Alveolar ridge augmentation of the atrophic posterior maxilla in conjunction with implant placement. What is the most appropriate surgical approach and grafting material?

Doctoral thesis by Thomas Starch-Jensen, DDS, PhD

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Believe those who seek the truth but doubt those who say they have found it.

Andre Gide, 1952

Thomas Starch-Jensen

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Publications

This doctoral thesis is based on the following peer-reviewed papers, which will be referenced to by their Roman Numerals (I-XX).

I. **Starch-Jensen T**, Schou S. Maxillary Sinus Membrane Elevation With Simultaneous Installation of Implants Without the Use of a Graft Material: A Systematic Review. Implant Dent 2017;26(4):621-33.

II. **Starch-Jensen T**, Aludden H, Hallman M, Dahlin C, Christensen AE, Mordenfeld A. A systematic review and meta-analysis of long-term studies (five or more years) assessing maxillary sinus floor augmentation. Int J Oral Maxillofac Surg 2018;47(1):103-16.

III. Aludden H, Mordenfeld A, Hallman M, Christensen AE, **Starch-Jensen T**. Osteotome-Mediated Sinus Floor Elevation With or Without a Grafting Material: A Systematic Review and Meta-analysis of Long-term Studies (5-Years). Implant Dent 2018;27(4):488-97.

IV. **Starch-Jensen T**, Mordenfeld A, Becktor JP, Jensen SS. Maxillary Sinus Floor Augmentation With Synthetic Bone Substitutes Compared With Other Grafting Materials: A Systematic Review and Meta-analysis. Implant Dent 2018;27(3):363-74.

V. Nissen KJ, **Starch-Jensen T**. Maxillary Sinus Floor Augmentation With Autogenous Bone Graft From the Ascending Mandibular Ramus. Implant Dent 2019;28(1):46-53.

VI. **Starch-Jensen T**, Deluiz D, Duch K, Tinoco EMB. Maxillary Sinus Floor Augmentation With or Without Barrier Membrane Coverage of the Lateral Window: a Systematic Review and Meta-Analysis. J Oral Maxillofac Res 2019;10(4):e1.

VII. **Starch-Jensen T**, Deluiz D, Bruun NH, Tinoco EMB. Maxillary Sinus Floor Augmentation with Autogenous Bone Graft Alone Compared with Alternate Grafting Materials: a

Systematic Review and Meta-Analysis Focusing on Histomorphometric Outcome. J Oral Maxillofac Res 2020;11(3):e2.

VIII. **Starch-Jensen T**, Deluiz D, Vitenson J, Bruun NH, Tinoco EMB. Maxillary Sinus Floor Augmentation with Autogenous Bone Graft Compared with a Composite Grafting Material or Bone Substitute Alone: a Systematic Review and Meta-Analysis Assessing Volumetric Stability of the Grafting Material. J Oral Maxillofac Res 2021;12(1):e1.

IX. **Starch-Jensen T**, Bruun NH. Patient's perception of recovery after osteotome-mediated sinus floor elevation with Bio-Oss collagen compared with no grafting material: a randomized single-blinded controlled trial. Int J Implant Dent 2021;7(1):20.

X. **Starch-Jensen T**, Ahmad M, Bruun NH, Becktor JP. Patient's perception of recovery after maxillary sinus floor augmentation with autogenous bone graft compared with composite grafts: a single-blinded randomized controlled trial. Int J Implant Dent 2021;7(1):99.

XI. **Starch-Jensen T**, Bruun NH. Patient's perception of recovery after sinus membrane elevation and blood coagulum compared with 1:1 mixture of autogenous bone graft and deproteinized porcine bone mineral. Secondary outcomes from a single-blinded randomized controlled trial. Clin Oral Implants Res 2022;33(1):65-77.

XII. **Starch-Jensen T**, Bruun NH, Spin-Neto R. Outcomes following osteotome-mediated sinus floor elevation with Bio-Oss Collagen or no grafting material: a one-year single-blind randomized controlled trial. Int J Oral Maxillofac Surg 2023;52(9):988-97.

XIII. **Starch-Jensen T**, Bruun NH, Spin-Neto R. Endo-sinus bone gain following osteotome-mediated sinus floor elevation with Bio-Oss Collagen compared with no grafting material: a one-year single-blind randomized controlled trial. Int J Oral Maxillofac Surg 2023;52(11):1205-15.

XIV. **Starch-Jensen T**, Spin-Neto R, Veiss-Pedersen P, Dahlin C, Bruun NH, Fink T. Radiographic outcome after maxillary sinus floor augmentation with allogeneic adipose tissue-derived stem cells seeded on deproteinized bovine bone mineral. A randomized controlled experimental study. J Craniomaxillofac Surg 2023;51(5):321-31.

XV. **Starch-Jensen T**, Bruun NH, Spin-Neto R. Maxillary sinus membrane elevation and coagulum compared with maxillary sinus floor augmentation and a composite graft: A 1-year single-blinded randomized controlled trial. Clin Implant Dent Relat Res 2023;25(6):1056-68.

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XVII. **Starch-Jensen T**, Bruun NH, Spin-Neto R. Endo-sinus bone gain following sinus membrane elevation without graft compared with sinus floor augmentation and a composite graft: a one-year single-blind randomized controlled trial. Int J Oral Maxillofac Surg 2024;53(4):319-32.

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XIX. **Starch-Jensen T**, Ahmad M, Bruun NH, Spin-Neto R, Hellén-Halme K, Becktor JP Radiographic graft changes following maxillary sinus floor augmentation with autogenous bone compared with composite grafts: a one-year single-blinded randomized controlled trial. Int J Oral Maxillofac Surg 2024;53:968-80.

XX. **Starch-Jensen T**, Aludden H, Dahlin C, Bruun NH, Fink T. Histomorphometric outcome following sinus floor augmentation with allogeneic adipose tissue-derived stem cells. A randomized controlled experimental study. J Craniomaxillofac Surg 2024, accepted.

