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Novel Approaches for Augmentation of Peri-implant Keratinised Mucosa

PhD Thesis

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LIST OF ABBREVIATIONS

ADM – Acellular Dermal Matrix

APPTF – Apically Positioned Partial Thickness Flap

ASG – Autogenous Strip Graft

ECTG – Epithelialised Connective Tissue Graft

FMBS – Full Mouth Bleeding Score

FMPS – Full Mouth Plaque Score

FGG – Free Gingival Graft

KM – Keratinised Mucosa

MGJ – Mucogingival Junction

PIKM – Peri-implant Keratinised Mucosa

PIKM-T – Peri-implant Keratinised Mucosa Thickness

PIKM-W – Peri-implant Keratinised Mucosa Width

PSTD – Peri-implant Soft Tissue Dehiscence

RCT – Randomised Clinical Trial

SCTG – Subepithelial Connective Tissue Graft

SD – Standard Deviation

XCM – Xenogeneic Collagen Matrix

XDM – Xenogeneic Dermal Matrix

1. INTRODUCTION

1.1. Background

Dental implants have become a cornerstone in modern dentistry, offering a reliable and effective solution for replacing missing teeth (Jung et al., 2012). They are widely recognised for their high survival rates, functional effectiveness, and favourable aesthetic outcomes (Pjetursson et al., 2012). However, the long-term success of these implants is not solely determined by their initial osseointegration but also by the health and stability of the surrounding soft and hard tissues (Borrell & Crawford, 2012). The biological seal formed by peri-implant tissues, including bone and mucosa, is critical in preventing bacterial invasion and mitigating mechanical trauma, thereby contributing significantly to the long-term success of dental implants. (Abrahamsson & Berglundh, 2006). Among the peri-implant tissues, adequate peri-implant keratinised mucosa width (PIKM-W) has garnered considerable attention for preserving peri-implant health (Berglundh et al., 2018a).

Peri-implant Keratinised Mucosa (PIKM) refers to the dense, keratinised band of tissue that surrounds a dental implant, akin to the gingiva that encircles natural teeth (Figures 1 and 2). This specialised tissue acts as a protective barrier against mechanical forces and microbial invasions, contributing to the overall stability of the peri-implant environment (Wennström & Derks, 2012). Adequate PIKM-W is particularly important because it helps to maintain a protective seal around the implant, reduces inflammation, and minimizes the risk of peri-implant diseases such as peri-implant mucositis and peri-implantitis—common inflammatory conditions that can lead to bone loss and implant failure (Schwarz et al., 2018a). Several studies have demonstrated that the presence of an adequate width of keratinised mucosa (≥2 mm) around implants is advantageous for maintaining peri-implant health by reducing inflammation, decreasing plaque accumulation, preventing mucosal recession, and ensuring both soft and hard tissue stability (Ravidà et al., 2020; Roccuzzo et al., 2016; Stefanini M et al., 2023). As a result, clinicians have a strong consensus regarding the need for strategies to maintain or increase the sufficient width of PIKM around dental implants (Roccuzzo et al., 2016; Sanz et al., 2022).

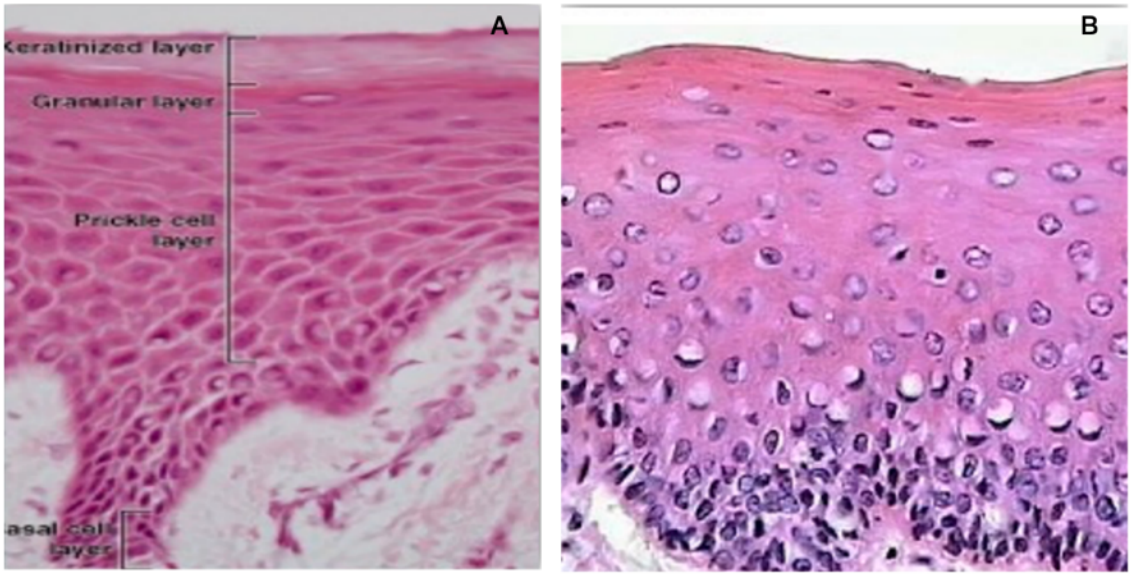

Figure 1. Histological structure of keratinised oral mucosa (A) and non-keratinised oral mucosa (B). Adapted from: Nanci A. Ten Cate's Oral Histology: Development, Structure, and Function. 8th ed. St. Louis: Elsevier; 2013.

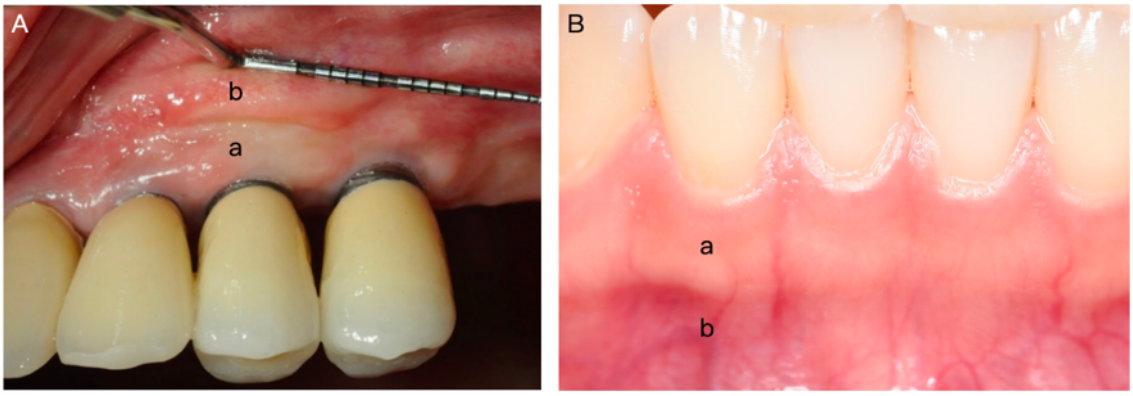

Figure 2. Clinical pictures of peri-implant keratinised mucosa (a) and non-keratinised mucosa (b), (A); and keratinised (a) and non-keratinised gingiva (b) around the natural tooth (B).

1.2. Clinical Significance of Peri-implant Keratinised Mucosa Width (PIKM-W)

The debate surrounding the clinical significance of PIKM-W has been ongoing for decades. Early studies suggested that dental implants could achieve favourable outcomes without the presence of PIKM-W, provided that meticulous plaque control was maintained (Bouri et al., 2008; Schrott et al., 2009; Wennström & Derks, 2012). However, a growing body of evidence indicates that the absence of sufficient PIKM-W may lead to several complications, including discomfort during brushing, increased plaque accumulation, mucosal recession, and peri-implant inflammation (Del Amo et al., 2020;

Roccuzzo et al., 2016; Souza et al., 2016). These complications can further progress to more severe conditions such as peri-implantitis, which significantly threatens the long-term stability of dental implants (Schwarz et al., 2018a).

Peri-implant diseases and conditions pose significant challenges to implant success and long-term stability. According to the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, peri-implant diseases are categorised into peri-implant health (Figure 3A), peri-implant mucositis (Figure 3B), peri-implantitis (Figure 3C), and the newly recognised peri-implant soft and hard tissue deficiencies (Berglundh et al., 2018b).

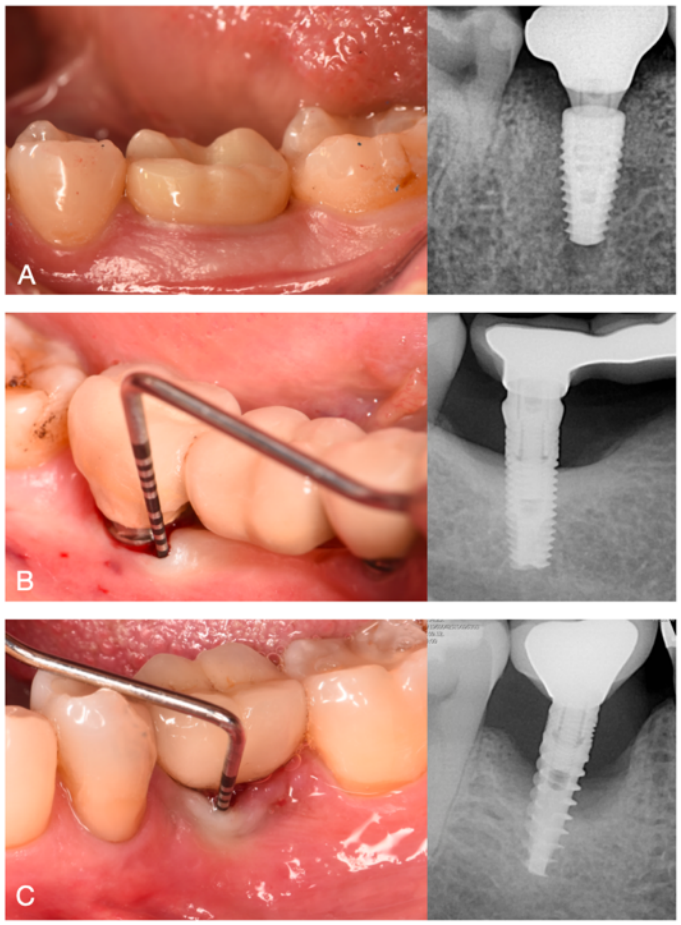

Figure 3. Clinical (left) and radiographic (right) images showing peri-implant health (A), peri-implant mucositis (B), peri-implantitis (C).

Peri-implant mucositis is defined by two primary criteria: the presence of inflammation in the peri-implant mucosa and the absence of continuing marginal bone loss. The most common clinical sign of inflammation is bleeding on probing (approximately 0.2 N), with additional signs potentially including erythema, oedema, and suppuration (Heitz-Mayfield, 2024). If left untreated, it can progress to peri-implantitis, a destructive condition defined by inflammation, increased probing depth, and

progressive loss of the supporting bone (Berglundh et al., 2018b; Sanz et al., 2012; Schwarz et al., 2018a).

Recent systematic reviews have highlighted substantial variation in the reported prevalence of these conditions, mainly due to differences in diagnostic criteria, observation periods, and study populations (Lee et al., 2017; Ravidà et al., 2022; Stefanini M et al., 2023). Specifically, the prevalence of peri-implant mucositis ranges from approximately 27% to 63% at the patient level, as reported by Romandini et al. (Romandini et al., 2021). In contrast, Lee et al. found a mean prevalence of 46.83% (Lee et al., 2017). In terms of peri-implantitis, prevalence estimates vary from 7% to 47% across studies (Romandini et al., 2021). However, Lee et al. reported a mean prevalence of 19.83% at the subject level and 9.25% at the implant level (Lee et al., 2017).

The aetiology of peri-implantitis is multifactorial, involving microbial biofilm accumulation, a history of periodontitis, smoking, diabetes, inadequate maintenance therapy, prosthetic design, excessive mechanical loading, and the lack of an adequate band of keratinised mucosa, etc. (Renvert & Quirynen, 2015; Schwarz et al., 2018b). Given its potential to compromise implant longevity, early diagnosis and the implementation of evidence-based preventive and therapeutic strategies are critical in modern implant dentistry.

