Novel Approaches for Augmentation of Peri-implant Keratinised Mucosa

PhD Thesis

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1. INTRODUCTION

1.1. Background

Dental implants are a reliable solution for replacing missing teeth and are valued for their high survival rates and favourable functional and aesthetic outcomes. Beyond osseointegration, the long-term success of implants depends critically on the stability and health of surrounding peri-implant soft tissues, particularly the biological seal formed by bone and mucosa. Among these, the peri-implant keratinised mucosa width (PIKM-W) has been identified as a vital factor in ensuring long-term peri-implant health. The PIKM forms a barrier against microbial invasion and mechanical trauma, aiding in the prevention of inflammation and recession. Adequate PIKM-W (≥2 mm) is associated with reduced plaque accumulation, inflammation, and mucosal recession. Consensus now supports maintaining or augmenting PIKM-W around implants to preserve peri-implant tissue stability.

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

Although early studies proposed implants could succeed without keratinised mucosa, under conditions of optimal oral hygiene, accumulating clinical evidence has increasingly demonstrated that inadequate PIKM-W may lead to discomfort, plaque retention, plaque accumulation, inflammation, and peri-implant diseases. These conditions can ultimately compromise peri-implantitis, the longevity, and functional stability of dental implants.

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases categorised peri-implant pathologies into peri-implant mucositis, peri-implantitis, and soft/hard tissue deficiencies. Peri-implant mucositis is inflammation without bone loss, which refers to reversible inflammatory changes in the soft tissues surrounding implants without continuing bone loss, while peri-implantitis is characterised by progressive bone loss and deeper probing depths. PSTD, or peri-implant soft tissue dehiscence, represents a distinct form of soft tissue breakdown, commonly observed in regions with mechanical stress or a thin mucosal biotype. Epidemiological studies have reported variable prevalence rates; mucositis affects 27–63% of patients, peri-implantitis 7–47%.

The aetiopathogenesis of peri-implantitis involves multiple contributing factors,

including microbial biofilm accumulation, a history of periodontitis, tobacco use, and insufficient PIKM-W. Sufficient PIKM-W plays a critical role in minimising mechanical trauma, facilitating effective plaque control, and maintaining long-term peri-implant soft tissue stability.

1.3. Evolution of Techniques for Increasing PIKM-W

Autogenous grafts, such as epithelialised connective tissue grafts (ECTG) and free gingival grafts (FGG), remain the gold standard due to their predictability and long-term results. However, these techniques have drawbacks, including donor site morbidity, colour mismatch, and patient discomfort. In response to these limitations， alternative biomaterials have been developed, including allogeneic and xenogeneic soft tissue substitutes such as acellular dermal matrices (ADM), xenogeneic collagen matrices (XCM), and xenogeneic dermal matrices (XDM), which aim to simplify surgical protocols while minimising donor site morbidity and improving patient acceptance.

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

ADM, e.g., NovoMatrix® (BioHorizons IPH, Inc., Birmingham, AL, USA), derived from human or porcine dermis, preserves extracellular matrix integrity while eliminating cellular antigens, supporting integration, angiogenesis, and volume stability. ADM demonstrates superior mechanical stability and volume preservation compared to xenogeneic collagen matrices (XCM). However, its application remains restricted in many European countries due to ethical regulations related to human-derived tissue.

XCMs, e.g., Mucograft® (Geistlich Pharma AG, Wolhusen, Switzerland), initially demonstrated favourable short-term outcomes in PIKM-W augmentation; however, their rapid resorption and significant contraction (~67%) limit long-term stability, particularly in mechanically demanding regions.

XDMs, such as mucoderm® (Botiss, Zossen, Germany), present denser collagen architecture, allowing for slower resorption, reduced contraction, and improved long-term volumetric stability. Clinical data indicate that XDM maintains approximately 72% of augmented tissue volume at 12 months, achieving keratinised mucosa widths comparable to autogenous grafts with reduced patient morbidity. Notably, XDM exhibits superior

performance in the maxilla compared to the mandible, likely due to site-specific anatomical and vascular differences.

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

To enhance long-term stability, combined techniques incorporating autogenous strip grafts (ASG) with xenogeneic matrices have been introduced. Initially described by Han et al. and later refined by Urban et al., this approach utilises the stabilising capacity of ASG together with the regenerative scaffold properties of XCM or XDM. The ASG is positioned apically for mechanical stability, while the matrix facilitates soft tissue integration and volume preservation.