Abbreviations

AAMSCs	Allogeneic adipose tissue-derived mesenchymal stem cells
ABG	Autogenous bone graft
ARA	Alveolar ridge augmentation
APM	Atrophic posterior maxilla
BBGM	Biphasic bone graft material
BD	Bone density
BIC	Bone-to-implant contact
BCP	Biphasic calcium phosphate
CBCT	Cone beam computed tomography
CT	Computed tomography
DBBM	Deproteinized bovine bone mineral
DPBM	Deproteinized porcine bone mineral
ESBG	Endo-sinus bone gain
FIL	Functional implant loading
HU	Hounsfield unit
IPL	Implant protrusion length
ISQ	Implant stability quotient
MS	Maxillary sinus

MSFA	Maxillary sinus floor augmentation
MSCs	Mesenchymal stem cells
MSME	Maxillary sinus membrane elevation
OHIP	Oral Health Impact Profile
OHQoL	Oral health-related quality of life
OMSFE	Osteotome-mediated sinus floor elevation
PICO	Population, intervention, comparison, and outcome
PIMBL	Peri-implant marginal bone loss
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROMs	Patient-reported outcome measures
RCTs	Randomized controlled trials
RARH	Residual alveolar ridge height
ROI	Region of interest
SM	Schneiderian membrane
VAS	Visual analogue scale

Table of contents

Summary of main findings

Implant placement in the posterior maxilla is often compromised due to atrophy of the alveolar ridge following loss of teeth. Alveolar ridge augmentation (ARA) of the atrophic posterior maxilla (APM) prior to or in conjunction with implant placement is, therefore, often required to achieve sufficient alveolar ridge height for placement of standard-length implants. Autogenous bone graft (ABG) has historically been considered as the ideal grafting material. However, ABG is associated with the risk of donor site morbidity and an unpredictable resorption. Various bone substitutes have, therefore, been used to simplify the surgical procedure and reduce the dimensional changes of the grafting material. However, consensus-based guidelines for implant-supported prosthetic rehabilitation of the APM are lacking including, well-defined criteria for the appropriated surgical approach, simultaneous versus delayed implant placement, amount of newly formed bone to generate sufficient bone-to-implant contact (BIC), as well as required augmented volume to facilitate adequate implant support. The intention of this doctoral thesis is, therefore, to contribute with new knowledge for evidence-based treatment guidelines of implant-supported prosthetic rehabilitation of the APM with a satisfying implant treatment outcome, high patient satisfaction, and diminutive discomfort.

This doctoral thesis includes seven systematic reviews (I-IV, VI-VIII), one retrospective study (V), two randomized pre-clinical trials (minipigs) (XIV, XVI, XX), and three randomized controlled trials (RCTs) in humans (IX-XIII, XV, XVII-XIX) that intend to analyze various grafting materials by standardized uniform assessment methods of clinical, radiographic, histologic, and patient-reported outcome measures (PROMs). The studies indicate that the surgical approach and grafting material is determined by the planned implant length and residual alveolar ridge height (RARH), since the amount of endo-sinus bone gain (ESBG) is correlated with the surgical approach, implant protrusion length (IPL) within the maxillary sinus (MS), RARH, and the applied grafting material.

The systematic reviews concluded that ARA of the APM using the lateral window or transcrestal approach is associated with a high survival rate of suprastructures and implants, limited peri-implant marginal bone loss (PIMBL), ESBG, few complications, and high patient satisfaction, regardless of the used grafting material. ABG generated most ESBG, and least volumetric stability compared with other grafting materials. However, RCTs assessing ABG in comparison with other grafting materials are limited, and characterized by bias, confounding factors, and heterogeneous assessment methods.

The pre-clinical and clinical studies substantiated that ARA of the APM is associated with high survival of suprastructures and implants, limited PIMBL, high implant stability, and low frequency of complications, regardless of the surgical approach or applied grafting material. However, the radiographic ESBG was significantly influenced by the surgical approach and grafting material. ABG generated higher bone regeneration and less volumetric stability than other grafting materials. Xenogenic bone substitute exhibited the highest volumetric stability, while the mixture of ABG and xenograft revealed improved volumetric stability and slightly less bone regeneration than ABG. Alloplastic bone substitute combined with ABG generated higher radiographic ESBG than ABG, but less than ABG mixed with xenograft. Coagulum generated radiographic ESBG, but substantially less than ABG combined with xenograft. Allogeneic adipose tissue-derived mesenchymal stem cells (AAMSCs) seeded on xenograft generated no beneficial effect on histologic or radiographic outcome compared with xenograft alone as evaluated by bone regeneration, volumetric stability, and BIC. Radiographic ESBG was overall positively correlated with IPL, and negatively correlated with RARH, regardless of the applied grafting material. However, the increased radiographic ESBG seems not to positively improve the clinical implant treatment outcomes. Based on the main findings of this doctoral thesis, the following conclusions and treatment guidelines are advocated for the selection of the appropriate surgical approach and grafting material in conjunction with ARA of the APM.

- Placement of standard-length implants in conjunction with ARA of the APM is associated with successful implant treatment outcomes and high patient satisfaction.
- Harvesting of ABG is associated with increased patient discomfort and prolonged sick leave.
- Volumetric reduction of the augmented area is inevitable, regardless of the grafting material. Thus, varying degrees of overcompensation are required, depending on the grafting material.
- Primary implant stability is achievable when the RARH of the APM is ≥3 mm, enabling simultaneous implant placement.
- The planned implant length and the RARH determine the appropriate surgical approach and grafting material.
- Recommended surgical approach and grafting material, when the RARH at the implant site is ≥3 mm and ≤6 mm:
  - ✓ Maxillary sinus floor augmentation (MSFA) with a mixture of ABG and a xenogenic bone substitute if an increase of the alveolar ridge height of ≥6 mm is intended.
  - ✓ MSFA with ABG and an alloplastic bone substitute if an increase of the alveolar ridge height of approximately 5 mm is intended.
  - ✓ Maxillary sinus membrane elevation (MSME) with coagulum if an increase of the alveolar ridge height of ≤5 mm is intended.
- Recommended surgical approach and grafting material, when the RARH at the implant site is ≥6 mm:
  - ✓ Osteotome-mediated maxillary sinus floor elevation (OMSFE) with a xenogenic bone substitute if an increase of the alveolar ridge height of ≥5 mm is intended.
  - ✓ OMSFE without a grafting material if an increase of the alveolar ridge height of ≤4 mm is intended.