Beyond inflammation-related peri-implant diseases, the 2017 classification introduced the Peri-Implant Soft and Hard Tissue Deficiencies as a distinct category (Berglundh et al., 2018b). Peri-implant Soft Tissue Dehiscence (PSTD) is now recognized as a clinical condition, characterised by the apical displacement of the peri-implant mucosal margin, with or without inflammation, often resulting from inadequate soft tissue volume, surgical trauma, implant malpositioning, or iatrogenic factors (Berglundh et al., 2018b; Del Amo et al., 2020). This updated classification reflects an evolving understanding that peri-implant health is not solely determined by inflammation-related conditions but also by structural deficiencies that may compromise aesthetic and functional outcomes (Berglundh et al., 2018b; Del Amo et al., 2020).

This classification change highlights the necessity of comprehensive peri-implant management, addressing not only peri-implant infections but also soft and hard tissue deficiencies, to optimize implant longevity and ensure successful patient outcomes (Berglundh et al., 2018b).

Adequate PIKM-W contributes to peri-implant health by providing a robust, keratinised layer that resists mechanical trauma and bacterial infiltration (Gharpure et al.,

2021; Lin et al., 2013; Sanz et al., 2022). Moreover, sufficient PIKM-W enhances aesthetic outcomes by minimising the risk of mucosal recession and exposure of implant components, which is particularly critical in aesthetically sensitive zones (Lin et al., 2013; Ravidà et al., 2022). Additionally, having a sufficient width of keratinised mucosa around implants facilitates better oral hygiene practices by reducing peri-implant inflammation and enhancing patient comfort. These factors collectively emphasise the importance of maintaining an adequate width of keratinised mucosa to achieve both biological stability and optimal aesthetic and functional outcomes in implant dentistry (Gharpure et al., 2021; Lin et al., 2013; Ravidà et al., 2022; Sanz et al., 2022; Souza et al., 2016; Stefanini M et al., 2023).

1.3. Evolution of Techniques for Increasing PIKM-W

The increasing recognition of the significance of peri-implant keratinised mucosa has led to the development of various surgical techniques to augment PIKM-W. The most widely used methods involve autogenous tissue grafting, such as free gingival grafts (FGG) or, more precisely, epithelialised connective tissue grafts (ECTG).

In addition, subepithelial connective tissue grafts (SCTG) have been extensively used as a gold standard for peri-implant soft tissue augmentation. SCTG offers excellent tissue integration, volume stability, and long-term functional success, particularly for soft tissue thickness augmentation and mucosal phenotype modification (Cairo et al., 2008; Del Amo et al., 2020; Thoma et al., 2018; Zucchelli et al., 2020). Comparative studies have consistently demonstrated superior outcomes of SCTG over xenogeneic substitutes in terms of long-term volumetric stability and soft tissue contour maintenance ((McGuire & Scheyer, 2016; Tavelli et al., 2021). However, similar to ECTG, SCTG harvesting requires a second surgical site, which increases patient morbidity, postoperative pain, and limited donor tissue availability (Cairo et al., 2008; Del Amo et al., 2020; Tavelli et al., 2021; Thoma et al., 2018). These disadvantages have accelerated the search for alternative substitute materials capable of replacing SCTG while reducing surgical invasiveness.

These techniques have been regarded as the gold standard for increasing PIKM-W due to their high predictability and effectiveness in providing stable and long-lasting results (Cairo et al., 2008; Thoma et al., 2014). The ECTG technique typically involves harvesting tissue from the hard palate and transplanting it to the peri-implant region. It is highly effective in both increasing keratinised tissue formation and improving peri-

implant stability (Cairo et al., 2008). However, they often result in a significant colour discrepancy between the graft and the surrounding tissue, which can be a disadvantage in aesthetically sensitive areas (Fu et al., 2021; Stefanini et al., 2023). Moreover, the donor site can experience significant pain, discomfort, and delayed wound healing, which can impact patient satisfaction and the overall acceptance of the procedure (Bitencourt et al., 2022; Fu et al., 2021).

Despite the effectiveness of autogenous grafts in increasing PIKM-W, the autogenous grafts come with inherent limitations, such as the need for a second surgical site for tissue harvesting, limited volume, increased patient morbidity, and potential aesthetic challenges. These limitations have driven the development and use of alternative materials and techniques that can achieve similar clinical outcomes with less invasiveness and reduced patient discomfort (Ashurko et al., 2022; Sanz et al., 2009; Tavelli et al., 2021).

1.4. Development and Clinical Evidence of Soft Tissue Substitutes: ADM, XCM, and XDM

Various xenogeneic and allogeneic soft tissue substitutes have been developed to overcome the limitations associated with autogenous grafting, such as donor site morbidity, limited tissue availability, and prolonged surgical times. These include acellular dermal matrix (ADM), xenogeneic dermal matrix (XDM), and xenogeneic collagen matrix (XCM). These biomaterials provide minimally invasive alternatives for peri-implant soft tissue augmentation, offering the added benefits of reduced patient morbidity and simplified surgical procedures (Sanz et al., 2009; Tommasato et al., 2024). ADM is primarily derived from human cadaveric dermis, though porcine-derived ADM variants are also available (Thoma et al., 2014). In contrast, XDM and XCM are exclusively xenogeneic in origin, derived from porcine or bovine sources. These biomaterials undergo rigorous processing to remove all cellular components, thereby reducing immunogenicity while preserving the extracellular matrix structure and facilitating host tissue integration. Each of these materials offers distinct advantages in PIKM-W widening by providing alternative solutions to autogenous grafting with reduced donor site morbidity (Papi & Pompa, 2018; Rothamel et al., 2004).

Acellular Dermal Matrix (ADM)

ADM is a decellularised allogenic graft, primarily derived from porcine or human dermis, that retains the extracellular matrix structure while removing cellular antigens. This process enhances host tissue integration and supports vascularisation, thus making ADM a valuable alternative to autogenous grafts for PIKM-W widening (Papi et al., 2021). Compared to XCM, ADM exhibits greater volume preservation, improved mechanical stability, and reduced postoperative contraction. Additionally, ADM has been shown to facilitate fibroblast migration and angiogenesis, further enhancing its regenerative potential (Tracy et al., 2016). Clinical studies suggest that ADM can effectively increase peri-implant soft tissue thickness and improve long-term stability, making it a preferred choice when volume preservation and integration are primary concerns (Papi et al., 2021).

However, the use of ADM is restricted in many European countries due to ethical concerns regarding the use of human-derived tissue products, in addition, during the maturation process, ADM has a tend to exhibit unpleasant odour. While porcine-derived ADM is available, its adoption has been limited compared to XDM and XCM, which are more widely accepted in European clinical practice. Consequently, ADM has been less frequently adopted than XDM or XCM in European practice.

Xenogeneic Collagen Matrix (XCM)

Xenogeneic collagen matrices (XCM), such as porcine-derived collagen scaffolds (e.g., Mucograft®, Geistlich Pharma AG, Wolhusen, Switzerland), which are typically derived from porcine or bovine sources, have been utilised as alternatives to autogenous grafts for augmenting peri-implant soft tissues. These matrices are advantageous because they are readily available, easy to handle, and avoid the need for a second surgical site. Clinical studies have demonstrated that XCMs can increase primary the thickness and secondary the width of keratinised mucosa; however, they are prone to significant postoperative contraction due to their porous structure, leading to lower PIKM-W during secondary wound healing compared to autogenous grafts (Sanz et al., 2009; Schmitt et al., 2016). As a result, their use is often limited to situations where minimal augmentation is required, the graft can heal in a closed manner by primary intention and the long-term stability is not a major concern.

Early clinical trials demonstrated that XCM can produce significant short-term gains in keratinised tissue width: Sanz et al. reported a mean increase of ~2.5 mm (Sanz et al.,

2009). Lorenzo et al. reported 2.7 mm at 6 months, comparable to connective tissue grafts (Lorenzo et al., 2012). However, their long-term dimensional stability remains questionable. A key limitation of XCM is its considerable contraction and resorption during healing, strongly associated with its loose, porous collagen structure. This fragile architecture predisposes the material to sloughing, maceration, and degradation, especially under open-healing conditions. Sanz et al. observed that roughly two-thirds of the initially gained tissue width was lost as the collagen matrix remodelled (approximately 67% shrinkage) (Sanz et al., 2009). These characteristics explain the rapid shrinkage and limited long-term width stability compared to autogenous grafts.

Recent findings by Yao et al. (2023) further substantiate these concerns. Their randomised controlled trial found that although XCM significantly increased the width of keratinised mucosa in the posterior mandible at 3 and 6 months, the tissue volume continued to decrease between 6 and 12 months. The shrinkage ratio was reported to be as high as 46% by the end of 12 months (Qiu et al., 2023). This progressive resorption further confirms the inferior long-term behaviour of XCM for width augmentation.
These findings suggest that while XCM may temporarily increase keratinised mucosa width, its biological characteristics favour applications for mucosal thickness augmentation, particularly when closed-healing protocols can be applied to protect the matrix from disintegration.

Xenogeneic Dermal Matrices (XDM)

Xenogeneic acellular dermal matrices (XDM) derived from porcine dermis (e.g., mucoderm®, Botiss, Zossen, Germany) have been introduced to overcome the shortcomings of collagen matrices. An XDM consists of a three-dimensional type I/III collagen scaffold processed to remove cellular components, yielding a dense matrix intended to resist rapid degradation (Papi & Pompa, 2018; Puisys et al., 2019). Unlike XCMs, XDMs have been reported to undergo less contraction during healing, owing to its structurally intact collagen architecture (Zafiropoulos et al., 2021).

It also features a quick rehydration time and slower resorption rate, which facilitates better graft persistence (Kasaj et al., 2016). Furthermore, XDMs promote angiogenesis and integration with host tissues: studies have noted that they readily attract host fibroblasts (and even osteoblasts) into the matrix, supporting revascularisation and tissue incorporation (Blatt et al., 2020). These properties suggest that XDM may provide a more stable scaffold for soft-tissue augmentation around implants than XCM. Initial clinical

evidence on XDM has been promising. Papi and Pompa conducted a study using an XDM for peri-implant soft tissue augmentation and reported successful outcomes after one year (Papi & Pompa, 2018). In their cohort, the width of keratinised mucosa increased and remained at an average of ~5.7 mm at the 12-month follow-up, representing about 72% of the initially achieved tissue width. This indicates that while some contraction occurred, a substantial band of attached mucosa was maintained over the long term. In a retrospective clinical study, Zafiropoulos et al. also demonstrated the effectiveness of XDM in the PIKM widening procedure (Zafiropoulos et al., 2021). They observed a mean gain of approximately 5.4 mm in keratinised mucosa width at 6 months post-operation using XDM. However, a significant portion of the graft dimension (around 3.9 mm) had remodelled during healing. Notably, Zafiropoulos et al. found the degree of shrinkage consistent across maxillary and mandibular sites, suggesting uniform remodelling behaviour of the XDM in different oral locations. Overall, these studies indicate that XDM can reliably increase peri-implant keratinised tissue, with final outcomes of 5–6 mm of attached mucosa in many cases and potentially less relative contraction than collagen-only matrices. Comparative research has shed light on how XDM performs relative to XCM and autogenous grafts. In a pilot study by Horváth et al., various grafting approaches were compared for increasing peri-implant keratinised mucosa. After 6 months, the xenogeneic dermal matrix achieved a mean keratinised mucosa width of about 3.0 mm, which was on par with the result obtained by using an epithelial connective tissue graft (~3.5 mm) and notably higher than the outcome with a subepithelial connective tissue graft (~1.0 mm) or a collagen matrix (~1.5 mm) (Horvath et al., 2014). This preliminary comparison suggested that XDM could match the efficacy of the gold-standard autogenous graft in the short term while outperforming the xenogeneic collagen matrix in terms of the amount of new keratinised tissue formed. More recently, a prospective clinical case series by Horváth et al. provided further evidence supporting the XDM's effectiveness. In that study, 24 patients were treated with a porcine XDM using a standardised technique, and the outcomes were evaluated at both 6 and 12 months. The authors reported that the mean PIKM-W increased from essentially 0 mm at baseline to about 3.2 mm after 6 months in the maxilla, and although some reduction occurred by 12 months, an average of 2.3–2.4 mm of keratinised tissue remained in the upper jaw at one year. In the mandible, the gains were more modest (approximately 1.6 mm at 6 months, decreasing to ~1.1 mm at 12 months) (Horváth et al., 2024). This corresponded with the graft dimensions shrinking by roughly 68% in the maxilla and 82% in the mandible at 6

months, with slight further remodelling by 12 months. Recent findings by Horváth et al. (2024) highlight a notable disparity in graft remodelling between the maxilla and mandible. Specifically, the maxillary sites exhibited less proportional contraction and sustained a greater width of keratinised mucosa compared to mandibular sites. This observation contrasts with earlier reports suggesting uniform shrinkage patterns across both arches. Such differences imply that anatomical factors, such as tissue biotype and vascular supply, may significantly influence the healing outcomes of XDM grafts. (Horváth et al., 2024; Zafiropoulos et al., 2021). In summary, the body of evidence to date indicates that xenogeneic matrices can effectively enhance peri-implant keratinised mucosa, but their performance varies with material type. XCMs (collagen matrices) have shown favourable short-term results comparable to connective tissue grafts, yet tend to undergo greater resorption, which can compromise long-term tissue stability.

