subjective esthetic score; STH, supracrestal tissue height; SUP, suppuration; Vol, volumetric changes, assessed in mm^3.
[a]BBD was listed as a phenotype-related outcome for simplifying the process of categorization of the different outcome measures, although readers should bear in mind that the original definition of periodontal and peri-implant phenotype do not include BBD.

evidence describing the root coverage outcomes of hADM (Table S1). Similarly, CMX has been utilized for more than a decade for soft tissue augmentation, with several single-center and multi-center clinical trials depicting its performance for the treatment of isolated and multiple gingival recessions (Figure 7, and Table S2). On the other hand, pADM and VCMX are more recent biomaterials, and at the present moment, there have been fewer clinical trials assessing their root coverage outcomes compared to hADM and CMX (Figure 8, and Tables S1–S4).

In this chapter, outcomes are grouped into four domains: (1) root-coverage efficacy, (2) soft-tissue augmentation parameters, (3) patient-reported outcomes, and (4) long-term outcomes.

Table 2 depicts in detail the weighted means and ranges for mRC, CRC, KT gain, and GT gain using graft substitutes, autogenous CTG, and flap alone for the treatment of RT1 gingival recessions. Overall, the estimated mean Root Coverage (mRC) in the first year using pADM, CMX, hADM, and VCMX was 69.0%, 71.5%, 75.1%, and 77.2%, respectively. The mRC following flap alone (without adding a soft tissue graft) was 67.6%. When autogenous CTG was harvested from the deep palate (subepithelial connective tissue graft [SCTG]), the mRC was 83.2%, while the respective value for CTG obtained as an epithelialized

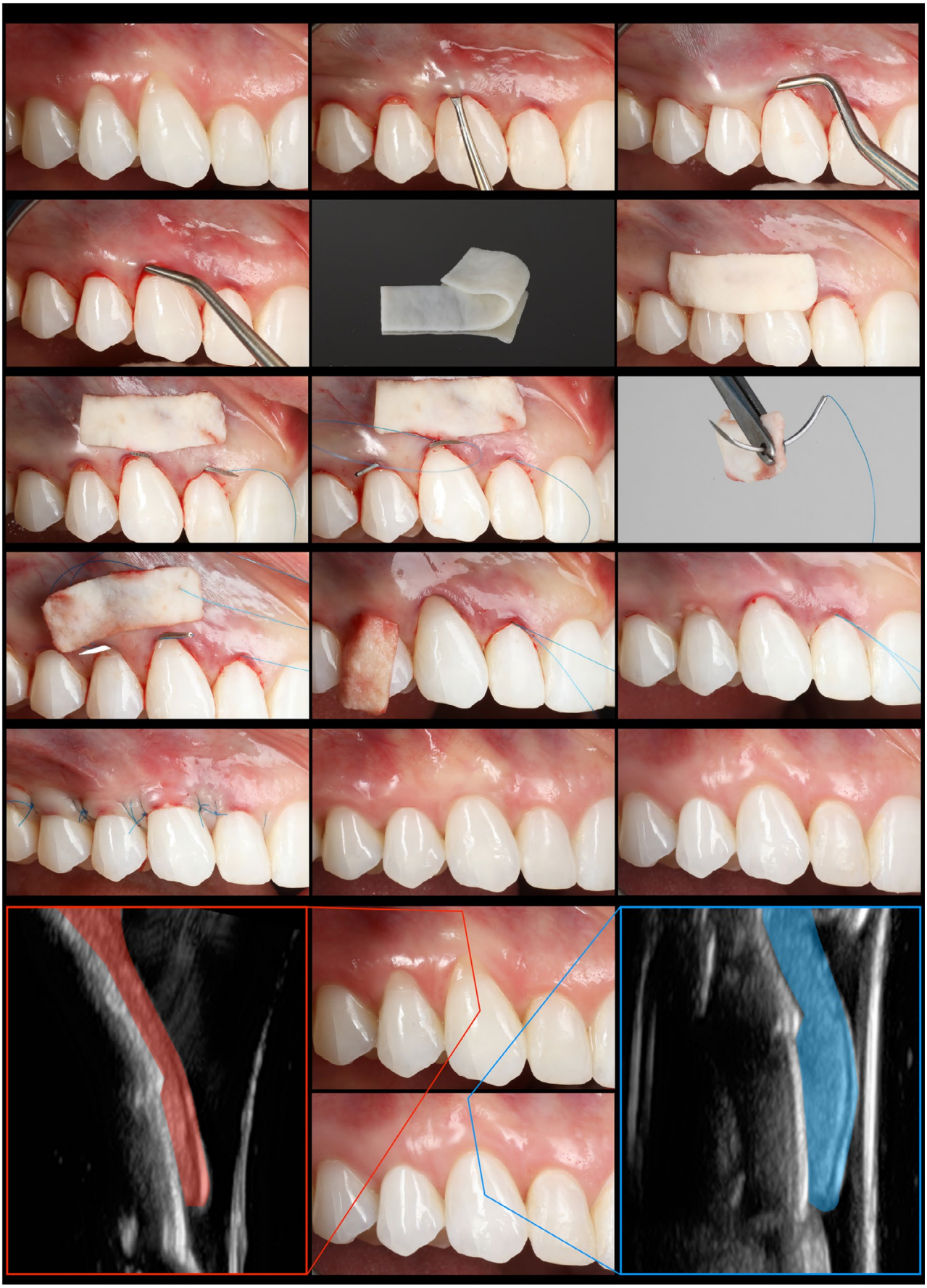

FIGURE 5 | Legend on next page.

FIGURE 5 | Tunnel technique in combination with a human-derived acellular dermal matrix (hADM, AlloDerm Select, BioHorizons, Birmingham, United States) for the treatment of multiple recessions in the right maxilla. The healing at 1 year and 3 years are reported. The ultrasound scans display in red the soft tissue of the canine prior to the root coverage procedure, and in blue the same anatomical region at the 3 year-follow-up.

gingival graft and then de-epithelialized (dCTG) was 91.6% (Table 2).

The frequency of complete root coverage (CRC) with pADM, CMX, hADM, and VCMX ranged from 48.4% to 53.2%, while the CRC for SCTG and dCTG was 61.9% and 77.4%, respectively (Table 2).

When assessing the study outcomes of the individual RCTs comparing head-to-head soft tissue graft substitutes with flap alone, hADM was often associated with a statistically significantly greater mRC and CRC than flap alone, while heterogeneous findings were reported when comparing CMX with flap alone (Table S4). When evaluating the findings of RCTs comparing head-to-head soft tissue graft substitutes with the "gold standard" CTG, the majority of the available RCTs ($n = 17$) reported that hADM and CTG obtained similar mRC. When interpreting these results, readers should consider that several RCTs, especially early pilot studies exploring CTG vs. hADM for the first time, did not involve a power calculation, and therefore, the lack of statistical significance for certain outcomes may be due to insufficient statistical power. When it comes to collagen matrices, 8 RCTs directly compared in a clinical setting CMX with CTG, while only one RCT has investigated and reported the outcomes of VCMX with CTG at the present moment. Some heterogeneity was observed between the studies when assessing the superiority of CTG over CMX. A multicenter RCT by McGuire et al. reported the superiority of autogenous CTG over VCMX in terms of mRC and CRC, while VCMX was associated with significantly lower post-operative pain than the autogenous graft [78]. A triple-blinded RCT by our group demonstrated that the root coverage outcomes of VCMX can be enhanced by saturating the matrix with rhPDGF. Teeth with multiple adjacent gingival recessions allocated to VCMX + rhPDGF exhibited indeed greater mRC and CRC than sites treated with VCMX alone after 6 months (on average mRC of 88.25% vs. 77.72% and CRC of 59.57 vs. 20.45 for VCMX + rhPDGF and VCMX alone, respectively) [96]. Saturating the graft substitute with the growth factor also promoted a significantly higher GT gain and volumetric gain compared to the graft without rhPDGF [96]. It can be therefore speculated that the addition of rhPDGF to VCMX may promote a faster revascularization of the matrix and resolution of the inflammatory phase, together with accelerated migration and proliferation of fibroblasts within the graft, all leading to reduced soft tissue shrinkage and enhanced clinical outcomes (Figure 8) [96]. In line with this assumption, in a recent publication from the same cohort, it was shown how VCMX loaded with rhPDGF results in significantly higher tissue perfusion outcomes within the graft and the flap at 2 weeks, together with greater expression of angiogenic wound healing biomarkers, compared to VCMX alone [175]. Therefore, it can be hypothesized that root coverage outcomes of soft tissue graft substitutes may become closer to the ones observed with autogenous CTG when biologic agents are also utilized. Nevertheless, further studies with longer follow-ups and multiple treatment arms are needed to verify this hypothesis.

When it comes to gingival phenotype modification-related outcomes, flap alone obtained a mean weighted KT gain of 0.32 mm, while graft substitutes exhibited a KT gain ranging from 0.44 to 0.93 mm, which was substantially less compared to the KT gain obtained with autogenous CTGs (Table 2). In terms of GT gain, CMX displayed an improvement of 0.39 mm in the first year, while pADM, VCMX, and hADM showed a weighted GT gain of 0.52, 0.52 ± 0.20, and 0.62 mm, respectively. The GT gain with flap alone, SCTG, and dCTG was 0.05, 0.74, and 0.88 mm, respectively (Table 2). These outcomes were not substantially affected by the flap design (coronally advanced flap [CAF] or tunnel technique [TUN]). All available RCTs reported greater GT gain when graft substitutes were used compared with flap-alone procedures, whereas heterogeneous outcomes were observed when comparing GT gain between graft substitutes and CTG (Table S4).

Most RCTs concluded that CMX and pADM significantly reduced post-operative morbidity compared to CTG, whereas post-operative pain following root coverage procedures with graft substitutes or flap-alone approaches was reported to be overall similar (Table S4). Additional outcomes from the RCTs directly comparing graft substitutes with CTG or with flap-alone procedures are presented in Table S4.

Limited evidence is available when assessing the long-term outcomes of root coverage procedures with soft tissue substitutes. In a 9-year follow-up of a split-mouth clinical trial, Molnar et al. reported a reduction of mRC of approximately 50% for both TUN + CMX and TUN + CTG from 1 to 9 years, with mandibular sites showing more relapse over 9 years than maxillary teeth [190]. On the other hand, McGuire et al. observed a mean mRC reduction of approximately 12% from 6 months to 5 years at teeth treated with CAF + CMX, while the respective value for sites allocated to CAF + CTG was 2% [185]. No differences were observed for the other clinical, esthetic, and patient-reported outcomes [185]. Other studies assessed the long-term outcomes of hADM for the treatment of isolated and multiple gingival recessions [24, 191–193]. Tavelli et al. concluded that CAF + hADM and TUN + hADM resulted in comparable root coverage outcomes both at 6 months and also at 12 years [24]. The mean mRC reduction from 6 months to 12 years was 22.8% for CAF + hADM and 25.7% for TUN + hADM. The regression analysis revealed that KT ≥ 2 mm at baseline and GT ≥ 1.2 mm at 6 months were predictors for the stability of the gingival margin from 6 months to 12 years [24]. This finding may explain the heterogeneous results reported in the literature when it comes to the long-term outcomes of root coverage procedures with soft tissue graft substitutes. It is likely that the long-term stability of the gingival margin largely depends on the initial KT width and on the ability of the soft tissue graft substitute to increase GT

FIGURE 6 | Tunneled Coronally Advanced Flap (TCAF) with human-derived acellular dermal matrix (hADM, AlloDerm Select, BioHorizons, Birmingham, United States) for the treatment of multiple gingival recessions in the anterior maxilla. This approach combines the principles of coronally advanced flap (CAF) and tunnel technique (TUN). Healing at 2 weeks, 1 year, and 3 years.

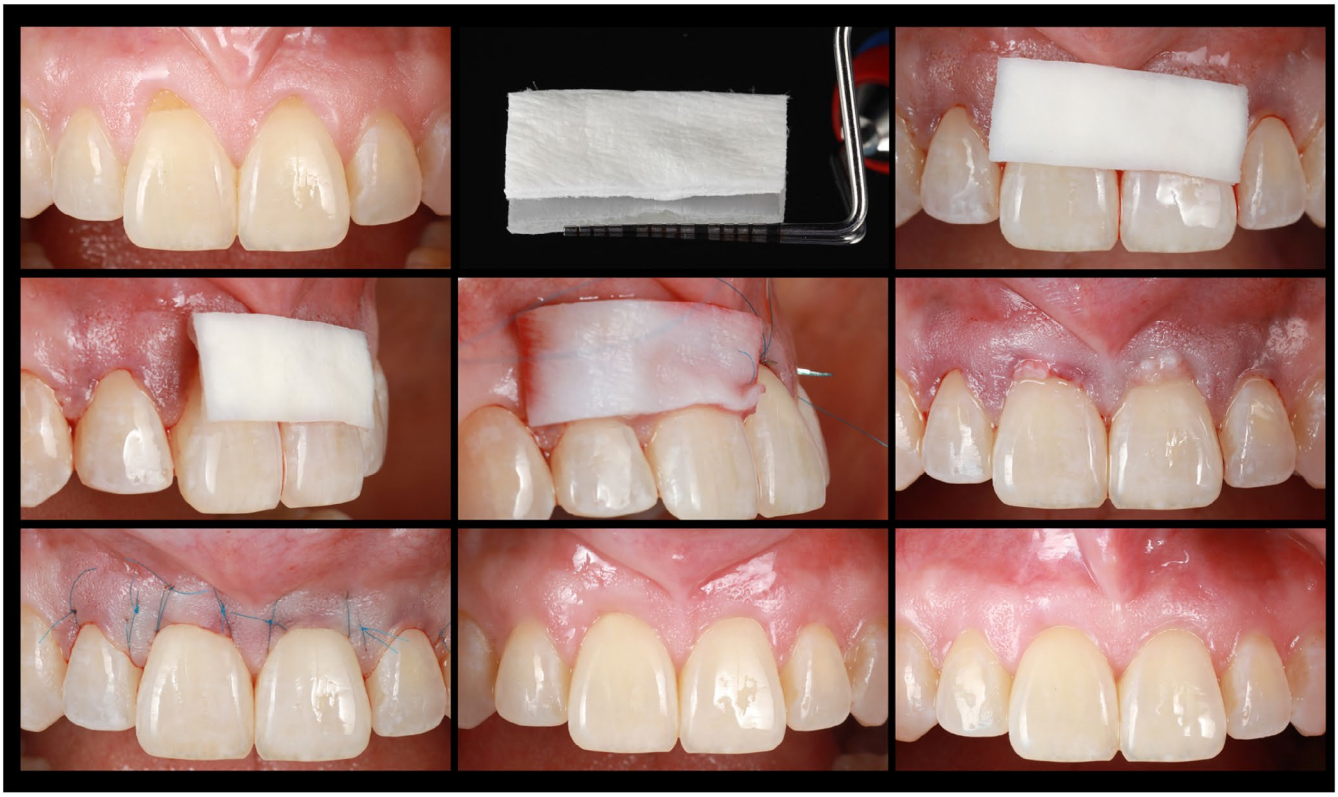

FIGURE 7 | Tunnel technique with a bilayered collagen matrix (CMX, Geistlich Mucograft, Geistlich Pharma, Wolhusen, Switzerland) for the treatment of two maxillary central incisors showing shallow gingival recessions. Results at 6 months and 3 years.