Dansk resumé (Danish summary)

Implantatindsættelse i den posteriore maksil er ofte vanskelig på grund af knoglesvind efter tandtab. Genopbygning af processus alveolaris er derfor ofte nødvendig for at sikre tilstrækkelig knoglehøjde til indsættelse af standardlængde implantater. Autolog knogletransplantat anses som det ideelle transplantationsmateriale. Anvendelse af autolog knogletransplantat er dog forbundet med risiko for gener svarende til donorstedet og en uforudsigelig resorption. Knogleerstatningsmaterialer anvendes derfor i stigende grad for at simplificere det kirurgiske indgreb og mindske resorptionen. Imidlertid mangler der evidens-baserede retningslinjer og rekommandationer for implantatretineret protetisk rehabilitering af den posteriore maksil inklusive valg af kirurgisk teknik og transplantationsmateriale, simultan versus forsinket implantatindsættelse, nødvendig knoglenydannelse og knogle-til-implantat-kontakt for etablering af osseointegration, samt volumen af transplantationsmaterialet for at skabe sufficient implantatstøtte. Nærværende doktorafhandling har derfor til formål at bidrage med ny viden til evidensbaserede behandlingsvejledninger for implantatretineret protetisk rehabilitering af den atrofiske posteriore maksil.

Denne afhandling inkluderer syv systematiske oversigtsartikler (I-IV, VI-VIII), en retrospektiv undersøgelse (V), to randomiserede prækliniske undersøgelser (XIV, XVI, XX), og tre randomiserede kliniske kontrollerede undersøgelser (IX-XIII, XV, XVII-XIX), som har til formål at vurdere forskellige transplantationsmaterialer til genopbygning af processus alveolaris i den atrofiske posteriore maksil ved hjælp af ensartet kliniske, radiografiske, histologiske og patient-rapporteret undersøgelsesmetoder. Resultaterne af undersøgelserne indikerer, at den hensigtsmæssige kirurgiske teknik og transplantationsmateriale bestemmes ud fra den planlagte implantatlængde og præoperative højde af processus alveolaris, idet knoglenydannelsen relateres til den anvendte kirurgiske teknik, implantatlængden, initiale højde af processus alveolaris, og det appliceret transplantationsmateriale.

De systematiske oversigtsartikler viste, at genopbygning af processus alveolaris ved vindue- eller osteotomteknik medførte høj overlevelse af suprastruktur og implantat, begrænset peri-implantært knoglesvind, knogleregeneration, få komplikationer og stor patienttilfredshed, uanset valg af transplantationsmateriale. Autolog knogletransplantat medførte mest knoglenydannelse og mindst volumenstabilitet sammenlignet med andre transplantationsmaterialer. Imidlertid er randomiserede kontrollerede undersøgelser af autolog knogle sammenlignet med andre transplantationsmaterier begrænset og karakteriseret ved bias, konfunderende variabler og inhomogen evalueringsmetoder.

De prækliniske og kliniske undersøgelser viste, at genopbygning af processus alveolaris ved vindue- eller osteotomteknik medførte høj overlevelse af suprastruktur og implantat, begrænset peri-implantært knoglesvind, høj implantatstabilitet, få komplikationer og stor patienttilfredshed, uanset kirurgisk teknik og transplantationsmateriale. Autolog knogle medførte mest knoglenydannelse og mindst volumenstabilitet sammenlignet med andre transplantationsmaterialer. Xenogen knogle viste bedst volumenstabilitet, mens autolog knogle blandet med xenogen knogle medførte bedre volumenstabilitet og mindre knoglenydannelse end autolog knogle. Alloplastisk knogle kombineret med autolog knogle medførte mere radiologisk knoglenydannelse end autolog knogle, men mindre end autolog knogle blandet med xenogen knogle. Koagel medførte knoglenydannelse, men mindre end autolog knogle blandet med xenogen knogle. Histologisk og radiologisk undersøgelse af allogene stamceller fra fedtvæv udsået på xenogen knogle medførte ikke bedre knoglenydannelse, volumenstabilitet og knogle-implantat-kontakt end xenogen knogle. Radiologisk knoglenydannelse var generelt positivt korreleret med implantatlængden og negativt med knoglehøjden, uanset transplantationsmaterialet. Imidlertid synes øget knoglenydannelse ikke at bedre behandlingsudfaldet eller patienttilfredsheden. På baggrund af ovenstående resultater anbefales følgende retningslinjer til implantatretineret protetisk rehabilitering af den atrofiske posteriore maksil.

- Indsættelse af standardlængde implantater i forbindelse med genopbygning af den atrofiske posteriore maksil medfører et succesfuldt behandlingsudfald og stor patienttilfredshed.
- Udtagning af autolog knogle er forbundet med øget patientgener og længere sygemelding.
- Svind af det genopbygget område er uundgåelig, uanset transplantationsmaterialet. Varierende grad af overkompensation er således nødvendig afhængig af transplantationsmaterialet.
- Primær implantatstabilitet er opnåelig, når højden af processus alveolaris er ≥3 mm, hvilket muliggør genopbygning af processus alveolaris med simultan implantatindsættelse.
- Valg af kirurgisk teknik og transplantationsmateriale bestemmes af den planlagte implantatlængde og den initiale højde af processus alveolaris svarende til implantatregionen.
- Anbefalet kirurgisk teknik og transplantationsmateriale, når højden af processus alveolaris svarende til implantatregionen er ≥3 mm og ≤6 mm:
  - ✓ Sinusløftproceduren med vindueteknik og kombination af autolog knogle og xenogen knogle, hvis en øgning af processus alveolaris´s højde på ≥6 mm er intenderet.
  - ✓ Sinusløftproceduren med vindueteknik og kombination af autolog knogle og alloplastisk knogle, hvis en øgning af processus alveolaris´s højde på ca. 5 mm er intenderet.
  - ✓ Sinusløftproceduren med vindueteknik og koagel, hvis en øgning af processus alveolaris´s højde på ≤5 mm er intenderet.
- Anbefalet kirurgisk teknik og transplantationsmateriale, når højden af processus alveolaris svarende til planlagte implantatregion er ≥6 mm:
  - ✓ Sinusløftproceduren med osteotomteknik og xenogen knogle, hvis en øgning af processus alveolaris´s højde på ≥5 mm er intenderet.
  - ✓ Sinusløftproceduren med osteotomteknik og koagel, hvis en øgning af processus alveolaris´s højde på ≤4 mm er intenderet.