In contrast, XDM has demonstrated greater long-term stability than XCM, with slower resorption and sustained PIKM-W observed up to one year postoperatively (Papi & Pompa, 2018; Zafiropoulos et al., 2021). Clinical studies indicate that XDM formulations yield equal or greater gains in PIKM-W than XCMs, with outcomes that approach those of autogenous grafts without the associated donor site morbidity. These findings reinforce the growing consensus that XDM represents a promising alternative to autogenous soft tissue grafts in PIKM-W widening (Horváth et al., 2024; Zafiropoulos et al., 2021).

However, variations in clinical outcomes have been observed depending on anatomical location, particularly between maxillary and mandibular sites, suggesting that site-specific factors, such as vascularisation, muscular attachment, biomechanical stress, and native tissue mobility, play a critical role in determining graft success (Del Amo et al., 2020). Although both XCM and XDM have been shown to facilitate peri-implant mucosal augmentation, XDM appears to provide more predictable volumetric stability and reduced contraction by preserving the augmented tissue more effectively over time compared to collagen-only matrices (Horváth et al., 2024; Lorenzo et al., 2012; Rokn et al., 2020; Sanz et al., 2009; Zafiropoulos et al., 2021). Given these advantages, further studies, are warranted to establish optimised protocols for site-specific applications of XDM in PIKM-W enlargement.

1.5. Combined Approaches: Autogenous Strip Graft with Xenogeneic Matrices (XCM and XDM)

Recognising the limitations of both autogenous and xenogeneic grafts when used independently, a combined approach was proposed to harness the benefits of each while minimising their drawbacks. Han et al. were the first to introduce the concept of an autogenous strip graft (ASG): a narrow epithelialised connective tissue graft to augment PIKM-W, aiming to reduce donor site morbidity and promote rapid healing (Han et al., 1995). Urban et al. later refined this approach by combining a gingival ASG with an XCM (Mucograft®, Geistlich pharma AG, Wolhusen, Switzerland) to treat mucogingival deficiencies in the anterior maxilla. Their technique leveraged the mechanical stability of an apically placed ASG and the regenerative scaffold properties of XCM, resulting in improved soft tissue stability and enhanced aesthetic outcomes (Urban et al., 2015, 2019, 2020). In this combination, the ASG acts as a biomechanical stabilizer at the apical aspect of the grafting site. At the same time, the XCM serves as a scaffold for soft tissue regeneration and epithelialisation, collectively resulting in improved tissue integration, keratinised tissue width and aesthetic outcomes.

In Urban et al.'s case series, the ASG+XCM technique achieved favourable clinical and later histological results (Urban et al., 2015, 2019). A key finding was a significant reduction in graft shrinkage—approximately 43% over 12 months with the combination approach, compared to over 50% when XCM was used alone (Sanz et al., 2009). Histologic evaluations in subsequent studies confirmed the development of keratinised epithelium that was virtually indistinguishable from native tissue and comparable to conventional FGGs (Urban et al., 2019, 2020).

Recently, Huang et al. conducted a prospective single-arm clinical trial evaluating the combined use of ASG and an XCM for PIKM-W widening procedure in the posterior mandible, an anatomically challenging site due to limited vestibular depth and dense mucosal attachments (Huang et al., 2024). Thirteen patients were included, and after six months, the mean gain in keratinised mucosa width was 3.3 ± 1.6 mm. Although the authors reported dimensional reduction of the grafted tissue over time, the final mucosal width remained clinically adequate to support peri-implant health and facilitate oral hygiene. Importantly, patients reported high satisfaction and experienced minimal postoperative discomfort, supporting the technique's clinical feasibility and reduced morbidity compared to traditional grafting procedures (Huang et al., 2024).

Importantly, this combination technique not only addresses the limitations of XCM alone, which is prone to significant volumetric contraction during healing, but also mitigates donor site morbidity by using a narrower graft harvested from a less invasive region. The labial donor site, in particular, has been associated with improved aesthetic outcomes due to its superior colour match with surrounding tissues (Urban et al., 2019, 2025). These advantages have positioned the ASG+XCM method as an efficient and aesthetically favourable alternative to conventional grafting in both the anterior and posterior zones.

Nevertheless, anatomical challenges in the posterior mandible, such as a shallow vestibule, muscle pull, and thin mucosa, can adversely influence the predictability of outcomes. While the ASG+XCM approach has been well validated in the anterior maxilla, its application in the posterior mandible is still under investigation. The literature currently lacks trials evaluating the efficacy of combining ASG with other xenogeneic materials such as XDM in high-stress anatomical regions. Moreover, the limited available volume of autogenous strip graft harvested from the palate further constrains the width of augmentation, and the inferior clinical performance of XDM alone in the mandible highlights the necessity for further procedural fine-tuning. Optimizing the graft combination ratio, surgical design, and stabilisation technique may enhance long-term volumetric stability and improve clinical predictability in these challenging sites. This represents a critical gap in knowledge and warrants future investigation, particularly to explore whether the volumetric stability and patient-reported outcomes of ASG+XCM can be replicated or improved upon with alternative materials.

1.6. Rationale for the Study

Adequate PIKM-W is essential for maintaining long-term peri-implant health. While XDM has demonstrated stable outcomes in the maxilla, its predictability in the mandible remains limited due to greater contraction. The two studies were therefore designed to address site-specific differences in graft behaviour. As XDM alone provided predictable outcomes in the maxilla but substantial contraction in the mandible, an additional study combining ASG with XDM was implemented to improve stability in the mandible. This approach aimed to develop site-specific augmentation protocols that ensure predictable and stable peri-implant soft tissue outcomes according to anatomical demands.

2. OBJECTIVES and HYPOTHESES

2.1. Objectives

The basis of the thesis is two clinical trials, aiming to evaluate the clinical performance of XDM alone and in combination with ASG for in peri-implant soft tissue augmentation by assessing its ability to increase PIKM-W and maintaining soft tissue stability over time. Additionally, it will analyse the surgical technique and handling properties of XDM and explore the effectiveness of a combined approach by using an ASG with XDM to improve stability in the mandible.

The specific objectives of this study are:

-To evaluate the changes in PIKM-W following augmentation with XDM over 12 months

-To analyse the contraction rates and stability of XDM in different anatomical sites (maxilla vs. mandible) and assess its remodelling characteristics

-To provide a detailed description of the surgical technique and evaluate the handling properties of XDM in clinical practice, including its integration with host tissues

- To examine the safety of the XDM and the effectiveness of a modified periosteal suture technique in stabilising XDM grafts and minimising micromovement during early healing.

-To assess the effectiveness of combining an ASG with XDM in improving PIKM-W and reducing contraction rates in the posterior mandible

2.2. Hypotheses

Central Hypothesis

XDM is an effective grafting material for peri-implant soft tissue augmentation, capable of producing stable and predictable increases in PIKM-W up to 12 months. In the mandible, a combined technique of XDM+ASG improves the clinical outcome of XDM alone by reducing the postoperative graft contraction.

Specific Hypotheses

H1: The tested material (XDM) and technique are safe.

H2: XDM results in an increase of PIKM-W at 12 months in the maxilla and mandible compared to baseline measurements

H3: Combining an ASG with XDM will improve peri-implant soft tissue stability by increasing PIKM-W and reducing graft contraction compared to XDM alone, particularly in the posterior mandible.

These objectives and hypotheses will be systematically evaluated through the clinical trials described in the following sections, aiming to provide clinically relevant evidence for optimising site-specific peri-implant soft tissue augmentation protocols.

3. MATERIALS AND METHODS

The thesis includes two prospective case series designed to evaluate the clinical outcomes of XDM in peri-implant soft tissue augmentation. The studies were conducted at the Department of Periodontology, Semmelweis University, Budapest, Hungary. All patients provided written informed consent, and the study protocol was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (approval number: SE RKEB 223/2017). Research adhered to the ethical principles outlined in the Declaration of Helsinki and followed standardised clinical protocols for peri-implant soft tissue augmentation (World Medical Association, 2013)

3.1. Patient selection

Patients were selected from the patient pool of the Department of Periodontology, Semmelweis University, Budapest, from 2018 to 2021. Eligible patients presented with an insufficient amount of PIKM-W (less than 2 mm buccally in the maxilla or mandible), as confirmed by clinical examination using a UNC-15 periodontal probe. The study was conducted on a patient-based level. The patients presented with multiple sites requiring keratinised mucosa (KM) augmentation, and the mean PIKM-W value per patient was used for statistical evaluation to ensure consistency in the data analysis.

Inclusion Criteria

1. Age ≥ 18 years
2. Presence of inadequate PIKM-W < 2 mm
3. PIKM augmentation procedure required for functional or aesthetic purposes either in the maxilla or mandible (for the XDM-alone study), or exclusively to the mandible (for the ASG + XDM study)
4. Good oral hygiene is defined as a full-mouth plaque score (FMPS) of less than 20%
5. No active periodontal disease, with a full-mouth bleeding score (FMBS) below 20%
6. Good compliance with follow-up protocols and willingness to participate in long-term maintenance programmes

Exclusion Criteria

1. General medical conditions contraindicating elective oral surgery, such as uncontrolled diabetes, immunosuppressive disorders, or long-term corticosteroid use, etc
2. Allergies to grafting materials
3. Active infectious diseases (e.g., HBV, HCV, HIV, TB, SARS-CoV-2)
4. Current smokers or individuals with a history of smoking within the past six months
5. History of radiation therapy to the cranial region within the past 2 years
6. Ongoing chemotherapy or radiation therapy
7. Pregnant or lactating women
8. Use of medications that could interfere with wound healing, such as bisphosphonates or anticoagulants
9. Untreated periodontitis
10. Lack of patient compliance with postoperative instructions and follow-up visits

3.2. Outcome variables and measurements

The primary outcome of this study was the overall change in PIKM-W, measured using a UNC-15 periodontal probe as the distance from the mid-crestal line of the edentulous ridge or mid-buccal margin of the implant to the buccal MGJ, with values rounded to the nearest millimetre.

The secondary outcomes included graft dimensional stability (shrinkage/contraction), which was analysed using the formula: [1-(PIKM-W at 6M in mm — PIKM-W baseline in mm)/ trimmed XDM width in mm] x 100 = %.

Additionally, PIKM-T was evaluated in the second study. PIKM-T was measured 2 mm apical to the mucosal margin using a needle with a rubber stop, with evaluations conducted at baseline, and at 1, 3, 6, 9, and 12 months postoperatively. All clinical measurements were performed by a single calibrated examiner (XL) who was not conducting the surgeries. Prior to the commencement of the study, the examiner underwent a calibration exercise on 10 non-study patients to assess intra-examiner reliability. Each outcome variable, PIKM-W and PIKM-T, was measured twice at a one-week interval using standardised instruments and techniques. The intra-class correlation coefficient for repeated measurements exceeded 0.90 for both variables, confirming excellent reproducibility. This calibration procedure ensured consistency and reliability of measurements across all follow-up intervals.