[1, 24, 26, 191, 192]. Other factors that can also contribute to the long-term stability of the gingival margin include a stringent maintenance protocol and patient toothbrushing habits [193, 194]. Barootchi et al. observed a relatively small relapse of the gingival margin (mean mRC reduction 14.9%) at single sites treated with hADM from 1 to 9 years [192]. Interestingly, non-treated adjacent sites showed an increase in recession depth over 9 years, which was significantly greater at teeth exhibiting a pre-existing recession at baseline [192].

7.1.1 | Clinical Takeaway

In summary, soft tissue graft substitutes used in combination with bilaminar techniques can achieve substantial coverage of both single and multiple gingival recessions, often yielding clinical outcomes superior to those obtained with flap procedures alone (Figures 5–9). However, autogenous CTGs remain the gold standard, consistently associated with the highest mRC. Similarly, while soft tissue graft substitutes lead to a notable increase in GT compared to flap-only approaches, the GT gain is generally inferior to that achieved with CTG. A gain in KT may also occur at sites treated with soft tissue substitutes, although the variability observed across studies suggests that these outcomes should be interpreted with caution. Long-term results of root coverage procedures involving graft substitutes may demonstrate some degree of relapse, likely influenced by the baseline gingival phenotype, patients' toothbrushing habits, and adherence to supportive maintenance care. Based on current literature, clinicians are encouraged to individualize root coverage strategies according to patient-specific anatomical and behavioral factors (Figure 9).

Beyond defect coverage itself, many patients with gingival recessions also present with an inadequate band of keratinized tissue, which justifies considering KT augmentation as a distinct, yet closely related, therapeutic objective.

7.2 | Soft-Tissue Substitutes for Keratinized Tissue Augmentation

As previously discussed, a certain degree of KT gain may be expected when using soft tissue graft substitutes in conjunction with bilaminar techniques to treat gingival recessions, with reported mean gains ranging from 0.44 to 0.93 mm. However, the wide standard deviations observed, along with clinical experience, warrant cautious interpretation of these outcomes. This is because bilaminar approaches using soft tissue graft substitutes are primarily designed to enhance soft tissue thickness and achieve defect coverage, rather than to increase the KT width itself [3, 14, 26]. Apically positioned flap (APF)-based techniques are indeed considered the approaches of choice when the primary goal is to increase KT [26, 195]. Limited evidence assessing the outcomes of soft tissue graft substitutes in combination with APF to gain KT around teeth is, however, currently available [26]. In this chapter, KT-augmentation outcomes are grouped into three domains: (1) dermal matrices, (2) collagen matrices, and (3) tissue-engineering approaches.

FIGURE 8 | Treatment of multiple gingival recessions in the lower anterior using coronally advanced flap with a volume-stable collagen matrix (VCMX, Geistlich Fibro-Gide, Geistlich Pharma, Wolhusen, Switzerland) loaded with recombinant human platelet-derived growth factor-BB (rhPDGF, GEM21S, Geistlich Pharma North America, Princeton, United States). Results at 6 months and 3 years. Reproduced with permission from John Wiley & Sons [97].

7.2.1 | Dermal Matrices

Although hADM was initially introduced as an alternative to FGG for increasing KT in combination with APF [110, 112, 113], only a limited number of studies have evaluated its performance for this indication [109, 110, 112–114, 196, 197]. Early clinical observations by Wei et al. showed erythematous areas 2 weeks after APF + hADM, with epithelialization completed after 1 month [113]. Keratinization generally appeared only after 6–8 weeks, indicating a healing process approximately 2 weeks slower than with APF + FGG, with maturation and stabilization typically occurring by 3 months. At 6 months, APF + hADM yielded an average KT gain of 3.25 mm, whereas APF + FGG achieved about 6.15 mm. Shrinkage was also substantially higher with hADM than with the autogenous graft (approximately 71% versus 16%) [113]. Histologic biopsies at 6 months revealed that tissues treated with APF + hADM resembled scar tissue with a composition similar to the graft material, and the degree of keratinization varied from patient to patient and even within sites of the same individual [110]. The authors therefore concluded that APF + hADM do not predictably generate true gingiva or reliably increase KT and attached mucosa [110].

Additional studies confirmed the superior clinical performance of FGG over hADM [114, 196]. de Resende et al. reported that

TABLE 2 | Expected root coverage outcomes following soft tissue graft substitutes and autogenous connective tissue graft when combined with bilaminar surgical techniques for the treatment of gingival recession type 1 (RT1) defects.

Intervention	mRC (mean ± SD), (min–max) (mm)	CRC (mean ± SD), (min–max) (%)	KT gain (mean ± SD), (min–max) (mm)	GT gain (mean ± SD), (min–max) (mm)
hADM	75.1 ± 16.0 (32.1–98.8)	53.2 ± 22.8 (0–94.2)	0.93 ± 0.72 (−0.53–3.00)	0.62 ± 0.24 (0.22–1.46)
pADM	69.0 ± 20.6 (29.5–92.8)	49.6 ± 22.4 (14.3–78.0)	0.74 ± 0.71 (0.05–0.98)	0.52 ± 0.33 (0.28–1.09)
CMX	71.5 ± 15.6 (57.7–92.6)	52.6 ± 24.8 (22.70–72.00)	0.75 ± 1.12 (−0.60–1.92)	0.39 ± 0.31 (0.05–1.00)
VCMX	77.2 ± 11.2 (63.2–88.3)	48.4 ± 18.4 (20.5–65.6)	0.44 ± 0.29 (0.09–0.80)	0.52 ± 0.20 (0.12–0.80)
Flap alone	67.6 ± 18.6 (31.8–98.0)	52.7 ± 23.0 (7.70–93.2)	0.32 ± 0.62 (−1.90–1.42)	0.05 ± 0.19 (−0.8–0.34)
SCTG	83.2 ± 12.6 (35.0–99.4)	61.9 ± 20.5 (13.3–96.6)	1.29 ± 0.83 (−1.00–4.8)	0.74 ± 0.35 (0.06–1.52)
dCTG	91.6 ± 5.4 (75.7–97.8)	77.4 ± 13.8 (38.0–93.0)	1.88 ± 0.96 (0.37–4.7)	0.88 ± 0.56 (0.5–2.64)

Abbreviations: CMX, bilayered collagen matrix; CRC, frequency of complete root coverage; dCTG, connective tissue graft obtained from the de-epithelialization of an epithelialized soft tissue graft; GT, gingival thickness; hADM, human-derived acellular dermal matrix; KT, keratinized tissue width; mRC, mean root coverage; pADM, porcine-derived acellular dermal matrix; SCTG, sub-epithelial connective tissue graft; SD, standard deviation; VCMX, volume-stable collagen matrix.

FIGURE 9 | Multiple gingival recessions in the left upper maxilla treated with a tunnel technique and a combination of autogenous connective tissue graft (CTG) and human-derived acellular dermal matrix (hADM, AlloDerm Select, BioHorizons, Birmingham, United States). The CTG was positioned on the left central incisor only; that was the patient's main concern. In order to reduce post-operative morbidity, the other sites were augmented with the graft substitute. Healing at 2 weeks and 6 months.

APF + hADM resulted in significantly lower KT and GT gains at 6 months than APF + FGG (mean KT gain 1.42 vs. 3.59 mm; mean GT gain 0.57 vs. 1.19 mm) [114]. Sites grafted with hADM also demonstrated a slight increase in recession depth at follow-up. Histologic findings showed delayed maturation with the allograft compared with the autogenous graft [114]. A 15-year follow-up of this same cohort confirmed these early trends, with APF + hADM showing mean KT gains of 1.39 mm compared with 4.47 mm for APF + FGG, and hADM-treated sites displaying increased recession, unlike FGG sites that benefited from creeping attachment [197].

It should also be noted that when hADM is used with APF and heals by secondary intention, patients commonly report aesthetic concerns, delayed healing, and odor during the early weeks [198–200]. While the healing characteristics of hADM can vary depending on processing and biomechanical properties, current recommendations favor its use primarily in bilaminar techniques to achieve primary-intention healing and avoid these limitations.

7.2.2 | Collagen Matrices

CMX has been explored not only for root coverage procedures but also in combination with APF for increasing/recreating KT and attached gingiva [132, 134, 198, 201, 202]. Sanz et al. reported how APF + CMX provided an average KT gain of 2.5 mm, while also being able to significantly reduce post-operative pain and medication intake compared to FGG [134]. A similar KT gain was also reported by Nevins et al. following APF + CMX (mean KT gain 2.3 mm). The authors also histologically assessed the augmented area after 13 weeks and observed that the biopsy specimens obtained from sites augmented with CMX and FGG were similar, with mature connective tissue covered by well-formed keratinized epithelium; no inflammatory cells were present [134]. Other studies obtained a similar amount of KT gain following APF + CMX, while they also showed how FGG results in a greater KT gain than CMX [201, 202]. In particular, in a long-term follow-up of a split-mouth RCT, McGuire et al. observed that the clinical outcomes obtained with APF + CMX and APF + FGG at 6 months were stable up to 8 years, with no differences between the two groups in terms of changes in the parameters of interest, leading the authors to conclude that CMX was not inferior to FGG to prevent further recession over time [198]. While the autogenous graft resulted in greater KT both at the short- and long-term visits, sites augmented with CMX showed significantly better tissue texture and color match with the adjacent native tissue, with 78% of the subjects that continued to prefer the appearance of the sites grafted with CMX compared to the ones treated with FGG [198].

7.2.3 | Tissue-Engineering Approaches

Several authors have also explored tissue engineering strategies to recreate KT around teeth in a minimally invasive manner [21, 183, 194, 195, 203, 204]. These approaches involved the use of living cells, either autologous or allogeneic, seeded on biocompatible and resorbable scaffolds ("living cellular constructs" [LCC] or tissue engineered constructs, Figure 10) [21, 183, 205]. Tissue-engineering strategies and their outcomes for KT augmentation have been reported in detail in the Table S5.

7.2.4 | Clinical Takeaway

In summary, soft tissue graft substitutes in combination with APF can increase KT width and attached gingiva width around teeth to a certain extent, even though APF + FGG remains the gold standard in terms of overall KT width gain. When FGG is not an option, CMX should be preferred over hADM due to its overall more favorable healing and behavior when left exposed. The expected KT width gain with APF + CMX may be further enhanced by adding a strip of autogenous epithelialized soft tissue graft ("strip gingival graft [SGG] technique"), as it has been more commonly performed around dental implants [206–210] (chapter/paragraph 7.2). Future tissue engineering approaches involving living cellular constructs may provide additional solutions for regenerating an adequate amount of KT in a minimally invasive manner.

While these KT-focused strategies primarily address the marginal tissue environment, soft tissue graft substitutes have also been applied in broader and more complex indications, such as combined restorative–periodontal defects and papilla reconstruction, which are discussed in the following section.

7.3 | Additional Applications of Soft Tissue Graft Substitutes Around Teeth

Soft tissue graft substitutes have been applied to clinical situations beyond traditional recession coverage, including the management of NCCLs associated with recessions [186, 211]. Mathias-Santamaria reported that combining partial restoration of NCCLs with CAF + CMX provided superior KT and GT gains compared with CAF alone, suggesting a potential role for soft tissue substitutes in the combined management of these defects [186].

Future applications may involve soft tissue phenotype modification during periodontal regenerative therapy and papilla reconstruction. In cases with an adequate band of KT, it has been proposed that soft tissue substitutes could serve as alternatives to autogenous grafts in approaches such as the soft-tissue wall technique for infrabony defects lacking buccal bone [20, 212]. In this context, these materials may contribute both to defect stabilization and to enhancement of the buccal soft tissue phenotype. Preclinical studies have shown that VCMX can support periodontal regeneration when used as a defect-filling scaffold in intrabony defects, encouraging future clinical evaluations of its adjunctive role in regenerative therapy [150, 157].