Background

Loss of teeth in the posterior maxilla due to periodontal disease, caries, failed endodontic treatments, or trauma affects the masticatory function and nutritional status of the patients. Moreover, missing teeth in the posterior maxilla have adverse consequences on the phonetics and remaining dentition as well as social and psychological well-being. WHO's global oral health status report from 2022 concluded that the incidence of edentulism varies worldwide and oral diseases may lead to e.g., body-image issues, sleeplessness, social isolation, pain, discomfort, fear, anxiety, and functional limitations.[1] A survey conducted in Denmark during 1987-2017 revealed that the incidence of partial or complete edentulism has declined in the last 30 years, but the prevalence of edentulous adults (>16 years) in 2017 was 3.4%, and 11.5% of the population had less than 20 teeth.[2]

Missing teeth have historically been replaced by removable or fixed prosthesis. In 1977, Brånemark introduced the concept of osseointegration defining a direct structural and functional connection between vital bone and a load-carrying titanium implant surface.[3,4] Nowadays, placement of titanium dental implants has become an acceptable treatment for replacing missing teeth and the implant treatment outcome has been characterized by successful long-term results of complete, partial, or single edentulism.[4-6] Moreover, prosthetic rehabilitation with an implant-supported prosthesis significantly improves the masticatory function and oral health-related quality of life (OHQoL) compared with removable dentures.[7,8] However, placement of implants in the posterior maxilla is frequently compromised or impossible due to poor bone quality and limited RARH caused by pneumatization of the maxillary sinus (MS) and dimensional changes of the alveolar ridge following loss of teeth.[9-11] ARA prior to or in conjunction with implant placement is, therefore, frequently necessary to increase the height of the alveolar ridge for placement of implants with sufficient length. However, the required implant length for an implant-supported prosthetic

rehabilitation of the APM is presently unknown. Moreover, the appropriate surgical approach and grafting material, with the highest patient satisfaction and least morbidity is inconclusive.

The intention of this doctoral thesis is, therefore, to contribute new knowledge for evidence-based treatment guidelines about implant-supported prosthetic rehabilitation of the APM with a satisfying implant treatment outcome, high patient satisfaction, and diminutive discomfort.

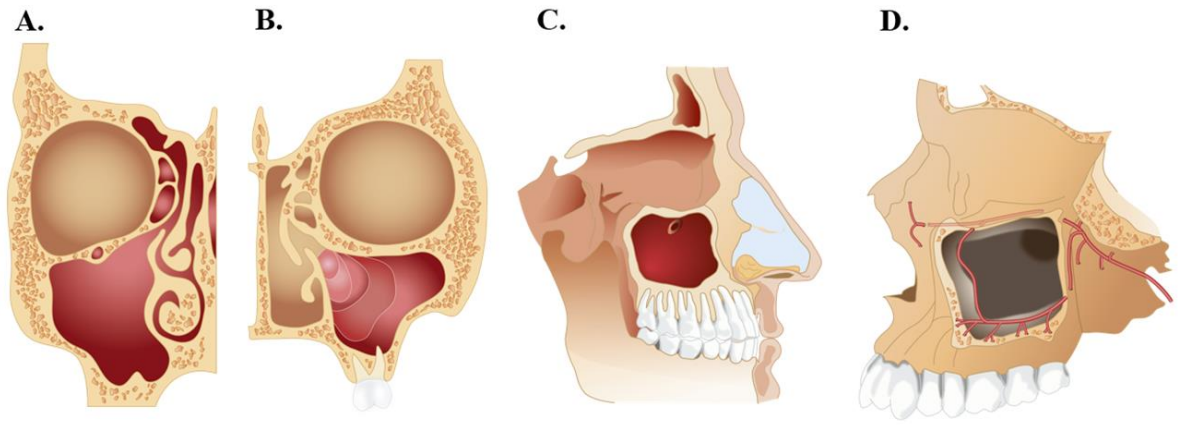
Introduction

ARA of the APM involves the elevation of the Schneiderian membrane (SM) to create a void between the raised SM and the original MS floor. A grafting material has historically been applied within the created cavity. However, the optimal grafting material to ensure a high long-term survival rate of suprastructures and implants, highest percentage of newly formed bone, and BIC with least patient morbidity is presently unknown as bone regeneration within the MS is affected by several parameters including the anatomy of the MS, RARH, surgical approach, and applied grafting material.

Maxillary sinus

The MS is the largest of the paranasal sinuses and was originally illustrated by Leonardo da Vinci in 1489 and later described by the English anatomist Nathaniel Highmore in 1651.[12] The MS develops in utero and increases in size until the end of the 18th year.[13-15] The MS is a pyramid-shaped air-filled cavity with an average volume of 15-18 cm^3 in adulthood. The MS drains to the nasal cavity through the ostium, which is located within the MS medial wall. The MS is innervated by the second branch of the trigeminal nerve, and the vascular blood supply is derived from the branches of the maxillary artery, including the posterior superior alveolar artery, the infraorbital artery, and the posterior lateral

nasal artery.[14] The exact function of the MS is unknown, although various theories have been proposed including weight reduction of the skull, phonetic resonance, participation of warming and humidification of inspired air, and absorption of forces delivered to the midface.[12,13]



A: Coronal image of the MS. B: Development of the MS until the 18th year. C: Sagittal image of the MS with the ostium located cranially within the medial wall. D: The vascular supply to the MS.

The MS is lined by the SM, which is a bilaminar membrane composed of pseudostratified ciliated columnar epithelial cells with goblet cells. The average thickness of the SM is 0.5-1 mm, but periodontitis, apical pathology, smoking, and seasonal changes may cause thickening of the SM.[16,17] The SM contributes to smell, immune defense of the respiratory system, and the secretion of mucus to moisturize and humidify inhaled air. Inhaled irritants lead to increased mucus secretion of the SM, which traps the irritants so they can be removed by ciliary movements.