3.3. Presurgical procedures

All patients underwent a standardised preoperative protocol to optimize the peri-implant soft tissue environment and minimize the risk of postoperative complications. Professional oral hygiene instructions were provided to reinforce meticulous plaque control. Comprehensive full-mouth supragingival scaling was performed to reduce microbial load and mitigate periodontal inflammation by ensuring an optimal peri-implant environment prior to surgery.

As part of the pharmacological premedication regimen, 400 mg of ibuprofen was administered one hour before surgery to modulate the inflammatory response and provide preventive analgesia. Prophylactic antibiotic therapy was not routinely prescribed unless indicated by patient-specific systemic conditions.

3.4. Surgical Procedures

3.4.1 Xenogeneic Dermal Matrix (XDM) Augmentation Technique

Following the administration of local anaesthesia, a horizontal supraperiosteal incision was performed at the MGJ by using a 15C blade, ensuring that the periosteum remained intact. Two vertical releasing incisions were placed at the mesial and distal borders of the edentulous site, extending into the mobile mucosa. A split-thickness flap was then meticulously elevated using either a blade or a periosteal elevator to prepare a recipient periosteal bed, with the dissection tailored according to the anatomical characteristics of each case.

To enhance vestibular depth and provide adequate soft tissue support, the rim of the mucosal flap was apically positioned and stabilised by using a continuous 6-0 monofilament absorbable suture (Monolac, Chirmax, Prague, Czechia). This approach facilitated a stable recipient site for graft placement while also deepening the oral vestibule.

Before placement, the XDM was fully rehydrated using sterile saline solution to improve its adaptability to the recipient bed. At the coronal margin, KM was carefully elevated to accommodate the coronal edge of the XDM beneath it, thus ensuring stable adaptation.

The mesial, central, and distal portions of the coronal graft margin were secured by using internal (mucosa) and external (graft) horizontal mattress sutures with 5-0 non-

resorbable monofilament sutures (Dafilon®, B. Braun, Rubí, Spain). To further stabilize the graft, deep periosteal internal horizontal mattress sutures were placed above the XDM, ensuring intimate contact between the graft and the periosteal bed while preventing blood clot formation, which could interfere with graft integration. XDM left for secondary healing. The detailed surgical workflow is shown in Figure 4. The figure is reprinted from: Horváth A, Windisch P, Palkovics D, Li X. Novel Technique to Reconstruct Peri-Implant Keratinised Mucosa Width Using Xenogeneic Dermal Matrix: A Clinical Case Series. Dent J. 2024;12(3):43. https://doi.org/10.3390/dj12030043

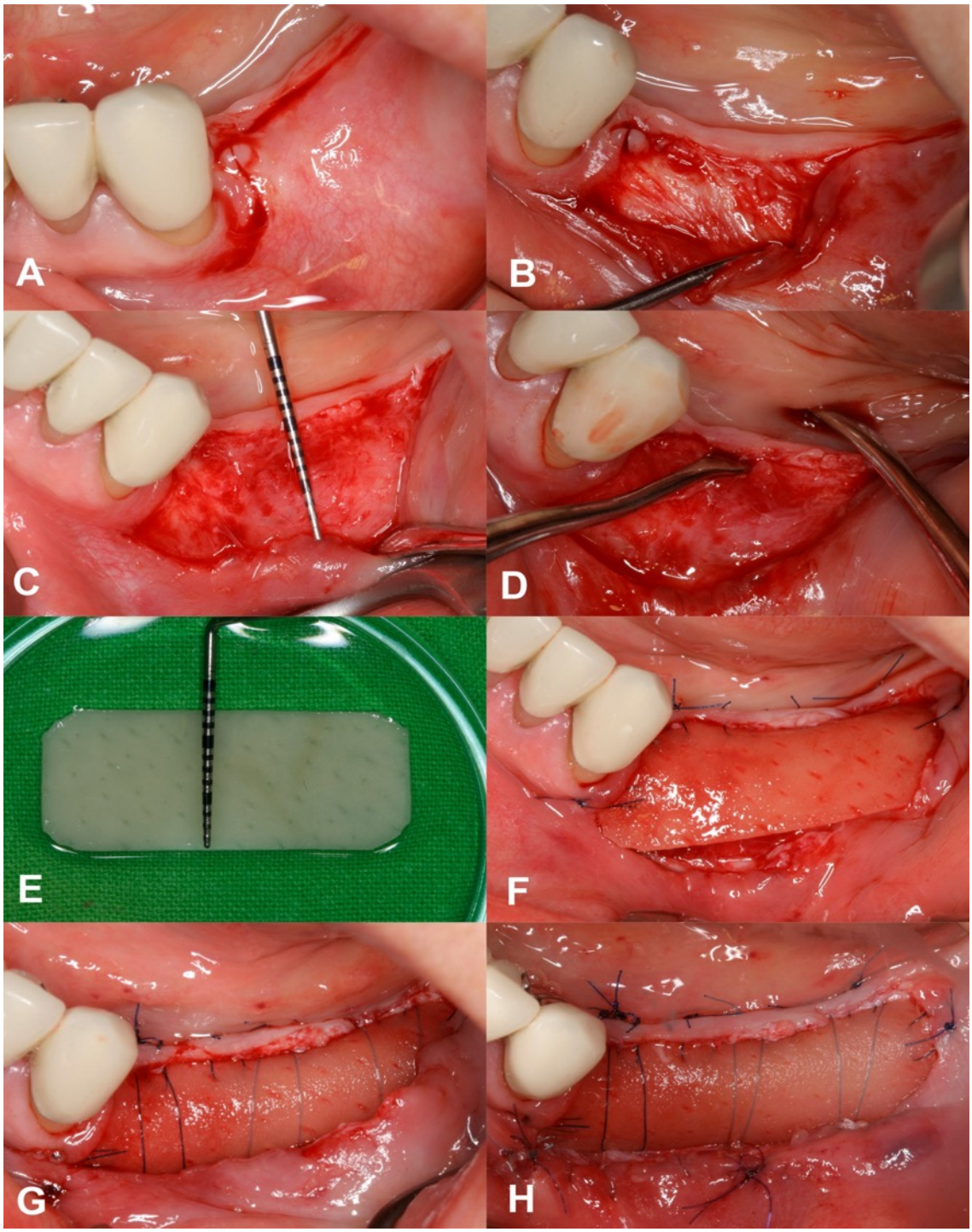

Figure 4. Step-by-step description of the surgical procedure when the XDM was used alone. (A) Split-thickness incision at the MGJ. (B) Flap mobilisation by using a blade or periosteal elevator. (C) Measurement confirming 10 mm recipient bed depth. (D) Gentle elevation of the lingual flap edge will facilitate placement of the XDM beneath it. (E) XDM was trimmed after rehydration in sterile saline. (F) XDM was positioned and fixed with a modified mattress and single interrupted sutures. (G) Periosteal internal horizontal mattress sutures were applied to ensure graft stabilisation. (H) The coronal

flange of the buccal mucosal flap was immobilised by suturing it to the apical section of the same flap by using a simple continuous technique.

3.4.2 Combined Autogenous Strip Graft (ASG) and Xenogeneic Dermal Matrix (XDM) Approach

Following local anaesthesia, a horizontal incision was made along the MGJ by using a 15C blade. Two vertical supraperiosteal incisions were placed at the mesial and distal aspects of the edentulous ridge, followed by an APPTF preparation by using either a blade or a periosteal elevator. The recipient periosteal bed was carefully dissected to ensure adequate vascularisation for the graft material. The mobilised mucosal flap was apically repositioned and secured to the most apical portion of the same flap using 6-0 resorbable monofilament sutures (Monolac, Chirmax, Prague, Czechia) to establish a stable grafting environment.

For the ASG harvest, a 2–3 mm wide ASG was obtained from the palate under local anaesthesia, with its length adjusted to match the mesiodistal dimension of the recipient site. Following donor site hemostasis, a bovine-derived absorbable collagen fleece (Lyostypt, B. Braun, Rubí, Spain) was applied and stabilised by using 6-0 non-resorbable sling sutures (Chiraflon, Chirmax, Prague, Czechia).

The harvested ASG was positioned in the apical portion of the recipient bed and secured with single interrupted sutures fixing the graft to the underlying periosteum by using 6-0 resorbable monofilament sutures. Subsequently, the XDM (mucoderm®, Botiss, Zossen, Germany) was trimmed to fit the remaining periosteal bed and positioned between the apically placed ASG and remaining keratinised mucosa coronally. The uncovered XDM was stabilised with single interrupted sutures using 6-0 resorbable monofilament sutures, ensuring optimal adaptation to the recipient site. Finally, deep periosteal internal horizontal mattress sutures were placed by using 6-0 non-resorbable monofilament sutures, securing the ASG and XDM to the periosteal bed. This technique provided tight adaptation, preventing graft micromovement and enhancing soft tissue stabilisation (Figure 5). This figure is reprinted from: Li X, Palkovics D, Windisch P, Perić Kačarević Ž, Horváth A. A combined approach using strip grafts and xenogenic dermal matrix for peri-implant keratinized mucosa augmentation in the mandible: A case series. Biomedicines. 2025;13(4):806. https://doi.org/10.3390/biomedicines13040806.

This approach aimed to combine the advantages of autogenous and xenogeneic grafts, maximising long-term peri-implant soft tissue stability while minimising donor site morbidity. All surgical procedures were performed by one experienced periodontal specialist (AH).

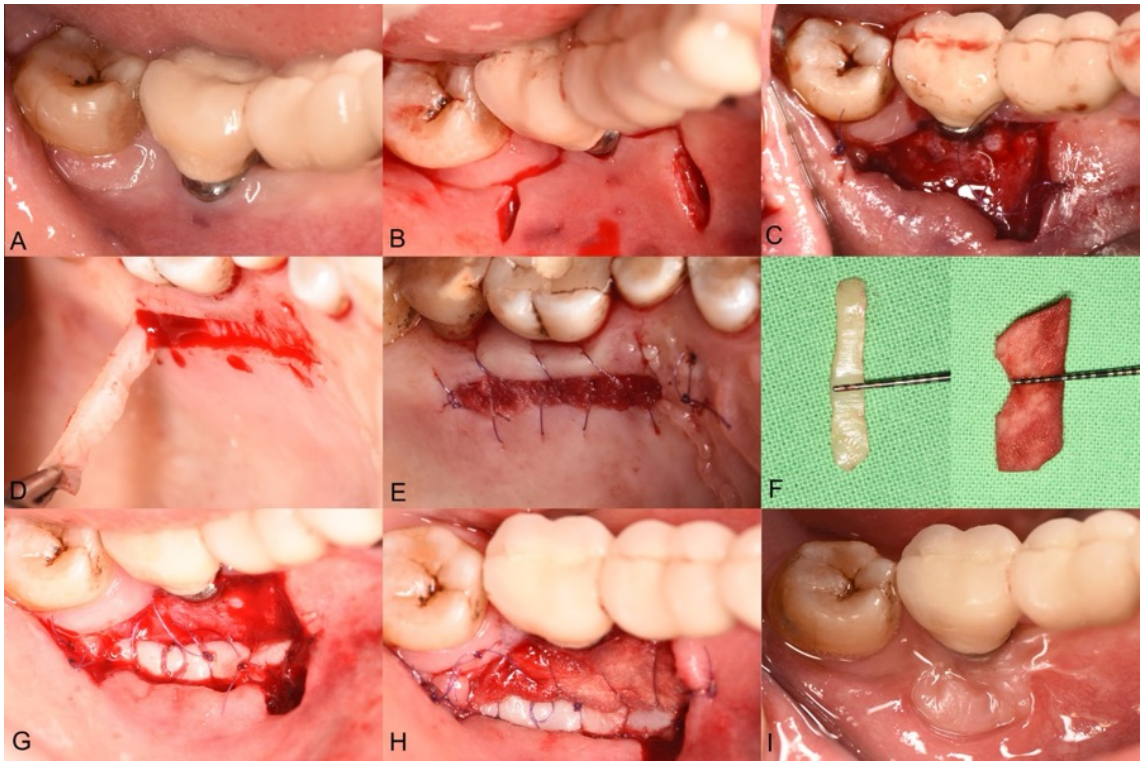

Figure 5. Surgical protocol and follow-ups for palatal autogenous strip graft (ASG) in combination with XDM. (A) Buccal view showing insufficient PIKM-W. (B) A horizontal incision was performed along the MGJ, followed by two vertical supraperiosteal incisions at the mesial and distal aspects. (C) The coronal flange of the buccal mucosal flap was immobilized to its apical portion using a continuous suturing technique. (D) The ASG was harvested from the hard palate. (E) A xenogenic collagen matrix strip is adapted and secured to the donor site. (F) XDM was trimmed and rehydrated with sterile saline, and ASG was harvested. (G) The ASG was secured apically using single interrupted sutures. (H) Both XDM and ASG were secured with deep periosteal internal horizontal mattress sutures. (I) The 12-month follow-up.