Soft tissue graft substitutes have also been used for papilla augmentation [213, 214]. Geurs et al. described a technique using micronized hADM injected beneath a surgically mobilized papilla through a vertical mucosal incision, achieving reductions in recession depth and improvements in papilla indices after 5 months [213]. More recently, a clinical trial comparing VCMX with SCTG for papilla reconstruction demonstrated comparable gains in papillary height and reductions in the contact

FIGURE 10 | Split-mouth non-root coverage soft tissue augmentation aiming at recreating adequate keratinized tissue and attached gingiva on lower premolars using a living cellular construct (LCC) and a free gingival graft (FGG). The photos at baseline (BL), the day of the surgery (Sx), 1 month (1 M), 6 months (6 M), and 13 years (13Y) are reported. Lugol's iodine solution was applied at baseline, 6 months, and 13 years to better identify the mucogingival junction for improving the accuracy of keratinized tissue width measurement. Reproduced with permission from John Wiley & Sons [196].

point–papilla distance at 6 months, with VCMX associated with significantly lower postoperative morbidity [214]. Despite these encouraging findings, papilla augmentation remains a highly technique-sensitive procedure with most successful reports based on CTG [3, 20, 215–218]. Therefore, replacing autogenous grafts with soft tissue substitutes for this indication requires advanced surgical experience, careful case selection, and cautious interpretation of the still limited evidence.

In summary, additional applications of soft tissue graft substitutes around teeth include the treatment of NCCLs associated with recessions, papilla augmentation, and phenotype modification during regenerative procedures. However, the current evidence base remains limited, supporting prudent use and further clinical investigation in these areas.

Taken together with the evidence on root coverage and KT augmentation, these adjunctive applications underline the need for a structured, phenotype-oriented framework to guide graft selection in daily practice, which is presented in the next section.

7.4 | Decision Tree for the Selection of the Soft Tissue Graft Materials in Root Coverage Procedures (Figure 11)

When selecting between autogenous grafts and soft tissue substitutes for root coverage procedures, clinical decision-making is not yet strongly supported by high-level evidence. Nevertheless, it is reasonable to consider several key factors—including the number of sites to be treated, the severity of the recession defects, and the width of the KT—to guide the choice of graft material.

In terms of recession severity, although no universally accepted cut-off exists, gingival recessions <3 mm deep may be reasonably classified as "shallow", while those ≥ 3 mm can be considered "advanced". We suggest, however, that the interpretation of these categories should ultimately rely on clinician expertise and case-specific considerations. Similarly, a midfacial KT width ≥ 2 mm may be considered "adequate", while <2 mm should be interpreted as "inadequate".

As autogenous CTG is considered the gold standard in terms of mean and complete root coverage, its use should be overall prioritized over graft substitutes at sites exhibiting advanced and challenging gingival recessions, in particular when KT width is inadequate. Soft tissue graft substitutes indeed demonstrated to promote root coverage, together with an increase in GT. Nevertheless, root coverage procedures with soft tissue graft substitutes do not seem able to induce a substantial and predictable gain in KT width, which remains a prerogative of autogenous CTG. Based on a long-term study from our group identifying GT ≥ 1.47 mm and KT width ≥ 1.5 mm at 6 months as the main predictors for the stability of the gingival margin over 10 years [1], it is reasonable to assume that soft tissue graft substitutes may be indicated when the baseline presurgical KT width is at least 1.5–2 mm. In addition, when using soft tissue graft substitutes, selecting sites with GT of at least 0.7–0.8 mm may be preferred, as the mean GT gain following non-autogenous grafts usually ranges between 0.4 and 0.8 [24, 26, 96, 191, 192].

In case of single advanced gingival recessions with an adequate KT width, the decision on the graft material may also be affected by the patient's considerations and expectations. CTG may be preferred over graft substitutes for patients prioritizing the amount of root coverage over post-operative morbidity, while graft substitutes may be preferred over the autogenous graft for patients prioritizing the minimally invasive nature of the intervention over the amount of root coverage.

For multiple adjacent gingival recessions, we recommend a site-specific evaluation of all sites based on the algorithm discussed above for single gingival recessions (Figure 11). Based on the assessment of the severity of the recession depth, KT width, and

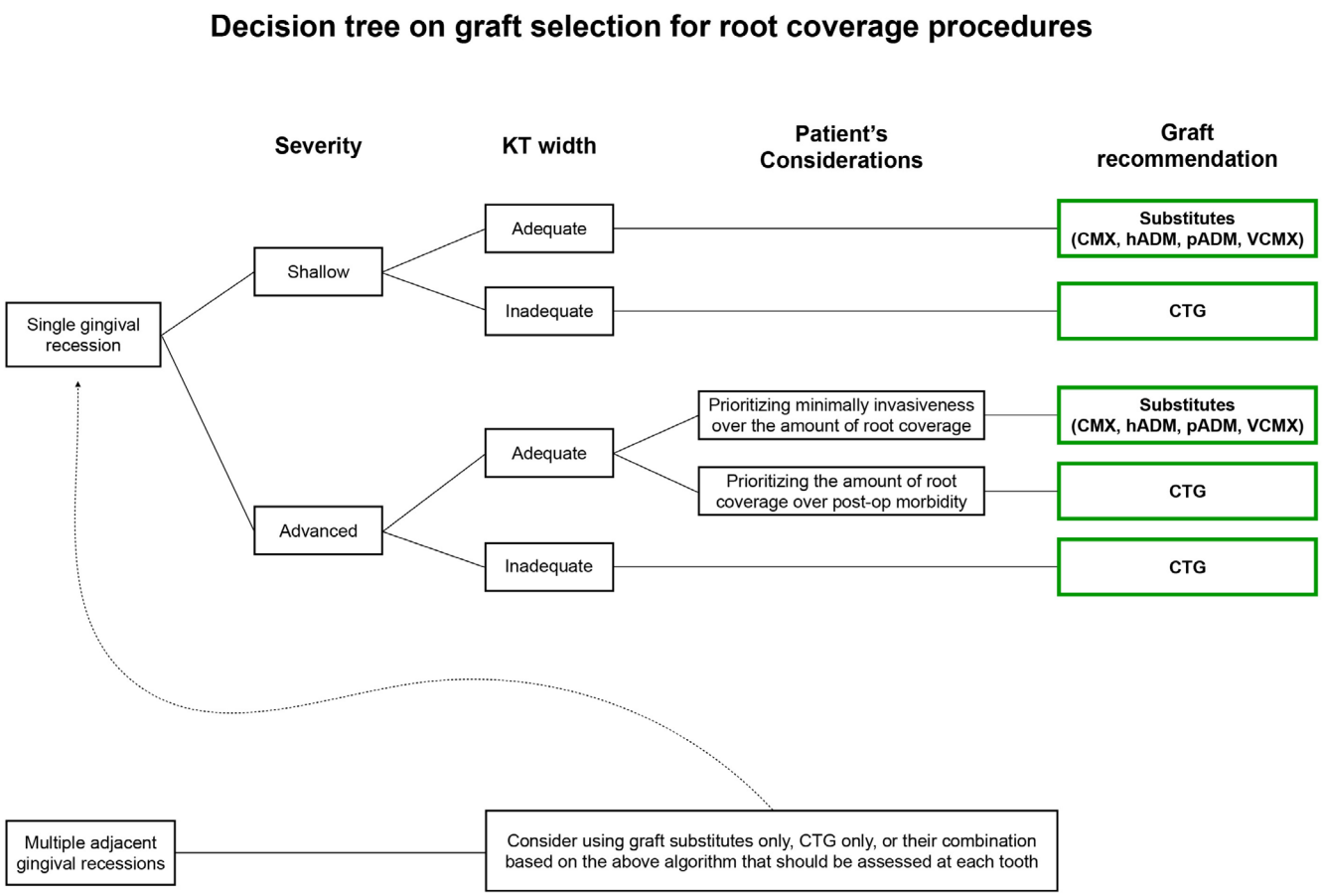

FIGURE 11 | Decision tree on graft selection for root coverage procedures. Soft tissue augmentation with a graft, whether autogenous or a substitute, is always recommended in this algorithm, as the long-term stability of the gingival margin is closely associated with adequate keratinized tissue width and gingival thickness (≥1.5 mm) [1]. Nevertheless, although uncommon, sites presenting with sufficient gingival thickness and keratinized tissue may be treated with flap surgery alone. Finally, the presence of non-carious cervical lesions, particularly when severe, should be considered an indication for the use of an autogenous connective tissue graft.

patient's considerations, it may be possible to treat multiple adjacent gingival recessions with flap alone only, graft substitutes only, CTG only, or their combination, in an attempt to limit the use and amount of CTG to reduce patient morbidity.

Patient-related factors can also affect the decision to use an autogenous graft or a substitute, including the patient's age, systemic conditions, previous experiences, preferences, and religious considerations. For certain patients, using grafts obtained from cadavers is not an option, while for other patients, animal-derived biomaterials may not be used for religious beliefs or other reasons [22, 65, 74, 204, 219]. On the other hand, previous painful experiences of palatal harvesting may prevent patients from undergoing the surgical procedure again, unless graft substitutes are utilized [22, 65]. Additional considerations that should be considered when deciding the graft material include patients' motivation and expectations, and clinicians experience with root coverage procedures. For patients with high esthetic demands, for whom every half millimeter is a crucial factor affecting their satisfaction with the treatment, autogenous CTG may be preferred for its clinical performance even if it is related to higher post-operative morbidity. For other patients who prioritize the post-operative sequelae of the surgery and its impact on the quality of life, rather than little differences in the clinical outcomes, graft substitutes may be considered instead of—or together with—CTG. The experience of the operator can also play a key role, as autogenous CTG may still be able to provide complete root coverage in the case of a minor flap sloughing due to possible mistakes during the surgery, while obtaining complete root coverage with graft substitutes usually requires flawless surgical procedures. Ultimately, the decision should also involve a conversation with the patient, explaining the pros and cons and the expected outcomes with autogenous grafts and substitutes based on the available scientific literature and clinical experience.

The proposed decision tree on graft selection for root coverage procedures should be interpreted as a "flexible" (and not strict) suggestion/algorithm aiming at maximizing clinical outcomes of root coverage procedures with a patient-centered mentality.

Just as the previous chapters addressed gingival recessions, KT deficiencies, and soft-tissue phenotype modification around natural teeth, similar but site-specific indications exist around implants. The implant analogue of a gingival recession is the PSTD, which poses comparable esthetic and biological challenges. Likewise, deficiencies in peri-implant KM and inadequate MT or STH parallel the soft-tissue considerations discussed for teeth, although their clinical management differs in important ways. For clarity and

continuity, the following section mirrors the same sequence used for teeth, beginning with the clinical indications for soft-tissue grafting at implant sites, followed by the use of graft substitutes for the treatment of PSTDs, KM augmentation, soft-tissue phenotype enhancement, and other implant-specific applications.

8 | Clinical Indications for Soft Tissue Grafting at Implant Sites

The clinical indications of soft tissue augmentation procedures at implant sites may include implants with an inadequate peri-implant soft tissue phenotype (in terms of KM width, MT, and/or STH), immediate implant placement, treatment of PSTDs, and peri-implant papillae reconstruction (Figure 12).

Having an adequate band of keratinized mucosa, which is also adherent/not movable, has been shown to positively contribute to peri-implant health, in terms of reduced plaque accumulation, soft-tissue inflammation, and dehiscence, compared to implants lacking this band of adherent KM [55, 180, 220–223], although this relationship has not been shown in all studies [224]. In addition, a recent study by Isler et al. showed that the absence of keratinized and adherent mucosa was significantly associated with peri-implantitis [38]. An adequate band of firm and adherent keratinized mucosa also positively affects patient-reported outcomes, including comfort during brushing and satisfaction with implant therapy [47, 50, 56, 225], as well as the stability of the peri-implant soft tissue margin over time [3, 34, 37]. Clinical studies have described KM augmentation procedures with autogenous grafts, CMX, or their combination.

Peri-implant MT plays a key role in the color and esthetic appearance of the peri-implant mucosa [58, 226–228], as well as on the stability of the peri-implant soft tissue margin and bone levels over time [2, 54, 229–231]. A cross-sectional study by Gharpure et al. observed that the prevalence of peri-implant mucositis, peri-implantitis, and discomfort during brushing was significantly higher in implants with thin MT compared to implants with thick MT [49]. MT augmentation at implant sites has been reported with autogenous grafts, hADM, pADM, CMX, and VXCM.

The vertical dimension of the soft tissue (supracrestal tissue height, STH) has been shown to affect the stability of crestal bone levels [181, 232–236]. There is evidence supporting the concept that more than 2 mm of STH is required to minimize physiological bone remodeling [46, 232, 233]. In a clinical trial, Linkevicius et al. demonstrated that crestal bone stability was maintained in the presence of a STH of at least 3 mm [237]. In a following study, the same group reported that naturally thick STH and STH surgically augmented using a dermal matrix were both preserving the stability of crestal bone levels [235]. STH augmentation procedures have been performed using autogenous soft tissue grafts, hADM, pADM, and VXCM.

Soft tissue augmentation procedures are also often performed at implants to maintain the stability of the soft tissue margin and volume at anterior sites, especially for post-extractive implant placement [238–241], to augment the peri-implant papillae for esthetic reasons [48, 216, 242, 243], and to correct implant esthetic complications (PSTDs) [43, 244, 245]. Surgical techniques involving autogenous CTG and graft substitutes (hADM, pADM, and VCMX) have been described for these purposes. In the following chapters, the outcomes of soft tissue augmentation at implant sites using graft substitutes are presented in three domains: (1) treatment of PSTDs, (2) KM augmentation, and (3) augmentation of MT, STH, and other applications.