MS septa, SM thickening, retention mucous cysts, and polyps are anatomic variants of the MS.[18,19] The prevalence of MS septa and SM thickening varies between 26.6-58.0% and 35.1-66.0%.[18,19] Most of the septa are observed in the middle region of the MS, followed by the posterior and anterior areas.[18] Sinusitis and opacification are common MS pathologies with a prevalence varying between 7.5-66.0%.[19] Benign MS neoplasms are common, primarily including inverted papilloma,

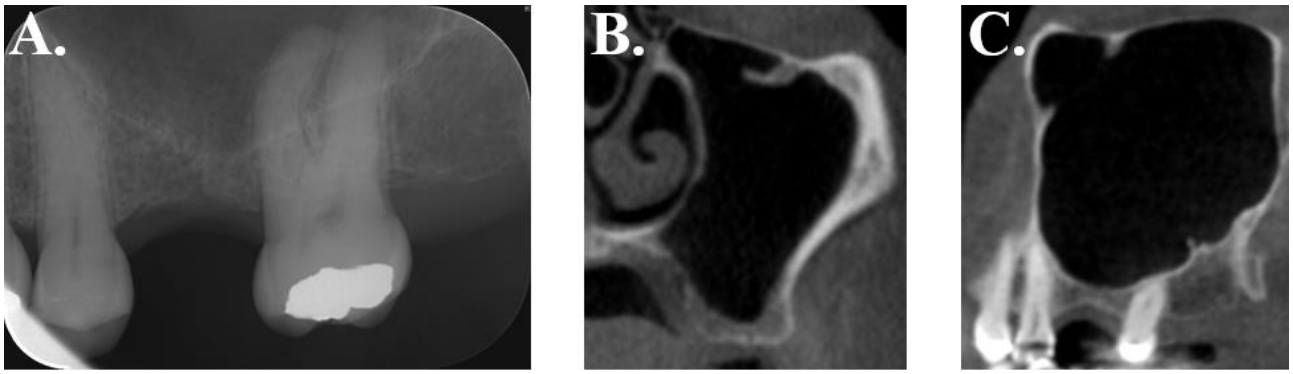
hemangiomas, and osteoma, while MS malignancies are rare, including squamous cell carcinoma, adenocarcinoma, and adenoid cystic carcinoma.

MS pneumatization is a physiological process in which the volume of the MS increases over time. The pathogenesis behind MS pneumatization is unclear, but various parameters seem to initiate and accelerate the progression, including bone quality, previous sinus surgeries, heredity, nasal mucous membrane pneumatization, craniofacial configuration, growth hormones, air pressure within the MS cavity, or an age-related process.[9] MS pneumatization has been reported after tooth loss, especially when multiple teeth have been extracted, proximity between the roots of the teeth and the MS floor, or an irregular MS floor.[9,20-22] However, a recently published retrospective study concluded that the dimensional changes of the alveolar ridge following tooth loss are primarily due to resorption of the alveolar ridge and not because of MS pneumatization.[21]

Alveolar ridge

The APM is categorized as bone type III/IV, indicating that the alveolar ridge is mainly composed of cancellous bone with a thin cortical plate.[23] The average buccal bone thickness of the posterior maxilla is 1.4 mm, whereas the width of the dentate alveolar ridge in the second premolar and first molar region is 9.6 mm and 12.4 mm, respectively.[24,25] Following tooth loss, an unpredictable resorption of the alveolar ridge is inevitable.[21] A systematic review revealed that the alveolar ridge is resorbed by 3.8 mm in the horizontal dimension, and 1.4 mm in the vertical dimension following tooth loss.[26] The resorption of the alveolar ridge is more pronounced in the early healing phase due to remodeling of the extraction socket, but the vertical resorption of the posterior maxilla gradually proceed with a rate of 0.1 mm per year, although large individual differences have been reported.[27] The pathogenesis behind these dimensional changes of the alveolar ridge is unclear, but it seems to

be influenced by duration of edentulism, number of extracted teeth, proximity between the roots and the MS floor, and the anatomy of the MS floor.[9,20-22] Thus, ARA of the APM is often necessary to achieve sufficient alveolar ridge height for placement of implants with sufficient length and diameter.



Pre-operative radiograph examination of the MS and alveolar ridge. A: Intraoral x-ray showing reduced RARH. B, C: Coronal and sagittal CBCT-scan images showing reduced RARH without anatomic variants or MS pathologies.

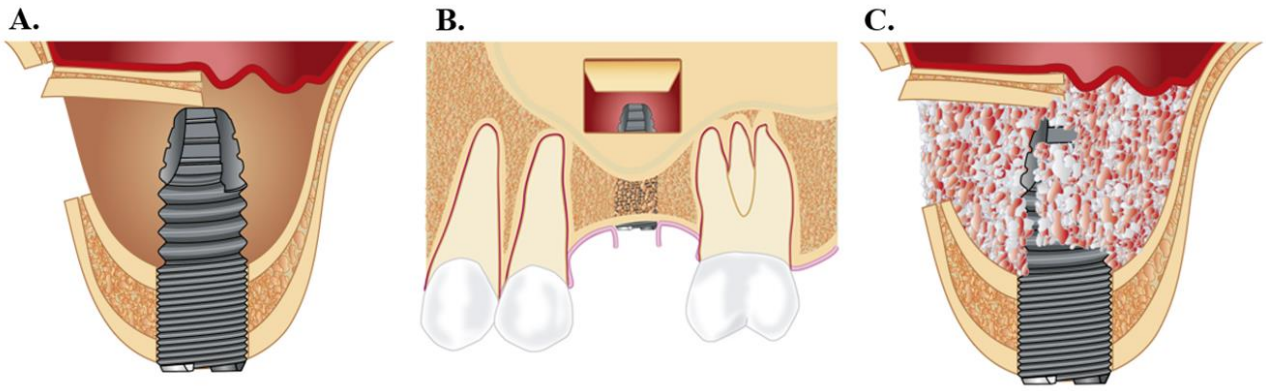
Surgical techniques for alveolar ridge augmentation of the atrophic posterior maxilla

Different surgical techniques have been used to obtain sufficient alveolar ridge height of the APM, including maxillary sinus floor augmentation (MSFA) and maxillary sinus membrane elevation (MSME) applying the lateral window technique, or osteotome-mediated sinus floor elevation (OMSFE) using a transcrestal approach. The appropriate surgical approach and necessary implant length for an implant-supported prosthetic rehabilitation is controversial and dependent on the number of missing posterior teeth, RARH, intra-sinus anatomy, and patient wishes.[28]