3.5. Postoperative protocol

A standardised post-surgical protocol was implemented following surgical intervention to promote optimal wound healing, minimize complications, and ensure graft stability. Patients were instructed to avoid mechanical plaque removal at the surgical site for the first two weeks to prevent trauma to the healing tissue. Instead, chemical plaque control was prescribed by using a 0.12% chlorhexidine + 0.05% cetylpyridinium chloride mouth rinse (Paroex, GUM Sunstar, Etoy, Switzerland), to be applied twice daily. To prevent infection, patients received a one-week course of 250 mg amoxicillin + 125 mg clavulanic acid (Augmentin 375, GlaxoSmithKline, Brentford, UK) three times daily. Postoperative pain management was tailored to individual patient needs, with diclofenac-potassium 50 mg (Cataflam 50, Novartis, Basel, Switzerland) prescribed as necessary. Follow-up assessments were conducted at 1 and 2 weeks, and subsequently at 6 and 12 months in the first study, in which XDM was used alone. In the second study (ASG+XDM), follow-ups were carried out at 1 and 2 weeks, and at 1, 3, 6, 9, and 12 months to evaluate healing progression, perform plaque control, and ensure stable soft tissue integration. Sutures were removed after 14 days.

3.6. Statistical analyses

All statistical analyses were performed on a patient level to ensure data independence and reduce potential bias introduced by site clustering. Specifically, in cases where multiple implant sites were treated in the same patient, site-level measurements were averaged to yield a single representative value per patient for each outcome variable. This approach allowed for standardised and consistent analysis across the study population.

In the first study, which evaluated the use of XDM alone in both the maxilla and mandible, descriptive statistics were computed for each variable, including the mean, range, and standard deviation (SD). To assess statistical significance, Student's *t*-tests (p-value < 0.05) were applied. Paired *t*-tests were used to compare PIKM-W values within each arch across different time points, while unpaired *t*-tests were used to assess differences between the maxilla and mandible.

In the second study, which investigated the combined use of ASG and XDM in the posterior mandible, the analysis included a broader statistical framework. Descriptive statistics were calculated for all study variables, including the mean, SD, minimum,

maximum, and median. The Shapiro–Wilk test was used to assess the normality of data distributions. As all variables met the parametric assumptions, a repeated-measures ANOVA was used to compare PIKM-W and PIKM-T across all the follow-up points (baseline, 1 month, 3 months, 6 months, 9 months, and 12 months).

In addition to p-values, effect sizes were reported by using partial eta-squared (η^2_p) and 95% confidence intervals (CIs) to assess the magnitude and clinical relevance of the observed changes. This approach enhances the interpretability of findings by moving beyond statistical significance to consider the strength of the observed effects. For a more focused analysis of mid- to long-term remodelling, paired sample t-tests were performed to compare differences between the 6-month and 12-month follow-up values. Effect sizes (Cohen's d or η^2_p, as appropriate) and corresponding 95% CIs were also calculated for these pairwise comparisons. This enables a nuanced interpretation of whether tissue changes plateaued or continued beyond the initial healing phase.

All statistical computations were conducted using IBM SPSS Statistics software (Version 26.0; IBM Corp., Armonk, NY, USA). Statistical significance was set at a two-tailed α level of $p < 0.05$.

The sample sizes were determined using an online sample size calculator for equivalence testing (www.statstodo.com), based on the following parameters: two-tailed $\alpha = 0.05$, power = 0.80, estimated standard deviation = 2.0 mm, and a minimum clinically relevant difference (tolerance) = 0.5 mm in PIKM-W. These parameters yielded a required sample size of 12 participants per group. No dropouts occurred during the study period; therefore, the initially calculated sample size was fully retained for final analysis.

Given the exploratory nature of both studies and the absence of prior long-term data specific to these techniques, the selected sample sizes were considered adequate to detect significant intra-subject changes over time. Post hoc analysis confirmed sufficient statistical power (partial $\eta^2 > 0.8$ for primary outcomes), validating the appropriateness of the sample size in each arm of the study.

4. RESULTS

4.1. XDM alone on the maxilla and mandible

To participate, all patients were required to meet all inclusion criteria and none of the exclusion criteria, as outlined below. Following eligibility screening, a total of 12 patients were enrolled for XDM-alone treatment. In this group, 12 maxillary and 12 mandibular implant sites were analysed separately. No patient dropouts occurred during the 12-month follow-up, and all sites were included in the final analysis.

4.1.1 Patient Demographics

A total of 24 patients (8 males and 16 females; mean age 56.9 ± 12.3 years, range 33–75) were enrolled in this prospective case series. The augmentation procedures were evenly split between maxillary and mandibular implant sites (12 cases each). Regarding implant location, maxillary grafts were placed at three premolar and nine molar sites, while mandibular grafts involved four premolar and eight molar sites. There were no complications or adverse events during the 12-month follow-up period.

4.1.2 Primary Outcome (Changes in PIKM-W)

By 6 months post-surgery, the PIKM-W had increased significantly in both arches compared to baseline (Figure 6). In maxillary sites, mean PIKM-W increased from 0.42 ± 0.47 mm to 3.17 ± 1.21 mm at 6 months ($p < 0.001$). Similarly, mandibular sites increased from 0.29 ± 0.45 mm to 1.58 ± 1.44 mm over the same period ($p < 0.05$). At the 12-month follow-up, some shrinkage of the augmented tissue was observed. The mean PIKM-W was 2.36 ± 1.34 mm in the maxilla and 1.08 ± 1.07 mm in the mandible; both values remained significantly higher than their respective baselines ($p < 0.05$). However, a modest but significant decrease in PIKM-W occurred from 6 to 12 months in both jaws (maxilla: ~0.8 mm reduction, $p = 0.009$; mandible: ~0.5 mm reduction, $p = 0.03$), indicating some late contraction of the initially achieved width (Tables 1 and 2). The corresponding clinical appearances at the 12-month follow-up are presented in Figure 7 and Figure 8.

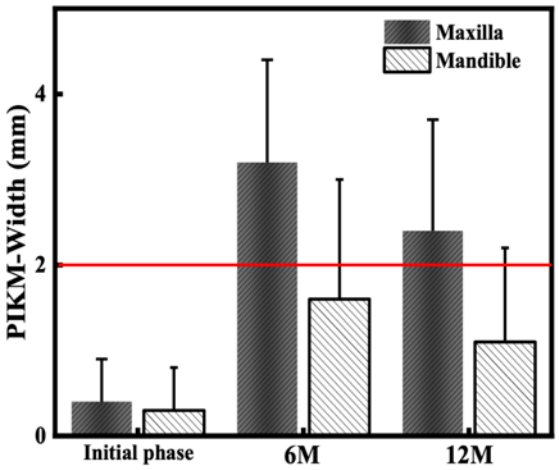

Figure 6. PIKM-W changes in the maxilla and mandible. The red line shows the minimum required width of 2 mm.

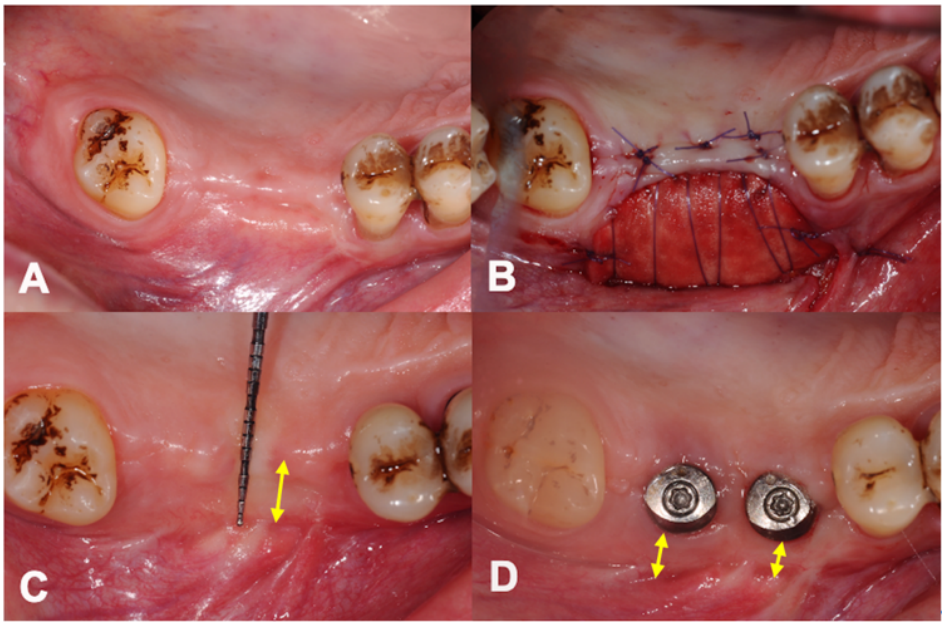

Figure 7. Treatment stages in the maxilla, (A) Lack of sufficient keratinised mucosa preoperatively. (B) Immediate view after surgery. (C) 6-month follow-up. (D) 12-month follow-up. Yellow two-way arrows indicate the measured buccal width dimensions of the newly formed PIKM. This figure is reprinted from: Horváth A, Windisch P, Palkovics D, Li X. Novel Technique to Reconstruct Peri-Implant Keratinised Mucosa Width Using Xenogeneic Dermal Matrix: A Clinical Case Series. Dent J. 2024;12(3):43. https://doi.org/10.3390/dj12030043 © 2024 by the authors. Licensed under CC BY 4.0.

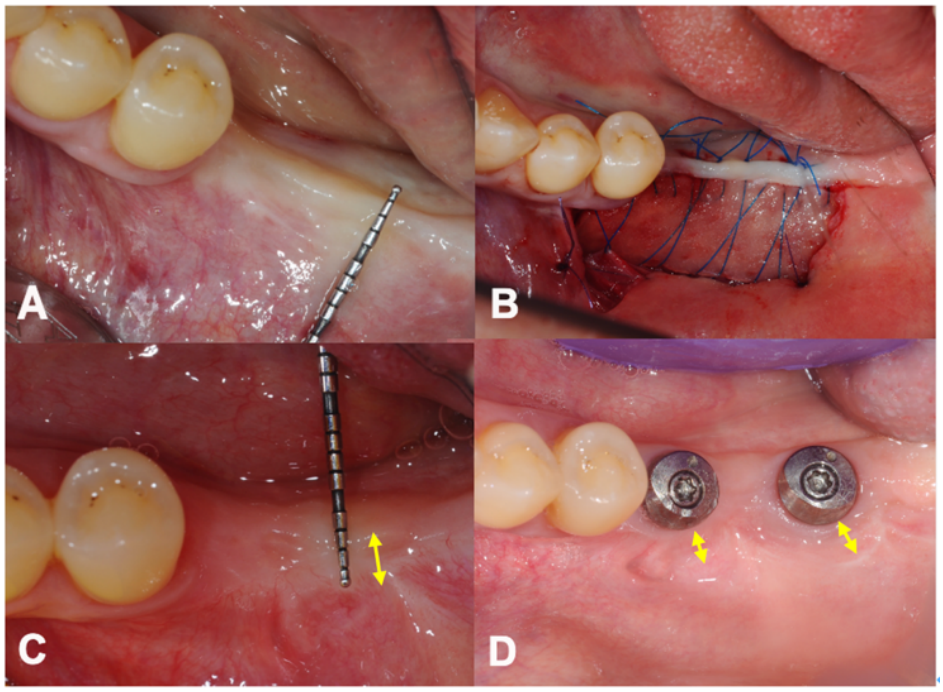

Figure 8. Treatment stages in the mandible, (A) Lack of sufficient keratinised mucosa preoperatively. (B) Immediate view after surgery. (C) 6-month follow-up. (D) 12-month follow-up. Yellow two-way arrows indicate the measured buccal width dimensions of the newly formed PIKM. This figure is reprinted from: Horváth A, Windisch P, Palkovics D, Li X. Novel Technique to Reconstruct Peri-Implant Keratinised Mucosa Width Using Xenogeneic Dermal Matrix: A Clinical Case Series. Dent J. 2024;12(3):43. https://doi.org/10.3390/dj12030043 © 2024 by the authors. Licensed under CC BY 4.0.