8.1 | Soft-Tissue Substitutes for the Treatment of PSTDs

Only few studies have explored the use of soft tissue substitutes for the treatment of PSTDs [89, 246, 247], which is probably also due to the novelty of this topic, compared to mucogingival surgeries around teeth. In addition, it is also reasonable to assume that the complexity of the treatment related to PSTDs, which very often also requires multiple prosthetic appointments, may induce clinicians to evaluate the outcomes of soft tissue graft substitutes for other applications first, such as root coverage procedures around teeth or peri-implant mucosal thickness augmentation, rather than the correction of PSTDs. In this chapter, PSTD-related outcomes of soft tissue graft substitutes are grouped into two domains: (1) dermal matrices, and (2) collagen matrices.

8.1.1 | Dermal Matrices

A case report by Mareque-Bueno described the use of hADM with a split-thickness flap to treat a 3-mm isolated PSTD on a maxillary lateral incisor [246]. The graft was stabilized over the implant-supported crown and completely covered by an advanced flap. After 6 months, partial PSTD coverage and increased soft tissue thickness were achieved, suggesting that this approach may be suitable for isolated defects in sites with adequate preoperative KM [246]. Anderson et al. conducted a pilot study comparing CAF + CTG with CAF + hADM for isolated anterior PSTDs [89]. At 6 months, mean PSTD coverage was 28% with hADM and 40% with CTG [89], values substantially lower than the coverage generally reported for root coverage procedures around teeth using the same grafts [15, 26, 72, 73]. Several factors likely contributed to these modest results, including case selection and prosthetic limitations. Variables such as crown design, implant position and angulation, interproximal bone and soft tissue height, and the periodontal status of adjacent teeth are known to strongly influence PSTD outcomes [29, 45, 48, 216]. In addition, the study did not allow for removal or modification of the existing implant-supported crown, which may have further restricted the potential for soft tissue advancement [89]. Despite the limited PSTD coverage, hADM produced slightly greater MT gain and more complete correction of buccal concavities than CTG, possibly due to the use of deep-palatal SCTG, which may undergo shrinkage depending on its glandular and fatty content [3, 43, 99]. Patients treated with hADM also reported lower painkiller intake, although clinician- and patient-reported esthetic outcomes were similar between the two groups [89].

8.1.2 | Collagen Matrices

In a preclinical study, PSTDs were surgically created at osseointegrated implants to compare CAF alone, CAF + CMX, and

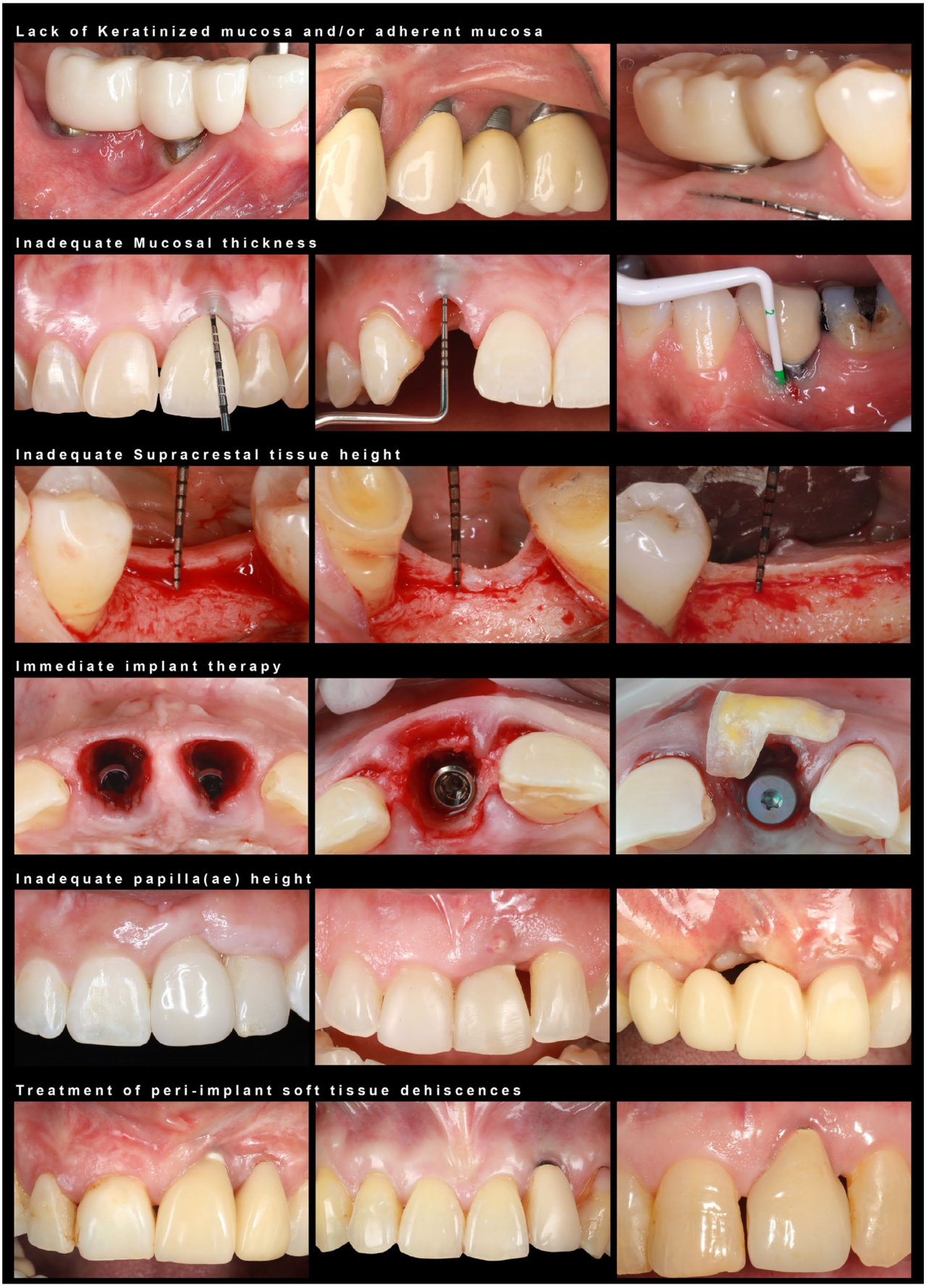

FIGURE 12 | Clinical scenarios where soft tissue augmentation at implant sites is indicated.

CAF + CTG [248]. After 3 months, all three approaches achieved similar PSTD coverage, with most sites showing complete defect coverage. CMX and CTG produced slightly greater vertical soft tissue gains than CAF alone. Histologic measurements showed comparable positions of the junctional epithelium and bone crest across the groups [248]. In a multicenter case series, Schallhorn et al. evaluated CMX for PSTDs associated with gray mucosal discoloration, buccal contour deficiency, and/or inadequate KM (< 2 mm) [249]. Mean baseline PSTD depth, KM width, and MT were modest (1.5, 1.7, and 1.5 mm). After flap elevation and complete coverage of CMX, no meaningful changes in PSTD depth were seen at 3 or 6 months, although both KM width and MT increased by approximately 0.7 mm at 6 months [249]. A recent multicenter randomized trial by Clem et al. compared VCMX with CTG for soft tissue phenotype augmentation around implants presenting "minimal recession" and thin mucosa [250]. Baseline PSTD depth was minimal (0.32 mm for VCMX and 0.24 mm for CTG). At 1 year, PSTD coverage remained limited for VCMX (approximately 9%), while CTG sites showed greater reduction (around 50%), although the between-group difference did not reach statistical significance [250]. This limited improvement likely reflects the inclusion of sites with minimal baseline recession and the study's focus on MT gain rather than PSTD coverage. Both materials substantially improved MT, with VCMX demonstrating non-inferiority to CTG (0.93 mm vs. 1.10 mm). The correction of "gray show-through" was also comparable, with nearly 90% of sites in both groups showing complete masking at 1 year. Postoperative pain was significantly lower with VCMX [250].

Our group has conducted a randomized clinical trial aimed at evaluating the clinical, esthetic, and patient-reported outcomes of a combined prosthetic-surgical approach using either autogenous CTG or VCMX + rhPDGF for the treatment of isolated anterior PSTDs [251]. Preliminary results appear to support the efficacy of VCMX + rhPDGF in achieving coverage of PSTDs, increasing MT, enhancing soft tissue contours, and improving patient-reported esthetics and satisfaction (Figure 13). Although it may be premature to directly compare the outcomes of VCMX + rhPDGF versus CTG at this stage [251], it is essential to emphasize the importance of identifying and addressing the underlying factors contributing to PSTDs. Equally critical is the multidisciplinary nature of the treatment protocol. This includes a presurgical prosthetic phase—often involving the modification of an existing crown or placement of a new provisional restoration—followed by surgical intervention and meticulous postsurgical prosthetic soft tissue conditioning. Each step plays a pivotal role in determining the final clinical and esthetic outcomes [245, 252, 253]. It is believed that such a structured and collaborative workflow can significantly improve the predictability and overall outcomes of soft tissue grafting for the correction of PSTDs, regardless of the type of graft used (Figure 14).

8.1.3 | Clinical Takeaway

In summary, the current evidence on the use of soft tissue graft substitutes for the management of PSTDs remains limited, preventing the formulation of definitive clinical recommendations at this stage. Well-designed clinical studies evaluating both short- and long-term outcomes of PSTD treatment with these materials are warranted to better inform future practice.

Given the close relationship between PSTDs and the underlying peri-implant phenotype, we next review the role of graft substitutes for KM augmentation.

8.2 | Soft-Tissue Substitutes for Keratinized Mucosa Augmentation

Most clinical investigations assessing soft-tissue substitutes for KM augmentation have focused on the combination of an APF with a CMX [134, 254–264] (Table 3; Table S6). This predominance is expected given the favorable handling properties of CMX and its capacity to heal uneventfully even when intentionally left exposed, an advantage not shared by many other soft-tissue substitutes.

Using evidence from randomized and prospective clinical studies identified through an updated search based on previous systematic reviews [2, 54, 182, 183], it becomes apparent that adding CMX to an APF consistently enhances KM width compared with APF alone. This effect is biologically plausible, as the matrix provides a scaffold supporting fibroblast, vascular, and epithelial repopulation from surrounding tissues [134, 257].

When APF + CMX is compared with autogenous techniques, the overall pattern suggests that FGG tends to yield the greatest KM augmentation, whereas SCTG produces more moderate increases (Table 3). However, five RCTs directly comparing APF + CMX with APF + FGG demonstrate mixed findings: some report superior KM gain with FGG [255, 261, 264], while others find no significant differences [258, 263] (Table S6). Despite these variations, the magnitude of KM width achieved with APF + CMX in the first postoperative year generally aligns with what is considered clinically adequate at implant sites [27, 51] (Table 3).

The variability observed across studies, that is reflected in a wide range of KM outcomes, likely stems from differences in surgical execution and site-specific factors, such as flap advancement, the residual KM incorporated into the APF, graft dimensions, buccal implant angulation, and implant exposure following flap elevation.

An important refinement of the APF + CMX approach is the strip gingival graft (SGG) technique [208–210]. The SGG is sutured on the apical portion of the periosteal bed, just above the APF. A CMX is then applied and stabilized on the periosteal bed coronal to the SGG. The SGG serves as a mechanical barrier that maintains the mucogingival junction at the desired apical position, while it also promotes the migration of living cells into the CMX, contributing to the recreation of a large band of KM, using a relatively small autogenous graft [208–210]. The goal of this technique is repositioning the mucogingival line and augmenting KM width in a minimally invasive manner [208–210] (Figure 15). The very limited height of the SGG can significantly reduce patient's morbidity compared to conventional FGG [254], in line with previous studies demonstrating that increasing graft height (apico-coronal dimension of the graft) is associated with