Maxillary sinus floor augmentation applying the lateral window technique

MSFA applying the lateral window technique was originally described by Tatum in the mid-70s and later published by Boyne and James in 1980 using autogenous iliac bone marrow and delayed placement of blade implant.[29,30] Nowadays, MSFA is still the most used surgical procedure to increase

the RARA of the APM before or in conjunction with implant placement. The MS is exposed through a crestal incision from the tuber maxillae combined with an anteriorly releasing incision. A mucoperiosteal flap is raised to reflect the lateral MS bone wall. A trapdoor osteotomy is created on the lateral MS bone wall with burrs or piezoelectric surgery. The trapdoor is in-fractured, and the SM is elevated from the MS floor and adjacent bone walls, creating a cavity between the raised SM and the original MS floor. Implants are inserted simultaneously if primary implant stability can be achieved. Otherwise, implant placement is performed in a delayed surgical procedure. A grafting material is applied within the created cavity, and the lateral window is usually covered by a fixated or non-fixated resorbable collagen membrane.

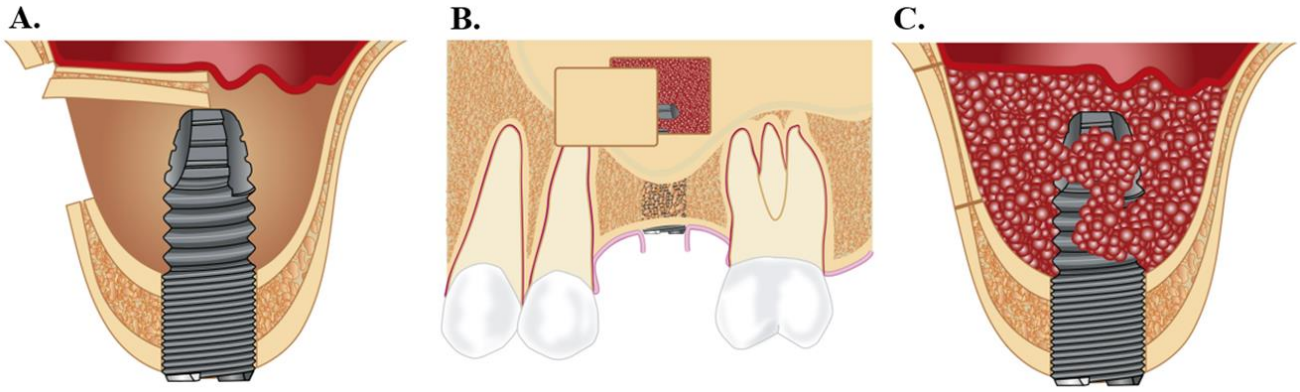


A,B: MSFA applying the lateral window technique with simultaneous implant placement. C: A grafting material is packed around the implant within the created cavity between the elevated SM and the original MS floor.

Maxillary sinus membrane elevation applying the lateral window technique

MSME applying the lateral window technique without a grafting material was originally described by Ellegaard in 1997 and later published by Lundgren in 2004.[31,32] MSME requires sufficient alveolar ridge height to achieve primary implant stability, as simultaneous implant placement is mandatory to maintain the SM in its raised position. The surgical approach, preparation of the lateral window, and SM elevation are similar to the method used for MSFA, although the lateral window is often dissected

free and removed from the underlying SM. No grafting material is applied. Instead, a blood coagulum is formed around the exposed implant surface between the raised SM and the original MS floor. The prepared lateral window to the MS is covered by a fixated or non-fixated resorbable collagen membrane or the dissected lateral bony window is repositioned.

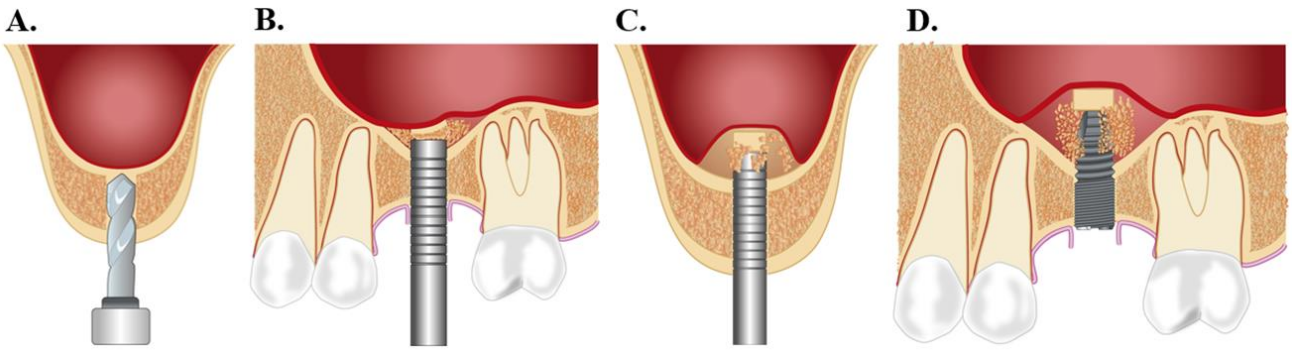


A: MSME applying the lateral window technique with simultaneous implant placement. B,C: Coagulum formation around the exposed implant surface within the created cavity between the raised SM and the original MS floor. The lateral bony window is repositioned to seal the created cavity.

Osteotome-mediated sinus floor elevation

The OMSFE was originally described by Tatum in 1986 involving a transcrestal approach for elevating the SM with the attached MS floor.[30] The technique was later modified by Summers using a set of matched tapered osteotomes with increasing diameters to improve the bone quality and create an up-fracture of the original MS floor.[33] The surgical approach involves a crestal incision at the implant site continuing into the gingival sulcus of the adjacent teeth. The mucoperiosteum is reflected to expose the alveolar ridge. An implant bed is successively prepared on the top of the alveolar crest, and the depth of the drilling procedure is ended at least 1-2 mm from the border of the MS floor. The MS floor with the attached SM is elevated to the planned implant length using either calibrated osteotomes, piezoelectric surgery, hydraulic pressure technique, gel pressure elevation, reamer mediators, or membrane balloon elevation technique.[34-39] The raised SM with the attached MS floor

creates a cavity within the MS, which can be filled with a grafting material through the transcrestal approach. OMSFE requires sufficient alveolar ridge height to achieve primary implant stability, since simultaneous implant placement is mandatory to maintain the SM with the attached MS floor in its raised position.