Clinical studies have demonstrated reduced contraction (~43% vs. ~67% with XCM alone) and improved aesthetic outcomes. Huang et al. reported a mean PIKM-W gain of 3.3 mm at 6 months using ASG+XCM in the posterior mandible, with minimal morbidity and high patient satisfaction. Although extensively documented for the maxilla, further investigation remains warranted for mandibular applications due to anatomical limitations such as reduced vestibular depth and muscle tension. Randomised trials specifically evaluating ASG+XDM combinations in posterior mandibular sites are still needed.

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 peri-implant soft tissue augmentation by assessing its ability to increase PIKM-W and maintain 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.

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 over a 12-month period. 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 autogenous 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.

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.

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 at the patient 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

First study (XDM alone):

Primary outcome: Change in PIKM-W, assessed using a UNC-15 periodontal probe as the distance from the mid-buccal implant margin (or mid-crestal line in edentulous sites) to the mucogingival junction (MGJ), rounded to the nearest millimetre. Measurements were performed in both the maxilla and mandible.

Secondary outcome: Graft shrinkage, calculated separately for the maxilla and mandible using the formula: [1-(PIKM-W at 6M in mm ― PIKM-W baseline in mm)/ trimmed XDM width in mm] x 100 = %.

Second study (ASG + XDM in the mandible):

Primary outcome: Change in PIKM-W, assessed using the same measurement protocol as described above.

Secondary outcomes: Graft shrinkage calculated using the same formula as for the XDM-alone study.

PIKM-T (peri-implant keratinised mucosa thickness), assessed only in the mandible, measured 2 mm apical to the mucosal margin using a needle with a rubber stopper at baseline, and at 1, 3, 6, 9, and 12 months.

All measurements were taken by a single, calibrated examiner who was not involved in the surgeries. Intra-examiner reliability was confirmed via repeated measurements on 10 non-study patients, with intra-class correlation coefficients exceeding 0.90 for both PIKM-W and PIKM-T, ensuring consistent measurement across all time points.

3.3. Presurgical procedures

All patients followed a standardised preoperative regimen to optimise peri-implant soft tissue conditions and minimise postoperative complications. Oral hygiene instructions were reinforced, and full-mouth supragingival scaling was performed to reduce microbial load and inflammation.

As part of pharmacological preparation, 400 mg ibuprofen was administered one hour before surgery for anti-inflammatory and analgesic purposes. Antibiotics were not routinely prescribed, except in cases with systemic indications.

3.4. Surgical Procedures

3.4.1 Xenogeneic Dermal Matrix (XDM) Augmentation Technique

(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) The 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

(A) A horizontal incision was performed along the MGJ, followed by two vertical supraperiosteal incisions at the mesial and distal aspects.
(B) The coronal flange of the buccal mucosal flap was immobilized to its apical portion using a continuous suturing technique.
(C) The ASG was harvested from the hard palate.
(D) A xenogenic collagen matrix strip is adapted and secured to the donor site.
(E) XDM was trimmed and rehydrated with sterile saline, and ASG was harvested.
(F) The ASG was secured apically using single interrupted sutures.
(G) Both XDM and ASG were secured with deep periosteal internal horizontal mattress sutures.

3.5. Postoperative protocol

To ensure optimal healing and graft stability, patients were advised to avoid mechanical plaque removal for two weeks. Instead, twice-daily rinsing with 0.12% chlorhexidine + 0.05% cetylpyridinium chloride mouth rinse (Paroex, GUM Sunstar, Etoy, Switzerland) was prescribed. Antibiotic prophylaxis included amoxicillin 250 mg + clavulanic acid 125 mg (Augmentin® 375, GlaxoSmithKline, Brentford, UK) three times daily for one week. Analgesia was provided as needed with diclofenac-potassium 50 mg (Cataflam® 50, Novartis, Basel, Switzerland).

Follow-ups occurred at 1 and 2 weeks, and at 6 and 12 months in the XDM-alone group. In the ASG+XDM group, additional reviews were conducted at 1, 3, 6, 9, and 12 months. Sutures were removed on day 14.

3.6. Statistical analyses

All analyses were performed on a patient-based level to ensure independence and avoid clustering bias. For patients with multiple implant sites, outcome variables were averaged per patient. Descriptive statistics (mean, standard deviation, range) were computed for all groups.

In the XDM-alone study (maxilla and mandible), to assess statistical significance, Student's *t*-tests (p-value < 0.05) were applied. Intra-group differences were evaluated using paired *t*-tests, and inter-arch comparisons were analysed with unpaired *t*-tests (α = 0.05).

In the ASG+XDM study (mandible only), data normality was confirmed using the Shapiro–Wilk test, and repeated-measures ANOVA was used to compare outcomes across all time points. Effect sizes (Cohen's d or partial η^2) and 95% confidence intervals (CI) were reported to complement p-values and assess clinical relevance. Analyses were conducted with SPSS v26.0 (IBM Corp., Armonk, NY, USA).