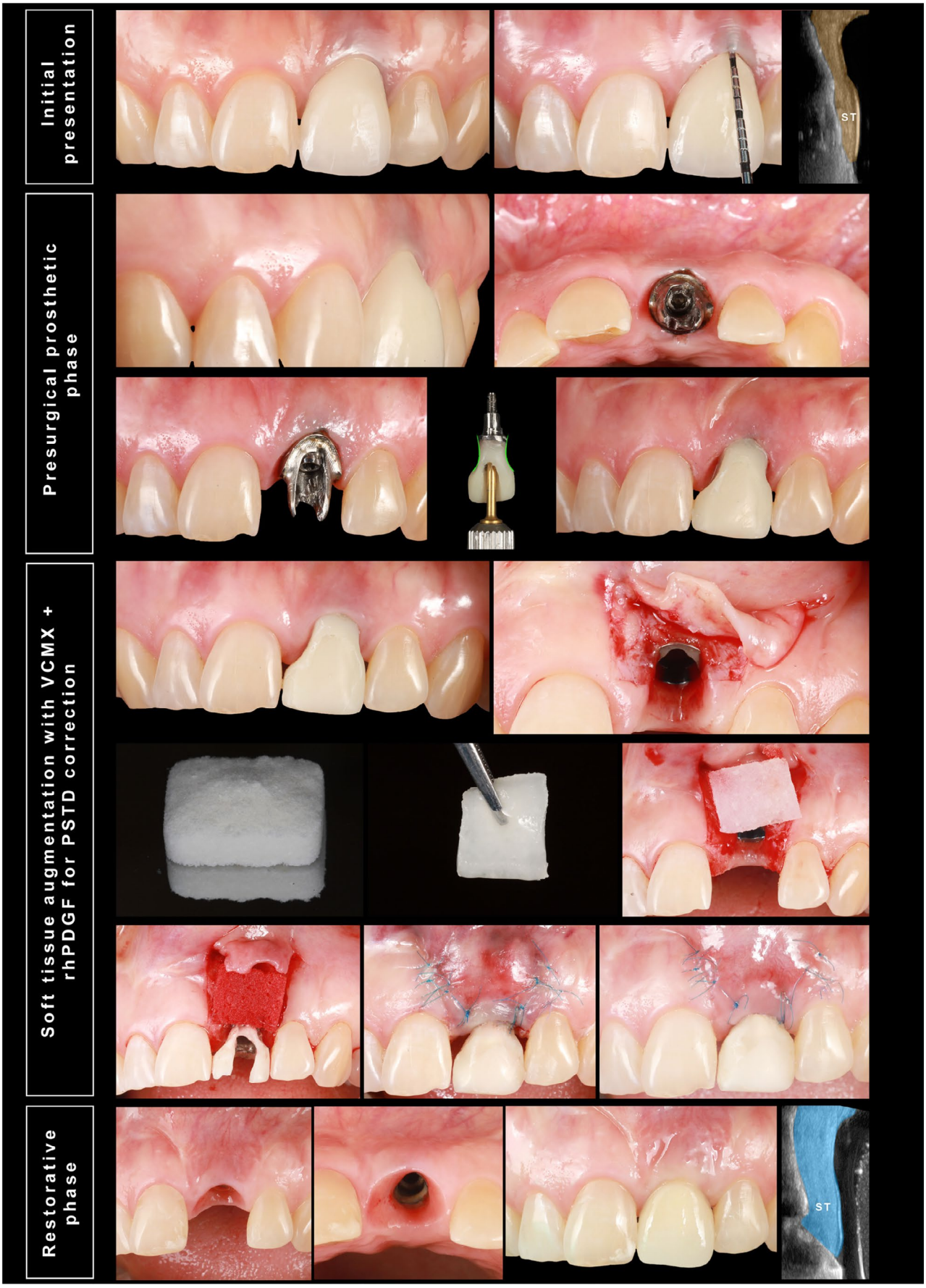

FIGURE 13 | Legend on next page.

FIGURE 13 | Treatment of an anterior peri-implant soft tissue dehiscence (PSTD) using a volume-stable collagen matrix (VCMX, Geistlich Fibro-Gide, Geistlich Pharma, Wolhusen, Switzerland) saturated with recombinant human platelet-derived growth factor-BB (rhPDGF-BB, GEM21S, Geistlich Pharma North America, Princeton, United States) involving the combined prosthetic-surgical approach. Outcomes at 1 year. The ultrasound scans at baseline and at the 1-year follow-up highlight (in orange at baseline, and in blue at 1 year) the buccal soft tissue component of the implant (ST) and the substantial MT gain.

greater post-operative pain [99, 266, 267]. A recent RCT confirmed that the SGG technique combined with CMX achieves KM augmentation comparable to FGG but with lower morbidity and superior esthetic evaluations [254]. Histological data from Urban et al. also support the biological validity of this method: regenerated tissues following the palatal SGG + CMX approach exhibit keratinized epithelium and a normal mucoperiosteal architecture indistinguishable from FGG reference samples [268]. Similar findings have also been reported for APF + CMX alone [256, 261, 262]. A more recent modification of the SGG technique involves the harvesting of the strip from the buccal aspect of teeth or edentulous areas presenting abundant keratinized tissue ("Buccal/labial SGG") [209, 210]. This approach may promote a better texture and color match of the augmented peri-implant mucosa resembling the buccal soft tissue of the adjacent regions [209, 210].

While autogenous FGG may still provide greater coronal soft-tissue thickness than CMX-based techniques, the latter primarily modify the soft-tissue phenotype by increasing KM rather than thickness. Further evidence is needed to clarify these dimensional differences.

Overall, the principal advantages of graft substitutes for KM augmentation include reduced postoperative morbidity, shorter surgical time, favorable esthetic outcomes, and the predictable creation of an "adequate" band of KM for peri-implant soft-tissue stability [134, 254, 255, 257–259, 261]. Given the heterogeneity of implant designs, abutment configurations, bone levels, and mucogingival relationships, the specific KM width required for long-term stability is likely case-dependent. Clinically, KM may be considered adequate when it appears firm, immobile, and resistant to displacement during gentle manipulation with a periodontal probe [27, 60].

Finally, one case series has explored the use of human acellular dermal matrix (hADM) for KM augmentation [265]. The modest KM increase reported was similar to that typically achieved with APF alone, reinforcing the notion that dermal matrices are best suited for bilaminar applications relying on primary-intention healing [2, 115, 198, 200, 269–273].

8.2.1 | Clinical Takeaway

In summary, available evidence suggests that APF combined with CMX, either alone or in conjunction with a SGG, can effectively increase KM at implant sites, while offering the additional benefit of reduced post-operative pain and lower analgesic consumption compared to conventional autogenous grafts. In contrast, the use of dermal matrices and VCMX in combination with APF is not currently supported for peri-implant KM augmentation.

Although KM width contributes to peri-implant health and patient comfort, the underlying MT plays a different and equally relevant role, particularly for esthetics and long-term marginal stability. Therefore, the next section focuses on the use of soft-tissue substitutes for increasing peri-implant MT.

8.3 | Soft-Tissue Substitutes for Augmenting Mucosal Thickness, Increasing Supracrestal Tissue Height, and Other Indications

The main indication and application of soft tissue graft substitutes around implants is currently augmenting the thickness of the soft tissue, in its horizontal (MT) and/or vertical (STH) dimension [272, 274–282] (Table 4; Table S7) (Figures 16–18).

8.3.1 | Soft-Tissue Substitutes for Increasing MT

Across the available literature assessing MT augmentation at implant sites, VCMX is the soft-tissue substitute that most closely approaches the outcomes of CTG. As summarized in Table 4, its performance generally falls within the range of CTG-associated MT gains, whereas CMX and dermal matrices tend to produce more modest increases. Multiple studies have compared VCMX with CTG [144, 250, 282, 287, 288, 290–294]. An early investigation by Thoma et al. established that VCMX can safely increase MT and that short-term outcomes are comparable to SCTG [144]. Follow-up studies over 3–5 years reported stable ridge contours with both materials [290, 291]. Large multicenter randomized clinical trials further demonstrated that VCMX achieves MT improvements similar to CTG at specific measurement points [250, 282], although CTG may outperform VCMX when MT is evaluated more coronally [250] (Table 4). However, other trials reported different results, with CTG consistently showing superior MT gain compared with VCMX [287, 294]. These findings were maintained at three-year follow-up, where CTG demonstrated a clear advantage in soft-tissue thickening [292] (Table 4). The divergent outcomes across studies may reflect differences in study design, MT-measurement techniques, and particularly the characteristics of the autogenous graft. Evidence shows that factors such as harvesting approach, donor-site region, and patient demographics can influence the composition and behavior of CTG, including its susceptibility to shrinkage [3, 22, 297].

These considerations are highlighted by an RCT using dCTG as the control graft, which is richer in collagen and contains minimal fatty and glandular components [288]. In that setting, dCTG achieved substantially greater MT augmentation than VCMX [288], a finding mirrored by recent data from our group evaluating dCTG in the treatment of PSTDs [43]. Collectively, these observations suggest that intrinsic graft quality and harvesting

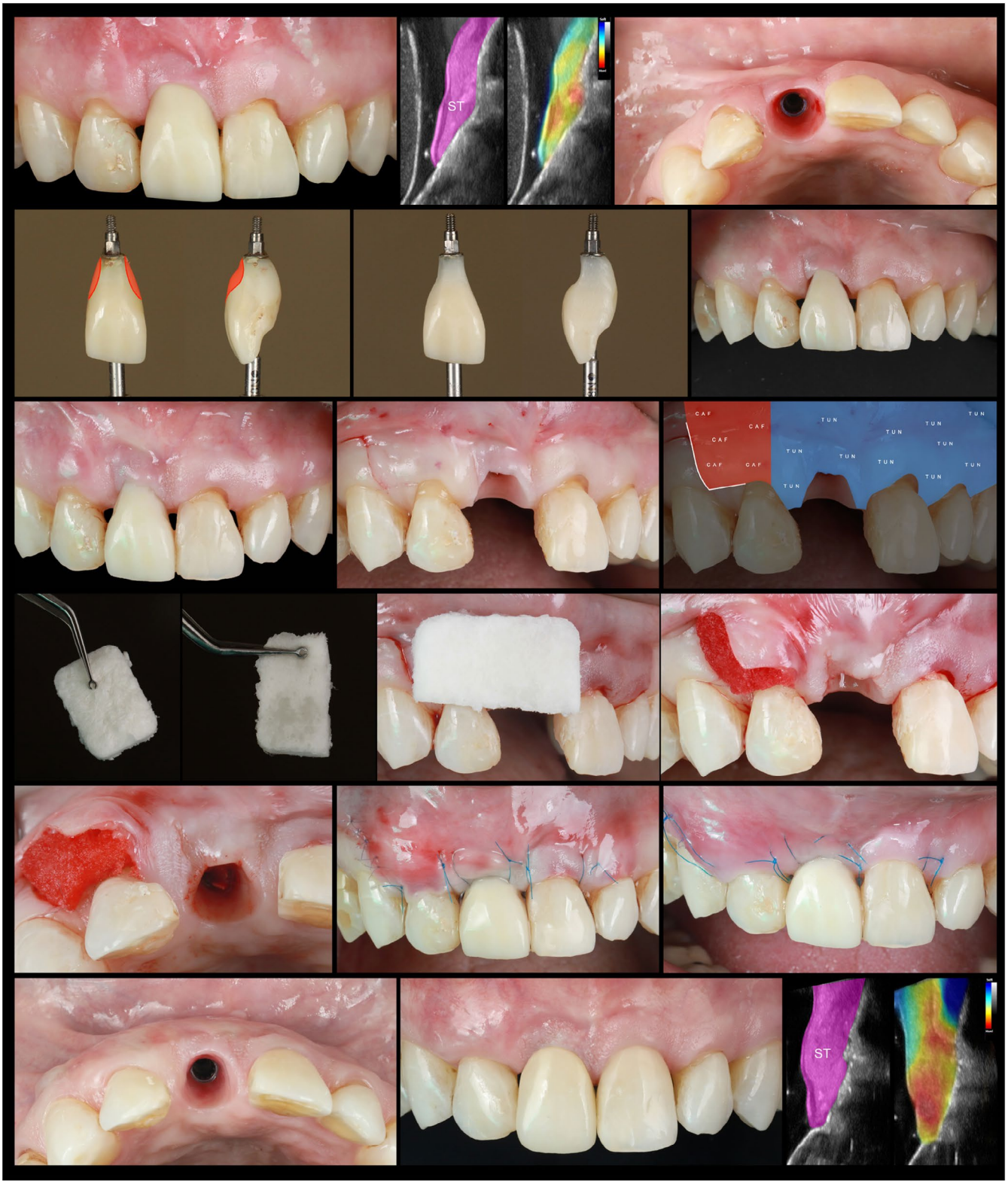

FIGURE 14 | Prosthetic-surgical approach for the treatment of an anterior peri-implant soft tissue dehiscence (PSTD) and adjacent gingival recessions. The surgical intervention involved a tunneled coronally advanced flap (TCAF) and the use of a volume-stable collagen matrix (VCMX, Geistlich Fibro-Gide, Geistlich Pharma, Wolhusen, Switzerland) saturated with recombinant human platelet-derived growth factor-BB (rhPDGF-BB, GEM21S, Geistlich Pharma North America, Princeton, United States). The panel reports the outcomes at 2 weeks, 6 months, and 1 year. The ultrasound scans at baseline and at the 1-year follow-up highlight in purple the buccal soft tissue component of the implant (ST). A substantial increase in MT and in tissue elasticity was observed, with the coronal portion of the peri-implant soft tissue that became thicker and stiffer after the intervention.

TABLE 3 | Expected gain in keratinized mucosa (KM) width following apically positioned flap-based approaches at implant sites.

Intervention	Studies (*n*), references	Overall patients (*N*), sites (*n*)	KM gain (mean ± SD), (min, max) (mm)
APF	2 [263, 264]	27, NR	1.56 ± 0.39 (1.38, 1.93)
APF + CMX	11 [135, 257–266]	170, 313	4.15 ± 1.87 (1.20, 7.13)
APF + FGG	9 [256, 257, 260–266]	156, 248	4.94 ± 1.96 (2.58, 8.13)
APF + hADM	1 [267]	10, 26	1.40 ± NR
APF + SCTG	2 [135, 259]	18, 18	2.63 ± 0.25 (2.40, 2.75)
APF + SGG + CMX	3 [210, 212, 256]	53, 53	5.77 ± 1.47 (3.63, 6.80)

Abbreviations: APF, apically positioned flap; CMX, bilayered collagen matrix; FGG, free gingival graft; hADM, human-derived collagen matrix; SCTG, sub-epithelial connective tissue graft; SD, standard deviation; SGG, strip gingival graft.