A: Drilling is ended 1-2 mm from the MS floor. B: The MS floor is fractured with calibrated osteotomes and elevated with the SM. C,D: A grafting material is applied before implant placement maintaining the MS floor in its raised position.

Bone grafting materials

The ideal bone grafting material for ARA of the APM is presently unknown. The application of a grafting material is intended to repair the bone deficit, facilitate bone regeneration, and provide mechanical support for the inserted implants. The optimal grafting material should, therefore, be biocompatibility without antigenic, carcinogenic, or teratogenic reactions and contain osteogenic, osteoinductive, and osteoconductive properties:

- Osteogenesis is the synthesis of new bone by osteoblasts or osteoprogenitor cells present in the recipient bone or derived from the grafting material.
- Osteoinduction is the capability of the grafting material to recruit mesenchymal stem cells (MSCs) and differentiate them into bone-forming cells.

- Osteoconduction is the process where the grafting material acts as a resorbable or non-resorbable scaffold that mechanically supports the ingrowth of capillaries and MSCs from the recipient bone.

Bone grafting materials are categorized as autogenous bone graft (ABG), allogenic bone graft, xenogenic bone substitute, and alloplastic bone substitute based on their origin. The osteogenic, osteoinductive, and osteoconductive potential of a grafting material is affected by the biomechanical characteristics, origin, surface topography, and biodegradation.

Autogenous bone

ABG originates from the same individual and possesses, therefore, no antigenic properties as the donor and the recipient are the same person. ABG can be harvested from extraoral or intraoral sites and applied as a block or particulate graft. Extraoral harvesting necessitates general anesthesia and hospitalization, while intraoral harvesting is often performed with local anesthesia on an outpatient basis. ABG contains osteogenic, osteoinductive, and osteoconductive properties due to the content of living cells, matrix proteins, and an optimal scaffold for the migration of osteoprogenitor cells. However, the amount of vital osteoprogenitor cells and osteocytes within ABG is dubious and influenced by the harvesting technique, particle size, processing, storage, cortico-to-cancellous ratio, and patient-related factors.[40]

ABG has been used as a block or particulate graft for ARA of the APM. Particulate ABG is generally preferred, as it is easier to apply and can be combined with bone substitutes. Moreover, particulate ABG has demonstrated higher osteogenic potential compared with autogenous bone block.[41] Particulate ABG can be harvested as bone chips from the cortical bone surface using manual bone scrapers or by bone fillers (slurry), which collect bone debris through a suction device from

low-speed drilling or piezoelectric devices. Pre-clinical (rabbits, minipigs) and clinical studies have shown large variations in the number of viable cells following harvesting of ABG with bone scrapers or bone fillers.[42-47] Improved cell viability has been reported in pre-clinical studies (rabbits, minipigs), when ABG was harvested by manual instruments or piezoelectric devices compared with rotary devices,[46] as well as a bone mill or bone scraper compared with slurry or piezoelectric device.[44] Improved cell viability and higher osteogenic potential have been reported in clinical studies when ABG was harvested by a bone scraper or low-speed drilling compared with trap filter,[45] chips compared with sludge,[47] and bone scraper compared with piezoelectric device.[42] Moreover, a significantly higher expression of bone morphogenetic protein-2 and vascular endothelial growth factor has been revealed by bone scraper and bone mill compared with piezoelectric device and slurry.[43] Additionally, ABG collected by filters is always contaminated by bacteria,[48,49] and the bacterial contamination is significantly higher with filters than with bone scrapers, trephine drills, and low-speed drilling.[50,51] Consequently, improved cell viability and higher osteogenic potential of ABG is achieved by manual bone scrapers and bone mills compared with alternative autogenous bone harvesting techniques.

The optimal ABG particle size to facilitate the highest osteogenic potential has been assessed in pre-clinical studies (rabbits, minipigs), and clinical studies.[43,52-55] It has been reported that a particle size between 125-1000 µm possesses a higher osteogenic potential than a particle size below 125 µm, since smaller particles rapidly resorb without facilitating bone regeneration.[54,56] A pre-clinical study (minipigs) revealed that the average size of ABG particles was 1400 µm, 1400 µm, 1000 µm, and 200 µm obtained by bone mill, bone scraper, piezoelectric surgery, and bone slurry, respectively.[43] Moreover, ABG particles obtained by a bone mill or bone scraper showed higher osteogenic potential compared with ABG particles from bone slurry and piezoelectric device, as evaluated by levels of

collagen, osteocalcin, and osterix.[44] Another pre-clinical study (rabbit) showed that the early stages of bone regeneration were improved by small particles (500 to 2000 μm^3) compared with larger particles (10000 mm^3).[52] A clinical study found that the average size of ABG particles obtained from bone slurry was 282.1 µm.[55] Consequently, the size of ABG particles influences the osteogenic potential, and the particle size obtained by manual bone scrapers or bone mills seems to be preferable.

Temperature, storage medium, and time interval between harvesting and application influences the osteogenic potential of ABG.[57,58] Thermal elevation of ABG may lead to apoptotic and diminish the number of viable cells.[59,60] Temperatures above 45-48°C lead to increased apoptosis of the osteoblast, as demonstrated in an in-vitro study.[61] A pre-clinical study (goat) reported that the optimal temperature for ABG storage is room temperature, while the incubator was the least favorable.[58] The hydrophilic properties of ABG make it easy to mix with saline or blood. A pre-clinical study (goat) revealed that the best medium for ABG storage was autologous blood compared with saline or Ringer's lactate.[58] The cell viability is preserved for up to two hours, if ABG is stored in saline, while degeneration of osteocytes increases when ABG are stored dried for 30 minutes.[57,62] Consequently, improved cell viability and higher osteogenic potential is obtained, if ABG is stored in autologous blood at room temperature with limited time between harvesting and application.