Sample sizes (n = 12/group) were calculated using StatsToDo (www.statstodo.com) with α = 0.05, power = 0.80, SD = 2.0 mm, and a clinically relevant difference of 0.5 mm in PIKM-W. Post hoc power analysis confirmed adequacy (partial $\eta^2 > 0.8$ for primary outcomes). No dropouts occurred during the study period; therefore, the initially calculated sample size was fully retained for final analysis.

4. RESULTS

4.1. XDM Alone in the Maxilla and Mandible

Patient Demographics:
24 patients (8 males, 16 females; mean age 56.9 ± 12.3 years) received XDM grafts, 12 in the maxilla, 12 in the mandible. No complications were reported during the 12-month follow-up.

PIKM-W Outcomes:
Both arches showed significant PIKM-W gains at 6 months (maxilla: from 0.42 ± 0.47 mm to 3.17 ± 1.21 mm; mandible: from 0.29 ± 0.45 mm to 1.58 ± 1.44 mm). At 12 months, values decreased to 2.36 ± 1.34 mm (maxilla) and 1.08 ± 1.07 mm (mandible) yet remained significantly higher than baseline ($p < 0.05$). The inter-arch difference in shrinkage was also significant ($p < 0.05$).

Graft Remodelling (Shrinkage/Contraction):
XDM contraction progressed from 67.7% (maxilla) and 81.6% (mandible) at 6 months to 75.9% and 87.4% at 12 months, respectively. Despite this, maxillary sites consistently maintained >2 mm PIKM-W, whereas mandibular results were more variable.

4.2. Combined ASG + XDM in the Mandible

Patient Demographics:
Twelve patients (11 females, one male; mean age 59.4 years) received ASG+XDM grafts in the posterior mandible. No adverse events occurred during follow-up.

PIKM-W Outcomes:
Baseline width was 0.39 ± 0.40 mm, increasing immediately post-op to 8.07 ± 1.43 mm. Shrinkage followed a gradual curve: 5.38 mm at 1 month, 5.16 mm at 3 months, 4.93 mm at 6 months, and stabilised at 4.58 ± 1.28 mm at 12 months. The changes over time were significant ($p < 0.0001$, $\eta^2_p = 0.90$), with no significant reduction from 6 to 12 months ($p = 0.0644$).

PIKM-T Outcomes:

Thickness increased from 1.36 ± 0.43 mm to 2.87 ± 0.82 mm by 1 month and remained stable through 12 months (2.83 ± 0.65 mm, $p = 0.91$), indicating rapid and sustained volumetric integration ($\eta^2_p = 0.44$).

Graft Remodelling (Shrinkage/Contraction):

Postoperative shrinkage was most pronounced in the early phase, increasing from 33.4% at 1 month to 36.5% at 3 months. Dimensional loss progressed steadily, reaching 39.2% at 6 months, 39.9% at 9 months, and 42.2% at 12 months. Repeated-measures ANOVA revealed a highly significant overall difference across time points ($p < 0.0001$). However, the intra-group comparison between 6 and 12 months did not reach statistical significance ($p = 0.06$), indicating that most remodelling occurred before the 6 months, with minimal additional shrinkage thereafter.

5. CONCLUSIONS

Corroborating findings:

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.

Publications related to the theme of the PhD thesis

1. **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)
2. 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)

Publications Not Related to the PhD thesis

1. 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.

2. Li, X. and Horváth, A. Efficacy of Augmentation Materials and Surgical Methods in Alveolar Ridge Preservation Post-Tooth Extraction. Archive of Orofacial Data Science, 2024;1(1).

3. Li X, Palkovics D, Kövér K, Windisch P, Horváth A. The results of ECTG versus XDM (Mucoderm®) in treating insufficient peri-implant keratinised mucosa in the maxilla: a randomised controlled trial. Clin Oral Implants Res. 2022;33(Suppl 24):102.

4. Li X, Kövér K, Sipos L, Windisch P, Horváth A. Clinical Efficacy of ADM (Mucoderm®) Versus ECTG to Treat Inadequate Width of Keratinised Mucosa in the Maxilla. Randomised Controlled Trial. J Dent Res.2022;101(Spec Iss C):1441.

5. Horváth A, Kövér K, Palkovics D, Windisch P, Li X. Patient-based outcomes following peri-implant keratinised mucosa widening with epithelised connective tissue grafts versus xenogenic dermal matrix combined with autogenous strip graft. Randomised clinical trial J Clin Periodontol 2022;49(S23):38.

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8. 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.