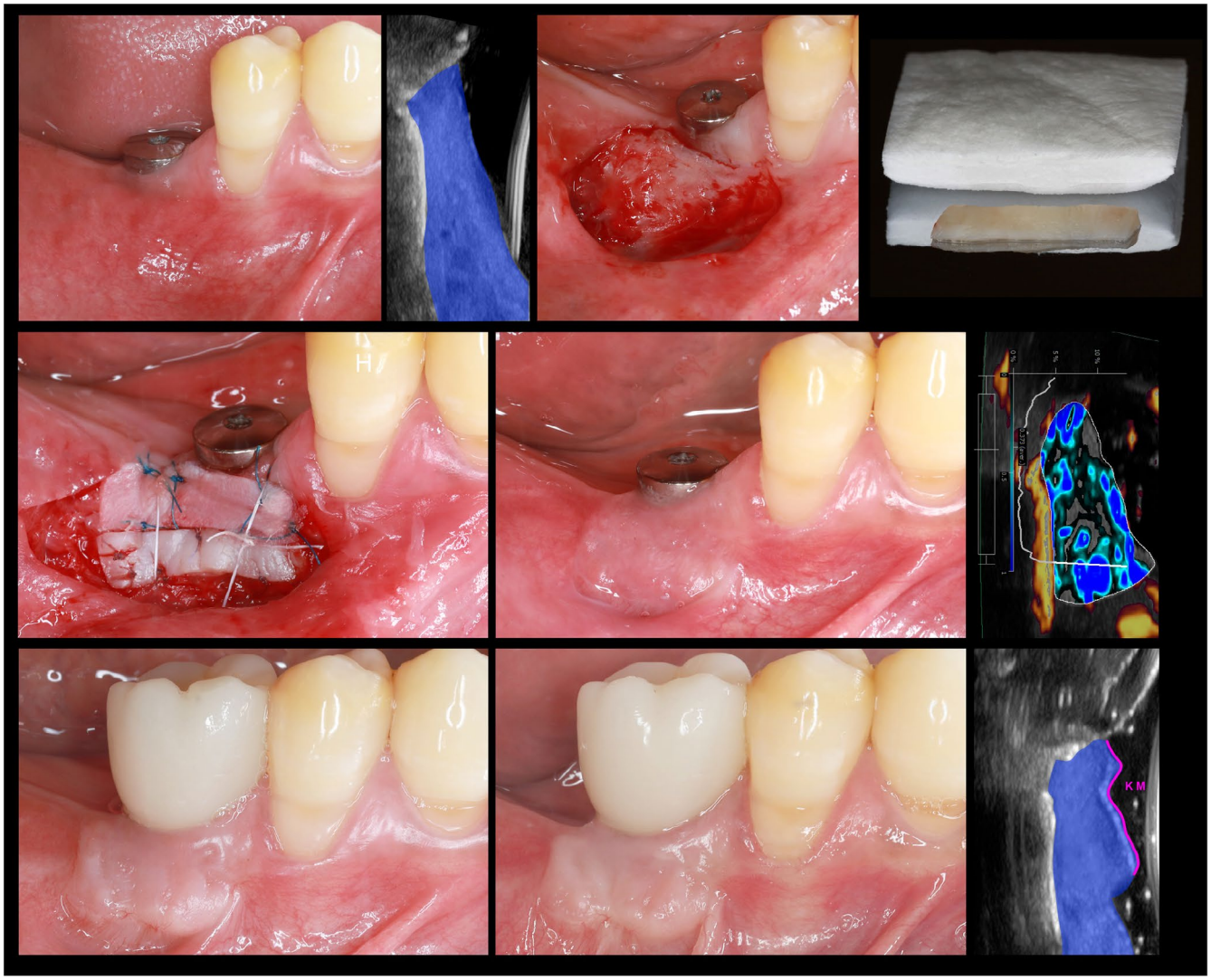

FIGURE 15 | Keratinized mucosa augmentation at a single posterior implant site using an apically positioned flap (AFP) in combination with a palatal strip gingival graft (pSGG) and a bilayered collagen matrix (CMX, Geistlich Mucograft, Geistlich Pharma, Wolhusen, Switzerland). The outcomes at 3 weeks, 6 months, and 5 years are shown. The ultrasound scan at baseline displays the peri-implant soft tissue in blue, while the scan at 3 weeks depicts the vascularization of the grafted area (pSGG and CMX). The final ultrasound scan is showing the peri-implant soft tissue in blue and the keratinized mucosa with a purple line.

TABLE 4 | Expected gain in mucosal thickness (MT), supracrestal tissue height (STH), and keratinized mucosa (KM) width using bilaminar techniques for peri-implant soft tissue phenotype modification.

Intervention	Studies (*n*)	Overall patients (*N*) and sites (*n*)	MT gain (mean ± SD), (min, max) (mm)	STH gain (mean ± SD), (min, max) (mm)	KM gain (mean ± SD), (min, max) (mm)
Bilaminar approach with hADM	4 [116, 274, 283, 284]	73, 75	0.85 ± 1.29	1.87 ± 0.75 (0.77, 2.21)	−0.45 ± 1.30
Bilaminar approach with pADM	5 [272, 275, 280, 285, 286]	88, 88	0.70 ± 0.30 (0.30, 0.89)	1.70 ± 0.14 (1.60, 1.80)	
Bilaminar approach with CMX	6 [137, 233, 251, 281, 287, 288]	102, 112	0.85 ± 0.30 (0.70, 1.16)	0.78 ± 1.15	0.77 ± 0.52 (0.17, 1.20)
Bilaminar approach with VCMX	13 [145, 252, 282, 289–298]	210, 210	1.01 ± 0.68 (−0.40, 2.23)	0.85 ± 0.90 (−0.19, 2.02)	0.85 ± 1.17 (−0.60, 3.45)
Bilaminar approach with SCTG	14, [116, 137, 145, 233, 272, 281, 287, 289, 290, 292–296]	150, 152	1.08 ± 0.26 (0.40–1.20)	0.84 ± 0.04 (0.80–0.85)	
Bilaminar approach with dCTG	1, [291]	10, 10	1.77 ± 0.76		

Abbreviations: CMX, bilayered collagen matrix; dCTG, connective tissue graft obtained from the de-epithelialization of an epithelialized soft tissue graft; hADM, human-derived acellular dermal matrix; KM, keratinized mucosa width; MT, mucosal thickness; pADM, porcine-derived acellular dermal matrix; SCTG, subepithelial connective tissue graft; STH, supracrestal tissue height; VCMX, volume-stable collagen matrix.

technique can significantly influence volumetric stability and MT outcomes, underscoring the need for further studies to clarify whether VCMX can be considered non-inferior to CTG across different timeframes.

Regarding CMX, existing trials consistently indicate that CTG provides superior MT augmentation [115, 136, 271, 279, 282, 285]. Direct comparative data between dermal matrices and CTG remain limited, though available evidence suggests that both hADM and pADM can effectively increase MT at implant sites (Figure 16), even if their performance relative to CTG requires further clarification.

While MT augmentation enhances the contour and stability of the coronal peri-implant soft tissue, the vertical dimension of the soft tissue, also known as STH, also plays a critical role in the preservation of crestal bone levels. For this reason, we next examine soft tissue substitutes used for increasing STH.

8.3.2 | Soft-Tissue Substitutes for Increasing STH

In the domain of vertical soft-tissue augmentation, the available literature consistently indicates that dermal matrices achieve the greatest increases in STH (Table 4; Table S7) [272, 273, 278, 299]. Both hADM and pADM have demonstrated favorable vertical gains in multiple clinical trials, often exceeding those reported for collagen-based xenogeneic matrices or connective tissue grafts. Importantly, these materials have shown predictable early incorporation into the peri-implant mucosa, with histological evidence confirming rapid integration and revascularization within the initial healing period [273, 299]. This early integration likely contributes to their capacity to maintain vertical tissue volume during the early phases of healing. Studies evaluating VCMX, SCTG, and CMX generally report more modest vertical dimensional changes (Table 4). However, outcomes for VCMX are notably heterogeneous. Some investigations comparing VCMX with SCTG have reported comparable STH increases during early healing phases [144], whereas others have found that VCMX does not achieve the same vertical gains as its autogenous counterpart [282]. Case series have described encouraging short-term volumetric improvements with VCMX, suggesting that the matrix may be capable of supporting vertical augmentation under certain site conditions [280]. Yet, more recent prospective evidence has indicated that these early gains are difficult to maintain over time. In particular, studies involving submerged healing have shown limited vertical thickening at 1 year, and when VCMX is used in non-submerged conditions with healing abutments, vertical augmentation tends to be minimal or even negative over time [295]. These contrasting findings underscore the sensitivity of VCMX outcomes to surgical and anatomical variables. Indeed, vertical soft-tissue augmentation is influenced by factors such as three-dimensional implant positioning, crestal bone levels, interproximal attachment of adjacent teeth, flap tension, compression of the substitute materials, and the amount of pre-existing KM, among others [48] (Figures 17 and 18). Overall, while dermal matrices currently appear to provide the most consistent vertical soft-tissue gains, xenogeneic collagen matrices such as VCMX may show benefits under specific conditions but remain highly technique-dependent.

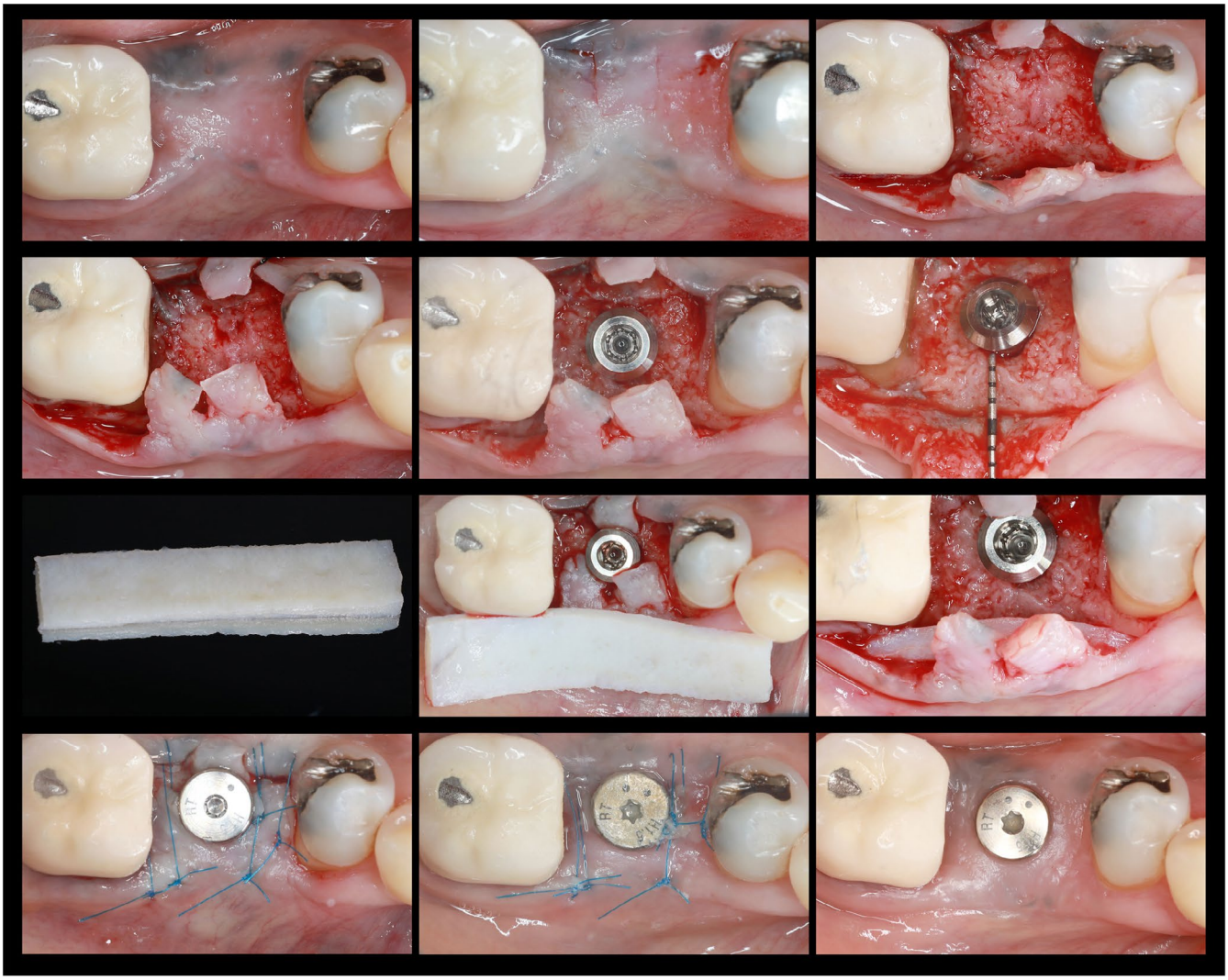

FIGURE 16 | Horizontal soft tissue augmentation at the time of implant placement. After an incision design aimed at moving some keratinized mucosa from the lingual to the buccal aspect, the flap was raised, and an implant was placed. The site had an adequate buccal bone and keratinized mucosa width, while the mucosal thickness at the implant site, as well as the gingival thickness at the adjacent dentition, was limited. A porcine-derived acellular dermal matrix (pADM, NovoMatrix, BioHorizons Camlog Italia, Casalecchio di Reno, Italy) was trimmed according to the recipient site and was secured with the flap to recreate an adequate ridge contour and to increase soft tissue thickness around the implant and the adjacent teeth. Healing at 3 weeks and 4 months.

Additional well-designed trials are warranted to clarify the indications and limitations of each material and to better understand which anatomical configurations and surgical strategies are most conducive to stable vertical augmentation.

Although MT and STH augmentation represent the principal indications for soft tissue substitutes around implants, these materials have also been applied in broader clinical scenarios, including immediate implant placement and the management of soft-tissue stability after extraction. The next section reviews these additional applications.