Table 1. Changes of PIKM-W in the maxilla (mm).

Time	Mean	SD	P value
Initial	0.42	0.47	
6-month	3.17	1.21	0.00002
Difference	2.36	1.34	
Initial	0.42	0.47	
12-month	2.36	1.34	0.00035
Difference	1.94	1.37	
6-month	3.17	1.21	0.009
12-month	2.36	1.34	
Difference	0.81	0.09	

Table 2. Changes of PIKM-W in the mandible (mm).

Time	Mean	SD	P value
Initial	0.29	0.45	
6-month	1.58	1.44	0.010
Difference	1.29	0.70	
Initial	0.29	0.45	
12-month	1.08	1.07	0.023
Difference	0.79	0.44	
6-month	1.58	1.44	
12-month	1.08	1.07	0.033
Difference	0.50	0.27	

4.1.3 Secondary Outcome (Shrinkage of the Graft)

The XDM graft was trimmed to match the dimensions of the recipient site, with an average width of 9.75 ± 0.62 mm in the maxilla and 8.58 ± 1.16 mm in the mandible. By the 6-month evaluation, the xenogeneic dermal matrix graft had undergone substantial dimensional shrinkage in both arches. The graft width had decreased by 67.7% ± 11.8% in the maxilla and 81.6% ± 16.6% in the mandible at 6 months. This contraction progressed further by 12 months, reaching a total shrinkage of 75.9% ± 13.9% in the maxillary sites and 87.4% ± 12.3% in the mandibular sites. The difference between the two jaws was statistically significant, with the mandible exhibiting a higher degree of graft contraction than the maxilla at both time points (inter-arch comparison, $p < 0.05$).

4.2. ASG+XDM in the mandible

Following eligibility screening, an additional 12 posterior mandibular sites were treated with the combined ASG + XDM protocol. No dropouts occurred, and all sites completed the 12-month follow-up.

4.2.1 Patient Demographics

Twelve patients (11 females, one male; mean age 59.4 years, range 51–70) comprised the study cohort. All patients were treated with a combined approach by using an ASG plus an XDM to augment the PIKM in the posterior mandible. There were no complications or adverse events during the 12-month follow-up period.

4.2.2 Primary Outcome (Changes in PIKM-W)

PIKM-W Changes Over Time: The combined graft technique remarkably increased keratinised mucosa width, followed by gradual remodelling over one year (Figure 9). At baseline, the mean PIKM-W was 0.39 ± 0.40 mm. Immediately after surgery, the mean new soft tissue width expanded to 8.07 ± 1.43 mm. Thereafter, the augmented mucosa underwent progressive contraction. By 1-month post-op, mean PIKM-W had diminished to 5.38 ± 0.93 mm; at 3 months, it was 5.16 ± 0.95 mm. The reduction in width showed in the subsequent intervals: at 6 months, mean PIKM-W was 4.93 ± 0.98 mm, and by 12 months, it stabilised at 4.58 ± 1.28 mm (Table 3). Thus, after an initial post-surgical peak, the PIKM-W stabilised between 6 and 12 months, showing a sustained net gain of roughly 4 mm in keratinised tissue width from baseline to one year. The repeated-measures ANOVA revealed a statistically significant change in PIKM-W across the different time points (F (6, 66) = 96.86, $p < 0.0001$), indicating a robust temporal effect. The effect size was exceptionally large, with a partial eta squared (η^2_p) of 0.90 (95% CI: [0.76, 0.94]), reflecting a substantial magnitude of change over time. The 6-month- and 12-month follow-up measurements were compared to assess late-phase stability. This analysis demonstrated no statistically significant difference between these two time points (p = 0.0644), suggesting that the grafted tissue had stabilised mainly by the 6 months (Table 4).

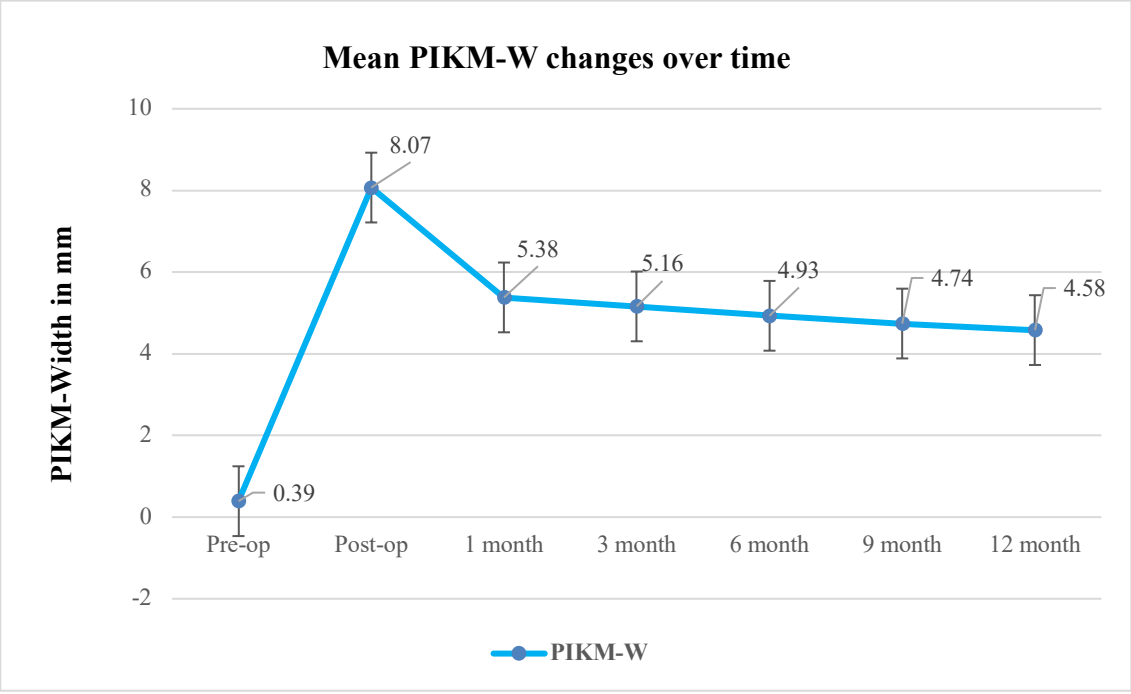

Figure 9. Twelve-month follow-up on PIKM-W changes following augmentation.

Table 3. PIKM-W changes over time (mm).

	Baseline	Postop	1M	3M	6M	9 M	12M
Mean	0.39	8.07	5.38	5.16	4.93	4.74	4.58
St. Dev.[1]	0.40	1.43	0.93	0.95	0.98	1.11	1.28
Min.	0.00	5.00	4.00	3.70	3.50	3.00	6.70
Max.	1.00	10.00	7.00	6.70	6.70	3.00	7.00
Median	0.40	8.15	5.00	5.00	4.85	5.00	4.50
p-value[2]	F (6, 66) = 96.86; p<0.0001						
[1]Standard deviation							
[2]Repeated measures ANOVA							

M = month

Table 4. Differences in PIKM-W measured over time (mm).

Difference(Δ)	Patients (n=12)		
	Δ	SD	*p*-value
Preop-1M	4.98	1.05	< 0.0001
Preop-3M	4.77	1.03	< 0.0001
Preop-6M	4.53	1.11	< 0.0001
Preop-9M	4.35	1.33	< 0.0001
Preop-12M	4.19	1.45	< 0.0001

M = month

4.2.3 Secondary Outcomes (PIKM-T and Graft Remodelling)

Changes in PIKM-T: The PIKM-T showed a significant improvement following the combined graft procedure (Figure 10). Mean PIKM-T increased from 1.36 ± 0.43 mm to 2.88 ± 0.80 mm at 6 months and was 2.83 ± 0.65 mm at 12 months. A repeated-measures ANOVA demonstrated a significant change in PIKM-T over time ($F(5,54) = 12.83$, $p < 0.0001$), corresponding to a large effect size ($\eta^2_p = 0.44$, 95% CI: [0.34, 0.54]). The lack of a statistically significant difference in PIKM-T between 1 and 12 months was not statistically significant ($p = 0.91$) (Table 5).

Graft Remodelling (Shrinkage/Contraction): The ASG+XDM underwent expected remodelling, with most dimensional changes occurring in the early healing phase. By the 3-month follow-up, the graft's width had decreased by 36.5% ± 14.3% relative to its immediate post-operative dimension. Contraction progressed slightly to 39.2% ± 14.1% at 6 months and reached 42.2% ± 16.8% by 12 months (Figure 11, Table 6). Repeated-measures ANOVA revealed a significant overall change in graft dimensions over time (p

< 0.0001), while the intra-group comparison between 6 and 12 months did not reach statistical significance (p = 0.06), confirming late-phase volumetric stability.

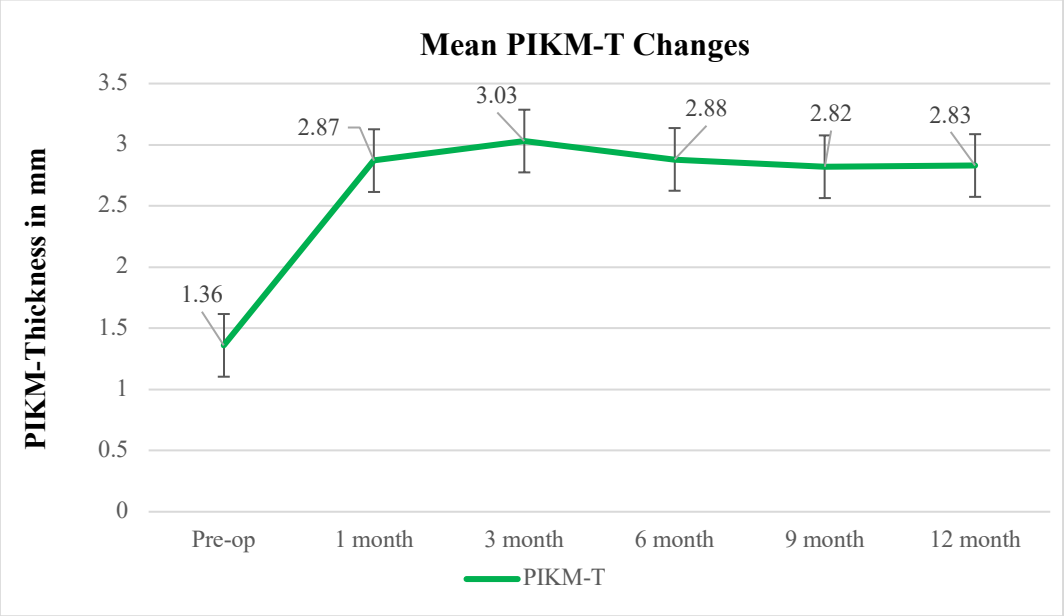

Figure 10. Overall changes in the PIKM-T at 12 months.