8.3.3 | Other Indications

Soft-tissue graft substitutes have frequently been incorporated into immediate implant protocols with the aim of limiting apical migration of the soft-tissue margin and mitigating post-extraction volume loss [184, 238, 239, 271, 277, 298, 300, 301] (Table S8). Some investigations have reported that substitutes such as hADM, CMX, and pADM can lead to modest improvements in peri-implant MT at the time of immediate implant placement [184, 238, 239, 277, 298, 300, 301], whereas another study found little benefit or even slight dimensional loss compared to sites that did not receive augmentation [274]. One study reported that the use of pADM has even been associated with slight dimensional loss over time [271]. In contrast, SCTG consistently demonstrates superior preservation of the level of the soft tissue margin and improved ridge contour when used at immediate implant sites [298], and some evidence indicates that pADM and tuberosity-derived CTG may achieve comparable short-term clinical and esthetic outcomes [277].

Interpretation of these findings requires caution, as comparisons across studies are complicated by differences in anatomical and surgical parameters. These include the morphology of

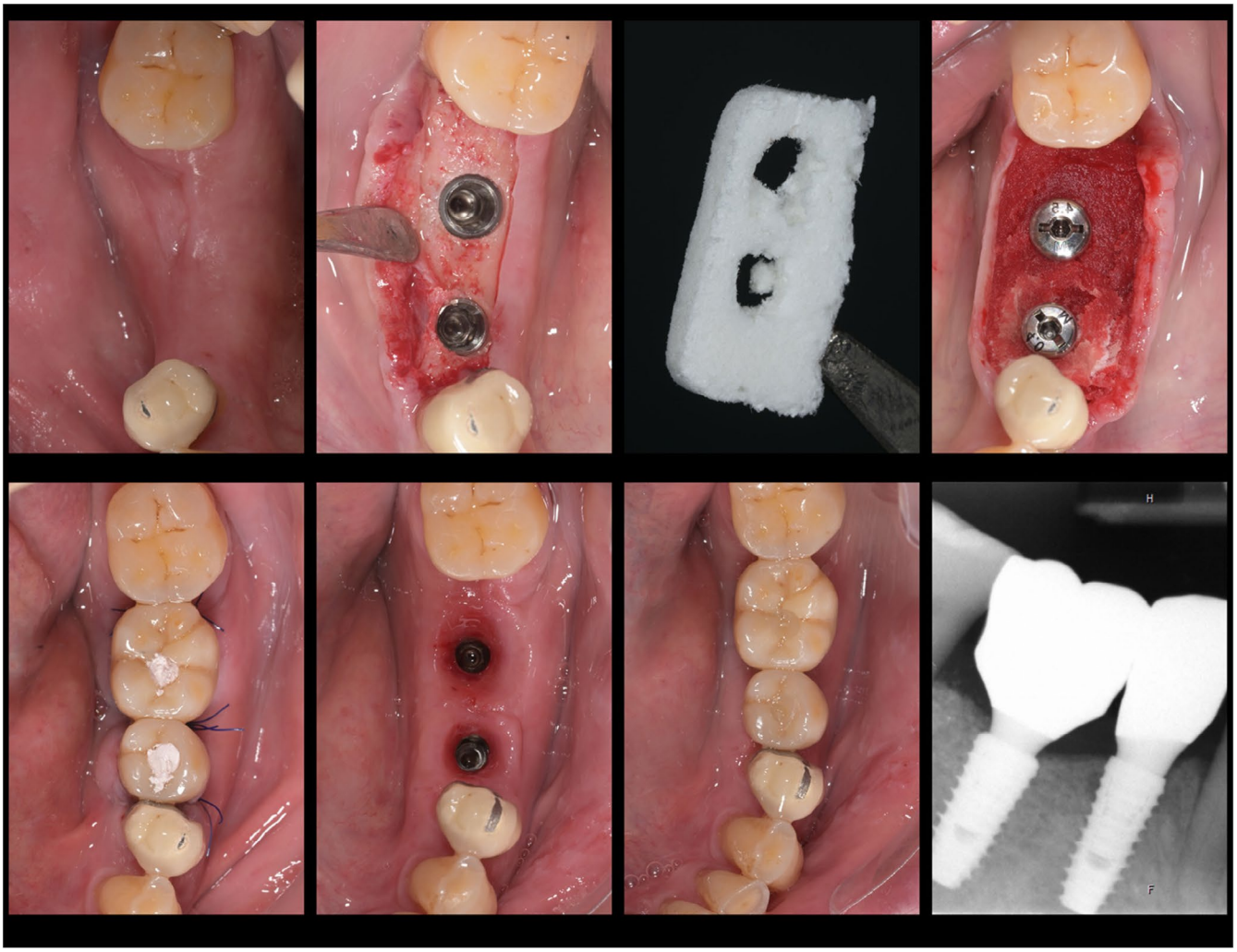

FIGURE 17 | Posterior implant placement with crestal/vertical soft tissue augmentation using a volume-stable collagen matrix (VCMX). The final zirconia-based restoration was inserted 48 h after surgery. Outcomes at 6 weeks and 1 year are shown.

the extraction socket, interproximal bone levels, residual buccal bone thickness, pre-existing soft-tissue phenotype, implant macro-design, depth and positioning of the fixture, use of surgical guides, and the presence or absence of immediate provisionalization [138, 238, 239, 300–305]. Such heterogeneity may substantially influence soft-tissue behavior around immediate implants, regardless of the grafting material used. More well-controlled studies are needed to clarify the specific indications and limitations of soft-tissue substitutes in this context.

Evidence regarding KM changes after immediate implant placement with graft substitutes remains limited and heterogeneous. Only a few studies have assessed KM width in this setting, and their findings vary widely (Table 4). At present, the literature does not support the predictable use of soft tissue substitutes for KM augmentation when used in bilaminar techniques around immediate implants. Therefore, from a clinical standpoint, these materials may be better indicated for MT and/or STH augmentation in cases where an adequate band of KM is already present.

Finally, several studies have consistently demonstrated that soft-tissue substitutes reduce surgical time and postoperative morbidity when compared with CTG [115, 136, 250, 271, 282, 288]. These benefits reinforce the importance of considering patient comfort, expectations, and treatment preferences when selecting grafting materials for soft tissue augmentation.

Together, these data illustrate the diverse and often site-specific roles of graft substitutes across multiple clinical indications. The following section synthesizes this information into a practical framework for graft selection.

8.3.4 | Clinical Takeaway

In summary, current evidence supports the efficacy of allogeneic and xenogeneic soft tissue graft substitutes in increasing MT at implant sites. However, the heterogeneous outcomes reported in comparisons with CTGs warrant cautious interpretation of the existing literature. Despite this variability, soft tissue substitutes appear capable of achieving a gain in MT of approximately 0.7–1 mm. Their use is most appropriate in cases where an adequate band of KM is already present. Clinical experience favors VCMX over CMX for xenogeneic MT augmentation, although further comparative studies are needed to establish the relative efficacy of different matrices. Preliminary evidence also

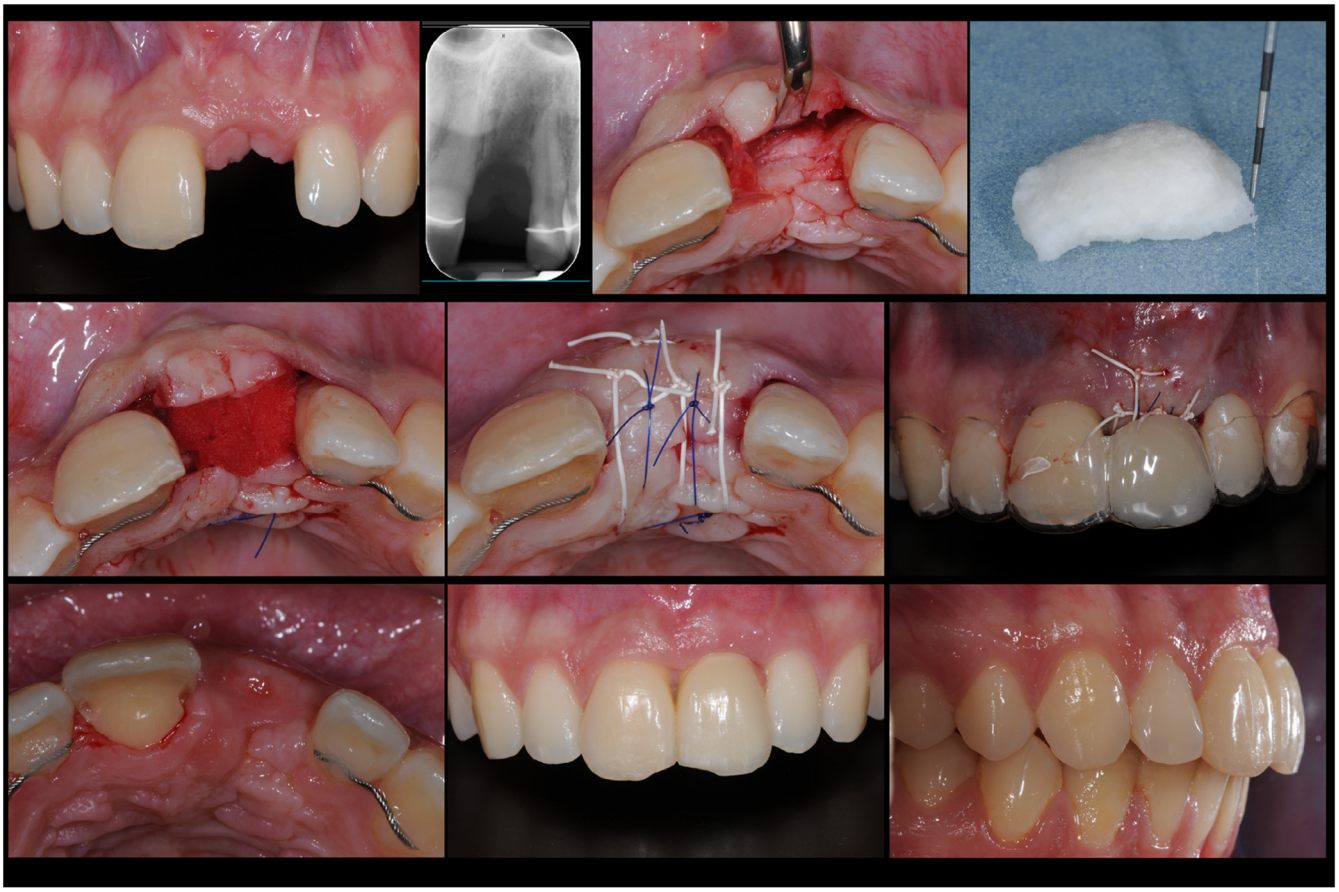

FIGURE 18 | Soft tissue augmentation in an anterior pontic site. Clinical situation with a missing central incisor and a substantial vertical and horizontal bone defect following a complicated implant surgery and implant failure. A split-thickness flap was opened to position a volume-stable collagen matrix (VCMX, Geistlich Fibro-Gide, Geistlich Pharma, Wolhusen, Switzerland) for crestal/vertical soft tissue augmentation. The matrix was placed crestally, at the transition between the buccal and crestal ridge and slightly on the buccal side, and sutured towards the palatal flap. The case was eventually restored with a zirconia resin-bonded bridge.

suggests that hADM and pADM show promise in augmenting STH when applied at the time of implant placement.

Taken together, the evidence on PSTD management, KM augmentation, and soft tissue phenotype modification around implants highlights the need for a structured and phenotype-driven framework to guide graft selection in everyday clinical practice. This provides the rationale for the decision tree presented in the following section.

8.4 | Decision Tree for the Selection of the Soft Tissue Graft Substitutes Around Implants

A clinical decision tree for the selection of soft tissue graft substitutes around dental implants is presented in Figure 19.

When interpreting this decision tree, readers should bear in mind that universal thresholds defining adequate or inadequate KM, MT, and STH cannot be established at present. This judgment is intentionally left to the clinician, based on patient- and implant-related factors.

When using an APF-based technique to increase peri-implant KM, the use of CMX, either alone or in combination with a SGG, is recommended over APF alone and should be considered the main alternative to the conventional FGG. In cases of completely missing KM, APF + FGG or APF + SGG + CMX are the preferred options to re-establish an adequate peri-implant KM. If buccal bone is completely missing or a substantial dehiscence is present, a conventional FGG may be preferred over the SGG + CMX approach, as the limited blood supply of the recipient bed may compromise both KM gain and the final position of the peri-implant soft tissue margin when using a small graft. Conversely, APF + SGG + CMX may be the treatment of choice in cases with intact and ideal buccal bone, owing to its efficacy in creating sufficient KM width with minimal patient morbidity. Implant sites with shallow buccal bone dehiscence may be treated with either APF + FGG or APF + SGG + CMX, depending on patient priorities, whether favoring implant coverage and final soft tissue level or minimally invasive surgery. APF + CMX should also be considered in sites with limited KM width that can be preserved during APF, especially at sites with intact buccal bone (or shallow buccal bone dehiscence). Ultimately, the choice of technique for KM augmentation should be based on patient-specific and anatomical considerations. At present, the use of hADM and pADM in combination with APF is not recommended.