Table 5. PIKM-T changes over time (mm).

	Baseline	1 month	3 months	6 months	9 months	12 months
Mean	1.36	2.87	3.03	2.88	2.82	2.83
St. Dev.[1]	0.43	0.82	0.74	0.80	0.59	0.65
Min.	1.00	2.00	2.00	1.50	2.00	2.00
Max.	2.00	5.00	4.00	4.00	4.00	4.00
Median	1.15	2.85	3.00	3.00	3.00	2.75
p-value[2]	F (5, 54) = 12.83, p<0.0001					

[1]Standard deviation
[2]Repeated measures ANOVA

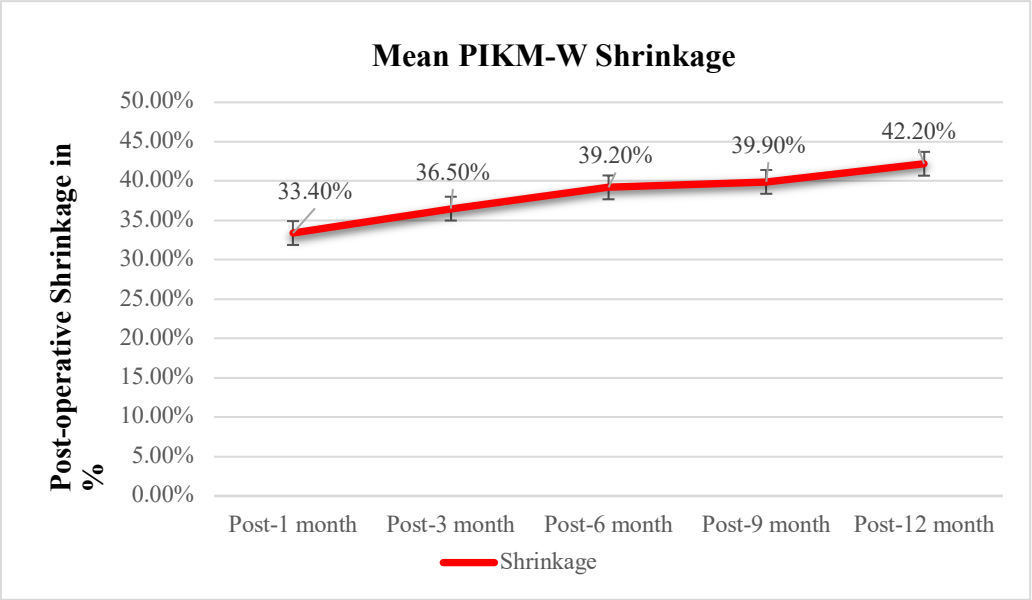

Figure 11. Postoperative progression of PIKM-W shrinkage.

Table 6. Graft contraction over time following surgical augmentation (%).

PIKM-W	Postop-1M	Postop-3M	Postop-6M	Postop-9M	Postop-12M
Mean	33.4%	36.5%	39.2%	39.9%	42.2%
SD	13.3%	14.3%	14.1%	16.0%	16.8%
P	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

M = month

4.3. Summary of Results

The study demonstrated significant increases in PIKM-W following augmentation with XDM. In the maxilla, mean PIKM-W increased and remained stable at 12 months, while in the mandible, contraction rates were notably higher. The incorporation of an ASG in combination with XDM in the posterior mandible significantly enhanced the dimensional stability of the augmented soft tissues, leading to a lower overall contraction rate and improved long-term maintenance of PIKM compared to XDM monotherapy.

All predefined hypotheses were confirmed:

H1: XDM and the surgical protocols were safe, with no adverse events.

H2: Significant PIKM-W gains were observed in both maxilla and mandible at 12 months.

H3: The ASG+XDM combination improved soft tissue stability and reduced contraction in the posterior mandible.

5. DISCUSSION

This study evaluated the clinical efficacy of xenogeneic dermal matrix for peri-implant keratinised tissue widening in both the maxilla and mandible, assessing its performance as a monotherapy and in combination with a narrow autogenous strip graft. The results demonstrated that while XDM alone is a viable approach for increasing PIKM-W in the maxilla, its application in the mandible is significantly limited due to higher contraction rates and anatomical constraints. In response to these limitations, the ASG+XDM combination was introduced, yielding superior outcomes in the mandible, achieving a stable and clinically sufficient band of keratinised mucosa over the 12-month observation period.

Clinical Significance of XDM Alone in the Maxilla

The first part of our investigation focused on the clinical efficacy of using XDM alone for PIKM-W widening in both the maxilla and mandible. In maxillary cases, the results were encouraging and clinically relevant. A mean increase from 0.42 ± 0.47 mm to 2.36 ± 1.34 mm was recorded over 12 months, achieving the clinically significant threshold of 2 mm (Afrashtehfar et al., 2023; Mahardawi et al., 2023; Roccuzzo et al., 2016; Wennström & Derks, 2012). These findings suggest that XDM can be considered a viable alternative to autogenous grafts in the upper jaw for achieving acceptable functional results with significantly less morbidity (Horváth et al., 2024).

The higher success rate in the maxilla can be attributed to several anatomical and biomechanical advantages: (1) greater vestibular depth, allowing for more stable flap apical positioning and less muscular interference; (2) reduced compressive and tensile forces from buccal musculature compared to the mandible; (3) better vascularisation due to the more favourable soft tissue architecture (Blasi et al., 2022; Buvinic et al., 2020; Shahbazi et al., 2021). Additionally, the maxillary keratinised mucosa tends to be thicker and more resilient, facilitating successful incorporation of graft materials undergoing secondary intention healing (Kim et al., 2025).

From a biomaterial perspective, the present XDM (mucoderm®, Botiss, Zossen, Germany) possesses a dense, acellular collagen dermal matrix architecture that promotes fibroblast migration, angiogenesis, and epithelialisation over time (Blatt et al., 2020; Papi & Pompa, 2018). These biological properties, combined with adequate mechanical stabilisation in the maxilla, result in reduced shrinkage (75.9 ± 13.9% at 12 months),

slower resorption, and more favourable clinical stability. This is consistent with previous research by Lorenzo et al. and Sanz et al., who reported comparable improvements in PIKM-W by using xenogeneic collagen-based matrices in maxillary sites (Lorenzo et al., 2012; Sanz et al., 2009).

While ECTG remains the gold standard, its use is often limited by significant donor site morbidity, bleeding, postoperative discomfort, and aesthetic mismatch (Agudio et al., 2008; Anand et al., 2012; M. Bassetti et al., 2015a; R. G. Bassetti et al., 2016; Rokn et al., 2020). Our study supports the notion that in the maxilla, especially in non-aesthetic zones such as posterior molars, XDM alone provides a predictable, safe, and patient-friendly option for soft tissue enhancement (Horváth et al., 2024).

Limitations of XDM Alone in the Mandible

In our first prospective case series, we aimed to assess the efficacy of a porcine-derived xenogeneic dermal matrix in augmenting PIKM-W via a split-thickness technique and secondary wound healing in both the maxilla and mandible. While the outcomes in the maxilla were promising, with an average gain from 0.42 ± 0.47 mm to 2.36 ± 1.34 mm at 12 months, the results in the mandible were less predictable and clinically inadequate. In mandibular sites, the mean PIKM-W increased from 0.29 ± 0.45 mm to 1.08 ± 1.07 mm at 12 months, failing to meet the generally accepted minimum threshold of 2 mm.

One plausible explanation for the suboptimal performance in the mandible is anatomical: mandibular posterior regions typically present a shallower vestibule and higher coronal adhesion of the buccinator and mentalis muscles, leading to a stronger muscular pull and mechanical stress on graft materials (Cairo et al., 2008; Grischke et al., 2019; Schrott et al., 2009). The reduced vascular supply and mobile mucosa in the posterior mandible further compromise the integration and revascularisation of grafts, particularly those dependent on secondary healing (Thoma et al., 2014). Our findings are aligned with prior literature by Schmitt et al. and Lorenzo et al., who also observed reduced graft stability and higher shrinkage in the mandible compared to the maxilla when using collagen-based matrices (Lorenzo et al., 2012; Schmitt et al., 2016).

The observed graft shrinkage further validates this limitation. Our study demonstrated a mean contraction of 87.4 ± 12.3% in mandibular sites treated with XDM alone at 12 months, compared to 75.9 ± 13.9% in the maxilla. Although both rates reflect

the inherent remodelling associated with xenogeneic matrices, the extent of shrinkage in the mandible renders XDM-alone insufficient as a standalone solution for posterior cases. These data underscore the need for adjunctive strategies to improve soft tissue stability in challenging anatomical areas.

Rationale and Efficacy of Combining ASG with XDM

Recognising the limitations of XDM alone, particularly in the posterior mandible, we utilised a novel combined technique integrating a narrow autogenous strip graft with XDM, placed via an APPTF. The ASG was harvested from the hard palate with a minimal donor site morbidity, as previously advocated by Han and Takei in their seminal description of the "strip graft" approach (Han et al., 1995). The strip is a lot narrower than the gold standard ECTG, which could be the explanation for reduced donor site morbidity. By placing the ASG apically and the XDM coronally, we aimed to leverage the mechanical and biological benefits of autogenous tissue while preserving the aesthetic and morbidity-related advantages of xenogeneic materials (Li X et al., 2025).

Our clinical outcomes from this combined approach clearly outperformed the XDM-alone group in all parameters. At 12 months, the mean PIKM-W reached 4.58 ± 1.28 mm, compared to only 1.08 mm in the XDM-alone mandibular sites. The PIKM-T also increased significantly from 1.36 ± 0.43 mm to 2.83 ± 0.65 mm. Furthermore, shrinkage was reduced considerably—42.2 ± 16.8%—less than half of that observed with XDM alone (87.4 ± 12.3%). These findings confirm that ASG plays a critical stabilising role, both mechanically and biologically (Li X et al., 2025).

Similar approaches have recently been investigated with encouraging outcomes. Farooqui et al. reported a significant gain in PIKM-W by using a combination of ASG and XCM in a randomised controlled trial, achieving an average increase of 4.23 ± 0.73 mm at 6 months in the mandible (Farooqui et al., 2023). Likewise, Huang et al. (2024) demonstrated that the combined use of an ASG and XCM yielded a mean gain of 3.3 ± 1.6 mm in keratinised mucosa width at 6 months (Huang et al., 2024). Although these studies had shorter follow-up durations, their results are consistent with our 12-month outcomes. They reinforce the concept that autogenous grafts enhance the mechanical stability and biological integration of xenogeneic materials, particularly in challenging anatomical sites such as the posterior mandible.

The mechanical advantage is derived from the apically positioned ASG acting as a "scaffold anchor," resisting muscle pull and micromovement, while the XDM ensures coronal coverage and tissue bulk (Huang et al., 2024; Li X et al., 2025; Urban et al., 2020, 2025). Biologically, autogenous grafts promote rapid revascularisation and cellular migration due to the presence of viable fibroblasts and extracellular matrix proteins. Urban et al. previously demonstrated similar success by using ASG + XCM in the anterior maxilla. Still, their technique had not been tested in the posterior mandible, where anatomical demands differ considerably (Urban et al., 2015, 2019, 2020, 2025).

Notably, the stabilisation of PIKM-W values between 6 and 12 months ($p = 0.0644$) suggests a steady state in graft remodelling, indicating that most shrinkage occurs within the early healing phase. This temporal dynamic aligns with previous studies on graft maturation and supports the reliability of our combined technique for long-term stability (Sanz et al., 2009; Thoma et al., 2009).

Implications for Clinical Practice

The comparative results of the two approaches in our thesis strongly indicate that treatment selection for PIKM widening must be anatomy-driven. In regions such as the anterior maxilla, where muscular stress is minimal and aesthetics is paramount, XDM alone may be sufficient. However, in high-stress zones like the posterior mandible, autogenous reinforcement via ASG is necessary to achieve predictable and stable PIKM-W.