The baseline amount of KM is also a key factor in determining the graft type for MT augmentation. Soft tissue graft substitutes

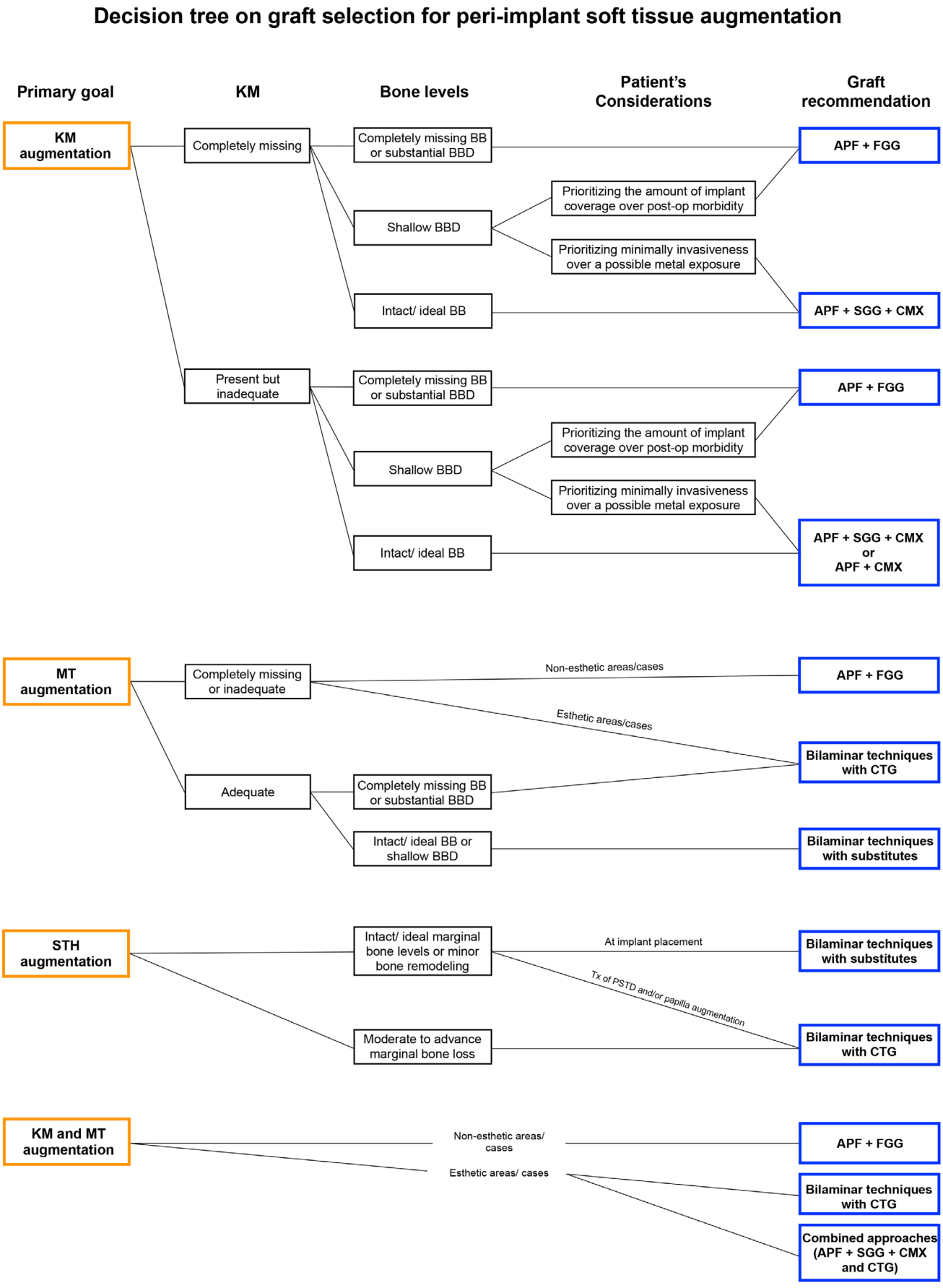

FIGURE 19 | Legend on next page.

FIGURE 19 | Decision tree on graft selection for soft tissue augmentation at the implant site. APF, Apically positioned flap; BB, Buccal bone; BBD, Buccal bone dehiscence; CMX, Collagen matrix; CTG, Connective tissue graft; FGG, Free gingival graft; KM, Keratinized mucosa; MT, Mucosal thickness; PSTD, Peri-implant soft tissue dehiscence; SGG, Strip gingival graft; STH, Supracrestal tissue height; Tx, Treatment.

have demonstrated substantial MT gains when used in bilaminar techniques, but their limited and variable effects on KM width suggest restricting their application to cases with an adequate band of KM. Among substitutes, VCMX provides MT gains most comparable to CTG and should be considered a principal alternative, especially given its favorable safety profile. Bilaminar techniques with graft substitutes are generally recommended in sites with adequate KM width and intact buccal bone or shallow buccal bone dehiscence. In cases of adequate KM width but completely missing or substantially dehisced buccal bone, CTG may be preferable, given the strong evidence supporting its efficacy even in severely compromised sites [43, 244, 245], while evidence for substitutes remains limited. When both MT and KM are lacking, APF + FGG can provide simultaneous improvement, especially at posterior, non-esthetic sites. However, for anterior esthetic areas, this approach is less favored due to the texture and color mismatch of the augmented mucosa [2, 3]. Bilaminar CTG techniques reliably increase MT and may occasionally promote KM gain over time, though the mechanisms driving keratinization of alveolar mucosa in CTG-augmented sites remain incompletely understood. In other words, when both KM and MT require augmentation, the treatment choice depends on site and esthetic demands: APF + FGG may be suitable in non-esthetic areas, whereas bilaminar CTG-based techniques or combined approaches such as APF + SGG + CMX with a coronally positioned CTG [210, 242] are preferred in esthetic zones.

STH augmentation with graft substitutes has shown predictable outcomes when performed at implant placement in sites with ideal marginal bone. Dermal matrices, in particular, have demonstrated promising results in posterior sites with STH < 3 mm and adequate crestal KM, where primary closure favors graft healing. In contrast, caution is warranted in anterior areas, where flap dehiscence and graft exposure may compromise esthetic results and necessitate corrective procedures. Both evidence and clinical experience suggest that more advanced indications, such as moderate to advanced bone loss, peri-implant soft tissue dehiscence coverage, and papilla reconstruction, remain more predictably treated with autogenous CTG.

Graft substitutes may also be used in immediate implant therapy and the management of PSTDs; however, limited evidence supports their efficacy in advanced or complex cases, where autogenous CTG should remain the first choice. Ultimately, graft selection should be guided by clinician expertise and patient-specific anatomical and esthetic considerations.

9 | Soft Tissue Graft Substitutes in Alveolar Ridge Preservation, Bone Augmentation, and Peri-Implantitis Treatment

Additional applications that have been described for soft tissue graft substitutes include their use for alveolar ridge preservation (ARP), soft tissue augmentation at pontic sites, bone regenerative procedures, and treatment of peri-implantitis [138, 275, 276, 306–312]. In particular, CMX has been extensively employed during ARP [138, 276, 310]. Fickl et al. observed that ARP + CMX resulted in less scar tissue formation compared to ARP + FGG [276]. Sites treated with autogenous grafts indeed often required additional appointments and therefore additional costs for soft tissue procedures related to the scar tissue [276]. A volumetric analysis by Natto et al. showed that although soft tissue contour alternations cannot be avoided after extraction and ARP with allograft, the use of a CMX was slightly better in minimizing the amount of volume loss compared to a collagen sponge [310]. An explorative trial by Thoma et al. compared the soft tissue changes occurring following ARP + CMX, ARP alone, and spontaneous healing [312]. After 2 months, the median thickness of the mucosa was 3.0, 2.1, 1.5 mm, at the sites allocated to ARP + CMX, ARP, and spontaneous healing, respectively. Additional bone augmentation at the time of implant placement was necessary in 66.7%, 53.8%, and 90.9% of the sites in groups ARP + CMX, ARP, and spontaneous healing [312].

Chappuis et al. reported a mean increase in peri-implant MT of 1.56 mm at 8 weeks following VCMX in combination with guided bone regeneration [275]. The volumetric analysis revealed that the tissue contour increase was most significant at a distance of 5 mm from the soft tissue margin, which corresponds to a tissue increase at the implant shoulder area [275]. Similarly, a case series by Papi et al. described a mean MT gain of 1.9 mm at implant sites augmented with guided bone regeneration procedures and pADM [309]. Simultaneous hard and soft tissue augmentation has also been described using hADM [307, 308, 313, 314]. One RCT finally employed hADM as a barrier membrane for bone graft during reconstructive therapy of peri-implantitis [306].

10 | Future Directions

Despite the remarkable progress achieved with autogenous grafts and soft tissue substitutes, significant challenges remain in balancing clinical efficacy with patient morbidity. The future of periodontal and peri-implant soft tissue augmentation will likely be driven by advances in tissue engineering, regenerative medicine, and biomaterials science [21, 183].

Emerging strategies focus on the development of next-generation scaffolds capable of mimicking the structural and biological properties of native mucosa. These scaffolds may be functionalized with controlled drug delivery systems, allowing for the localized release of growth factors, angiogenic molecules, or anti-inflammatory agents to optimize healing and reduce complications. Incorporating biologically active molecules into these engineered constructs could further accelerate vascularization and integration, narrowing the performance gap with autogenous grafts. In parallel, advances in cell-based therapies hold promise. Tissue-engineered constructs seeded

with autologous or allogeneic fibroblasts, keratinocytes, or stem cells have already demonstrated the ability to regenerate keratinized mucosa in pilot studies [21, 195, 204]. The future may see these constructs combined with gene therapy approaches, enhancing the regenerative capacity of resident cells through targeted modulation of signaling pathways involved in angiogenesis, keratinization, or extracellular matrix synthesis. Another frontier involves smart biomaterials and bioactive scaffolds, designed with tunable porosity, biodegradability, and mechanical strength. These materials could serve as platforms not only for structural support but also as carriers for nanoparticles or microspheres delivering biologics or genetic material in a sustained and spatially controlled manner. Such multifunctional scaffolds may ultimately overcome the variability observed with current substitutes and provide predictable long-term stability [315]. In line with these technological advances, future investigations should also explore the cost–benefit ratio of these therapies compared to conventional grafting procedures. Although this analysis cannot yet be performed based on the currently available evidence, economic and patient-centered outcomes should represent a priority for future research to ensure the clinical translation and accessibility of these grafting solutions.

Collectively, these innovations suggest that the reliance on autogenous grafts may gradually diminish. In the long term, tissue-engineered, bioactive, and patient-specific grafts may allow clinicians to achieve outcomes equal to, or potentially superior to, those of CTG and FGG while minimizing patient morbidity. The integration of biologics, advanced scaffolds, and gene-modulating technologies represents a transformative horizon, where personalized regenerative solutions may replace the current gold standard and redefine the practice of periodontal and peri-implant soft tissue surgery. Future investigations should also include systematic reviews and meta-analyses to quantitatively validate the findings summarized in this narrative review and to provide stronger evidence on the comparative effectiveness of different soft-tissue substitutes.

11 | Conclusions

Soft tissue graft substitutes have been widely used in periodontology and implant dentistry to reduce the invasiveness of surgical procedures, increase patient acceptance by minimizing postoperative morbidity, and decrease surgical time and complexity.

Based on the current evidence, the following conclusions can be drawn:

i. Soft tissue graft substitutes can improve root coverage outcomes–specifically mRC and GT gain–compared to flap procedures alone, although CTG remain the most effective approach.

ii. In non-root coverage KT augmentation procedures at natural teeth, the combination of APF and CMX can increase KT width and attached gingiva, although APF + FGG yields superior clinical results.

iii. At implant sites, APF + CMX–either alone or combined with a strip gingival graft–can effectively augment KM, offering clinical outcomes often comparable to autogenous grafts while significantly reducing postoperative morbidity.

iv. Soft tissue graft substitutes can lead to meaningful gains in MT and STH at implant sites.

v. Patient-reported outcomes frequently favor soft tissue graft substitutes over autogenous grafts.

vi. Additional potential applications of soft tissue graft substitutes include use during alveolar ridge preservation, bone augmentation, immediate implant placement, treatment of PSTDs, and papilla augmentation.

vii. The selection of a soft tissue graft material should be guided by a balance between clinical efficacy, costs and patient morbidity, along with anatomical and operator-related considerations.

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Conflicts of Interest

Lorenzo Tavelli, Maria Elisa Galarraga Vinueza, and Shayan Barootchi have previously lectured for Geistlich Pharma, Straumann, and BioHorizons. Daniel Thoma has previously lectured for Geistlich Pharma.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix S1:** Supporting Information. **Table S1:** Root coverage outcomes following the use of human acellular dermal matrix (hADM) for the treatment of gingival recession type 1 (RT1) defects. **Table S2:** Root coverage outcomes following the use of xenogeneic collagen matrices (CMX and VCMX) for the treatment of gingival recession type 1 (RT1) defects. **Table S3:** Root coverage outcomes following the use of porcine-derived acellular dermal matrix (pADM) for the treatment of gingival recession type 1 (RT1) defects. **Table S4:** Summary of the randomized clinical trial reporting favorable, similar, and unfavorable outcomes when soft tissue graft substitutes are compared to flap alone or to connective tissue graft (CTG) for the treatment of RT1 gingival recessions. **Table S5:** Characteristics and outcomes of clinical studies evaluating the efficacy of soft tissue graft substitutes seeded with living cells (living cellular constructs [LCCs]) for KT width augmentation in natural dentition. **Table S6:** Characteristics of the included studies reported the outcomes of soft tissue graft substitutes in combination with an apically positioned flap for keratinized mucosa augmentation at implant sites. **Table S7:** Characteristics of the included studies reported the outcomes of soft tissue graft substitutes in combination with bilaminar techniques for mucosal thickness (MT) and/or supracrestal tissue height (STH) augmentation at implant sites. **Table S8:** Characteristics of the included studies reported the outcomes of soft tissue graft substitutes at the time of immediate implant therapy.