The ASG+XDM technique offers significant advantages over traditional epithelialised connective tissue graft from a patient morbidity perspective. While ECTG remains the gold standard due to its minimal contraction and robust histological outcomes, it involves extensive palatal harvesting, increased risk of excessive bleeding and postoperative pain, as well as potential aesthetic mismatch (M. Bassetti et al., 2015b; Sanz et al., 2009; Thoma et al., 2009; Urban et al., 2015, 2020). In contrast, our ASG harvest was minimally invasive (2–3 mm wide), resulting in rapid donor site healing and acceptable patient postoperative morbidity.

Moreover, the described technique involves a split-thickness flap preparation without requiring extensive flap mobilisation or coronal advancement. The apical positioning of the flap, combined with the sequential placement of the ASG and XDM, ensures graft stability through mechanical compression without excessive flap tension.

Notably, our suturing protocol, by employing deep periosteal internal horizontal mattress sutures in addition to standard single interrupted fixation, was designed to provide firm and passive stabilisation of both graft components directly onto the periosteum. This critical step, rarely detailed in previous studies, enhances immobilisation and may contribute to improved revascularisation, integration that resulted in uneventful healing and no maceration or sloughing of the graft. The overall flap design preserves vascular integrity while minimising surgical trauma. The favourable soft tissue outcomes, reduced shrinkage, and acceptable donor site morbidity suggest that this combined approach, with its defined and reproducible suturing strategy, offers a clinically applicable and biologically robust method for PIKM-W widening in the posterior mandible.

Clinical Implications of XDM Shrinkage and the Rationale for Graft Oversizing

One of the key observations from this study is the quantification of long-term graft contraction and its implications for clinical technique. Despite achieving favourable clinical outcomes in both arches, the results confirmed that XDM, particularly when used alone, undergoes substantial volumetric shrinkage over time. The mandibular contraction rate approached 87.4%, compared to approximately 75.9% in the maxilla, highlighting an anatomical disparity in remodelling Behaviour. This reinforces the clinical necessity of oversizing XDM grafts at the time of placement to ensure a sufficient final band of keratinised mucosa. Due to the minimum size of the present xenograft as it is available in the market is 15x20 mm, therefore oversizing is not an issue at all, since the 15x20 box has already been opened.

To illustrate, consider a case in the maxilla where the baseline PIKM-W is 1 mm, and the desired outcome is 3 mm. A 2 mm gain is therefore required. Considering the observed 75.9% shrinkage rate, the graft must be oversized significantly. Applying a simple predictive formula—target gain ÷ (1 – contraction rate)—the required initial graft dimension would be 2 mm ÷ (1 – 0.76) ≈ 8.3 mm. In other words, to achieve a net increase of 2 mm after remodelling, at least 8.3 mm of grafted width must be placed initially. This example highlights the clinical importance of tailoring graft dimensions to contraction behaviour, particularly in planning for predictable outcomes in site-specific augmentation.

While the principle of oversizing has not been explicitly addressed in previous literature, this study is among the first to provide quantitative, arch-specific evidence supporting the practice. Notably, the combined ASG+XDM approach exhibited markedly

lower shrinkage (42.2%), suggesting that proactive oversizing and strategic reinforcement with autogenous tissue can improve graft stability. These insights contribute to developing standardised clinical guidelines that tailor graft dimensions and techniques to anatomical site-specific contraction risks, ultimately enhancing predictability in peri-implant soft tissue augmentation.

Limitations and Future Directions

Despite the promising results, our studies are not without limitations. First, the sample size remains relatively small, particularly in the case series, limiting generalizability. Second, although we followed patients for 12 months, longer-term data beyond one year would be valuable to assess proper tissue stability. Third, we did not include histological or patient-reported outcomes such as pain, satisfaction, or aesthetic perception, which are essential for comprehensive evaluation.

Further investigations with larger sample sizes and longer follow-up are warranted to validate these dimensioning strategies and evaluate their impact on long-term peri-implant tissue maintenance. In addition, randomised controlled trials comparing XDM with the gold standard ECTG in the maxilla and ASG + XDM with ECTG in the mandible, incorporating broader clinical and patient-centred outcomes should be carried out as next step. Furthermore, volumetric assessments using ultrasound imaging may enhance our understanding of graft remodelling dynamics (Hamdy et al., 2024; Tavelli et al., 2025).

6. CONCLUSIONS

This thesis work demonstrated that peri-implant soft tissue widening using XDM either as a monotherapy in the maxilla or in combination with a narrow ASG in the mandible—is both clinically safe and effective for increasing the width of keratinised mucosa around dental implants. Both case series showed significant PIKM-W gains, consistently achieving or surpassing the clinically recommended 2 mm width associated with improved peri-implant health. In the maxilla, XDM alone provided stable tissue augmentation, with mean gains exceeding 3 mm at 6 months and remaining above 2 mm at 12 months. In the mandible, where contraction was more pronounced, the ASG+XDM combination achieved stable PIKM-W values of 4–5 mm at 12 months. No complications or adverse events were observed, confirming procedural safety. Furthermore, the addition of ASG contributed not only to improved width stability but also to increased mucosal thickness, resulting in a more robust and stable peri-implant soft tissue phenotype. Taken together, the overall outcome of these investigations supports the use of XDM-based grafting techniques as viable, less invasive alternatives to traditional autogenous gingival grafts for enhancing peri-implant soft tissue contours. However, given the case series design of these studies, these findings should be interpreted within the limitations of a case series design.

<u>Corroborating findings:</u>

1. **Arch-Specific Performance of XDM in the Maxilla:**

   The study confirmed that XDM alone can effectively increase PIKM-W in the maxilla, maintaining values above 2 mm at 12 months.

2. **Clinical Value of Autogenous Reinforcement:**
   Consistent with prior findings, the combination of a narrow autogenous strip graft with a xenograft improved soft tissue stability in the mandible. This confirms the mechanical and biological benefits of autogenous reinforcement in anatomically challenging sites.
3. **Early Shrinkage and Importance of Graft Oversizing:**
   The study supports the established principle that initial graft oversizing is necessary

to compensate for predictable early remodelling and ensure long-term dimensional stability.

New findings:

1. **The investigated XDM material and refined surgical technique statistically increase the PIKM-W in the maxilla and in the mandible after 12 months, with a statistically significant difference between the two arches.**
2. **XDM presents with a significant postoperative shrinkage in the mandible compared to the maxilla, which is statistically significant. The shrinkage continues even after 6 months, up to 12 months. Therefore, the investigated material and methods seem to be predictable in the maxilla and unpredictable in the mandible.**
3. **ASG+XDM serves as a predictable method for reestablishing the PIKM-W in the posterior mandible.**
4. **The width shrinkage occurs within the first 6 months; changes between 6 and 12 months are not statistically significant.**
5. **The investigated material and refined surgical technique (ASG+XDM) result in an increase in soft tissue thickness by 1 month. After 1 month, it remains stable for 12 months.**

7. SUMMARY

Peri-implant soft tissue augmentation is critical for maintaining long-term peri-implant health, preventing mucosal recession, and ensuring optimal functional and aesthetic outcomes. This doctoral research assessed the clinical effectiveness and dimensional stability of XDM-based techniques, used alone and in combination with a narrow ASG, for increasing PIKM-W.

The first study evaluated XDM alone in both the maxilla and mandible. XDM provided stable and clinically sufficient PIKM-W (>2 mm) in the maxilla at 12 months. However, mandibular applications showed marked contraction (87.4%) and variable outcomes, highlighting anatomical differences in graft behaviour and the necessity for region-specific strategies.

To address this drawback, a second study investigated the ASG+XDM technique in the mandible. This combination significantly enhanced mucosal stability, achieving a mean PIKM-W of 4.58 mm at 12 months with improved resistance to shrinkage. Importantly, PIKM-T in the mandible increased significantly from 1.36 ± 0.43 mm at baseline to 2.87 ± 0.82 mm at 1 month, remaining stable at 12 months (2.83 ± 0.65 mm, $p = 0.91$), indicating rapid integration and sustained volumetric stability of the ASG+XDM construct.

One key finding was the time-dependent remodelling pattern, with most dimensional changes occurring within the first three months postoperatively, followed by stabilisation from 6 to 12 months. This emphasises the need for extended follow-up in augmentation studies to avoid underestimating long-term outcomes. Importantly, the research quantified graft shrinkage across sites, reinforcing the clinical need for oversizing grafts at placement. The data support tailoring graft dimensions to anatomical location to achieve predictable results.

Clinically, this thesis work validates the use of XDM as a reliable alternative to autogenous grafts in the maxilla while supporting the ASG+XDM technique in the posterior mandible to ensure long-term peri-implant soft tissue stability. These findings inform evidence-based, anatomy-driven surgical protocols that enhance outcomes and reduce patient morbidity.

8. ÖSSZEFOGLALÁS

A periimplantáris lágyrész augmentáció kulcsszerepet játszik a hosszú távú periimplantáris egészség fenntartásában, a mukózális recesszió megelőzésében, valamint a megfelelő funkcionális és esztétikai eredmények elérésében. Jelen doktori kutatás az XDM technikák klinikai hatékonyságát és dimenzionális stabilitását vizsgálta – önállóan és keskeny ASG kombinálva – a PIKM-W növelése céljából.

Az első vizsgálat során az XDM monoterápiát alkalmaztuk a felső és az alsó állcsonton. A maxillán az XDM 12 hónap után stabil és megfelelő PIKM-W-t biztosított (>2 mm), míg a mandibulán jelentős zsugorodás (87.4%) és nagyobb variabilitás voltak megfigyelhető, alátámasztva az anatómiailag eltérő megközelítés szükségességét.

A második vizsgálatban az ASG+XDM kombináció a mandibulában alkalmazva szignifikánsan javította a szövetstabilitást, 12 hónap után 4,6 mm átlagos PIKM-W-t eredményezve. A periimplantáris keratinizált mukóza vastagsága (PIKM-T) is szignifikánsan nőtt – 1,36 ± 0,43 mm-ről 2,87 ± 0,82 mm-re 1 hónap alatt –, és 12 hónapig stabil maradt (2,83 ± 0,65 mm; p = 0,91), jelezve a kombinált graft gyors integrációját és tartós térfogatstabilitását.

A legtöbb dimenzionális változás az első három hónapban történt, majd 6–12 hónap között stabilizálódott, kiemelve a hosszú távú utánkövetés szükségességét. A graft zsugorodás mértékének kvantifikálása megerősítette a beültetéskori túlméretezés klinikai fontosságát, és alátámasztotta az anatómiailag célzott graftméretezés szükségességét a kiszámítható eredmények eléréséhez, amihez pontos útmutatást adtunk.

Összességében a dolgozat igazolta az XDM alkalmazását megbízható alternatívaként a felső állcsonton, és az ASG+XDM technika előnyét a mandibula poszterior régiójában, hosszú távú szöveti stabilitás biztosítása érdekében. Az eredmények hozzájárulnak az evidencia-alapú, anatómiailag irányított sebészi protokollok kialakításához, javítva a kiszámíthatóságot és egyben csökkentve a páciens morbiditását.

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10. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

10.1. Publications related to the theme of the PhD thesis

Li X, Palkovics D, Windisch P, Perić Kačarević Ž, Horváth A. A Combined Approach Using Strip Grafts and Xenogenic Dermal Matrix for Peri-Implant Keratinised Mucosa Augmentation in the Mandible: A Case Series. Biomedicines. 2025; 13(4):806. (IF=3.9)

Horváth A, Windisch P, Palkovics D, Li X. Novel Technique to Reconstruct Peri-Implant Keratinised Mucosa Width Using Xenogeneic Dermal Matrix. Clinical Case Series. Dentistry Journal. 2024; 12(3):43. (IF=2.5)

10.2. Other publications by the author

Li X, Kövér K, Palkovics D, Sipos L, Windisch P, Horváth A. Peri-implant keratinized mucosa width augmentation in the maxilla: ECTG vs. xenogenic dermal matrix – a randomized clinical trial. J Clin Periodontol. 2025;52(S28):26.

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Horváth A, Li X, Hegedűs M, Windisch P. Successful augmentation of peri-implant keratinised mucosa without an autograft. Case series J Clin Periodontol 2018;45(S19):347.

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