ABG can be harvested as cortical, cancellous, or cortico-cancellous bone. Cortical bone structure is denser with a limited number of osteoprogenitor cells and a higher concentration of growth factors as compared with cancellous bone, which contains higher levels of viable osteoprogenitor cells.[63] Cancellous ABG is characterized by a large surface area, which promotes faster neovascularization and graft incorporation, while the denser structure of cortical ABG hampers neovascularization.[64] ABG harvested from the calvarium, ascending mandibular ramus, or zygomatic buttress consists mainly of cortical bone, whereas ABG from the iliac crest, tuber maxillae, and chin is composed of

cortico-cancellous bone. Pre-clinical studies (rats, rabbits) have shown that the architecture of cortico-cancellous bone enables earlier, and faster neovascularization compared with cortical bone graft.[65,66] Likewise, a clinical study showed substantial amounts of non-vital bone and weak neovascularization following ARA with a mono-cortical autogenous bone block from the ascending mandibular ramus.[67] Consequently, cancellous ABG is associated with higher levels of viable osteoprogenitor cells and improved osteogenic potential compared with cortical ABG.

The biodegradation of ABG is influenced by the particle size and the cortico-cancellous ratio. A pre-clinical study (rabbits) revealed that the biodegradation of small particles (500-2000 μm^3) was more pronounced compared with large particles (10000 μm^3) in bi-cortical skull defects.[52] Another pre-clinical study (minipigs) disclosed an average reduction of the augmented area by 65% following MSFA with particulate ABG (500-2000 μm^3) from either the mandible or iliac crest.[68] A clinical study showed significantly higher biodegradation with cortico-cancellous ABG from the iliac crest compared with cortical ABG from the calvarium in conjunction with onlay block augmentation.[69] A long-term clinical study revealed that the reduction of the augmented volume was more pronounced within the first year following MSFA with particulate ABG from the iliac crest or mandible, after which the resorption creased.[70] Consequently, biodegradation of ABG seems to be reduced by larger cortical particles compared with smaller particles and is more pronounced in the early healing period.

The osteogenic potential of ABG is also affected by patient-related factors.[47,71] Smoking habits and alcohol consumption negatively influence vital bone formation following MSFA,[71] and higher osteogenic potential has been revealed in patients younger than 60 years as compared with older age.[47] Moreover, ASA status, bone degenerative diseases, dysregulation of diabetes, radiotherapy, gingival phenotype, acute and chronic rhinosinusitis compromises implant survival, bone regeneration, and frequency of surgical and biological complications following ARA of the APM.[72-74]

Allogenic bone graft

Allogenic bone graft originates from the same species but from another individual. Allogenic bone graft contains, therefore, a theoretical risk of disease transmission or host immunogenic response.[75,76] Allogenic bone graft is categorized according to the processing technique and manufactured as fresh, fresh frozen bone, freeze-dried bone, and demineralized freeze-dried allogenic bone graft. Allogenic bone is provided as a block or particulate graft containing cortical, cortical-cancellous, or cancellous bone. Allogenic bone graft is used less frequently as grafting material for ARA of the APM, although pre-clinical (minipig), and long-term clinical studies have demonstrated satisfying implant treatment outcomes.[77,78]

In this doctoral thesis, allogenic bone graft was not used as a grafting material either alone or in combination with ABG or other bone substitutes, and therefore, not described further.

Xenogenic bone substitute

Xenogenic bone substitute consist of bone mineral derived from other species, like calves, deer, and pigs, or bone-like mineral derived from calcifying corals or algae, and commercialized as cortical, cancellous, and cortico-cancellous bone blocks or particles. Xenografts are often used for ARA due to their structural and morphological resemblance with human bone.[79,80] Xenografts are purified from all organic components to prevent disease transmission, immunological response, and antigenicity. Xenografts consist, therefore, mainly of hydroxyapatite and are considered as a biocompatible grafting material. However, due to the origin, a theoretical risk of disease transmission or activation of an immune response exists,[81,82] although no disease transmission has previously been reported.[83] Xenografts contain solely osteoconductive properties and serve as a scaffold for angiogenesis, cellular

adhesion, osteogenic differentiation, and integration within the recipient bone. However, the osteoconductive potential is influenced by the purification method, particle size, origin, surface topography, porous structure, and biodegradation.[84] In this doctoral thesis, xenografts of bovine and porcine origin were used, while bone-like mineral derived from algae was used in combination with beta-tricalcium phosphate.

Purification of the organic components has been performed by various methods, including thermal treatment, chemical methods, and/or γ-radiation.[79] However, the purification method influences the structural and chemical features of the grafting material.[79,85,86] Commercially available xenografts are processed at temperatures ranging between 300°C and 1200°C.[85] It has been reported that a temperature of 500-650°C is required to completely remove the organic component, while temperatures above 800°C enable the reduction of transmissible spongiform encephalopathies to an acceptable level.[85,87,88] Thermal treatment alters the structural properties including particle size, crystallinity, porosity, surface area, mechanical stability, and interconnected pore system, which affect the cellular adherence and angiogenesis. Temperature above 500°C causes the apatite crystals to increase in size, reduces the porosity, and decreases the surface area.[89,90] Temperature up to 1000°C causes melting of the crystalline structure leading to increased particle size and loss of mechanical resistance, surface hydrophily, and porosity.[84,89,90] The increased crystallinity and density of xenografts processed at high temperatures causes reduced biodegradation compared with purification at low temperatures.[91] Moreover, the calcium-to-phosphate ratio is lower, when xenografts are processed at low temperatures compared with higher temperatures.[84,91] Consequently, thermal treatment at different temperatures changes the structural and chemical features of xenografts as well as the osteoconductive properties.

Chemical purification involves baths of alkaline solution with increasing pH to remove the organic remnants and bone matrix proteins.[83] Chemical purification preserves the mechanical resistance, porosity, and hydrophilic properties, which is beneficial for angiogenesis and cellular adhesion. However, complete removal of the organic components by chemical purification is impossible, and levels of organic remnants and animal RNA have been documented following chemical purification.[92] Thermal treatment combined with chemical purification led to the complete removal of the organic components. Moreover, thermal treatment combined with chemical purification enables the temperature of the purification process to be lowered. Consequently, thermal treatment up to 300°C combined with chemical purification has proven to be the most effective technique to remove the organic components and preserve the osteoconductive potential of the xenograft.[83,93,94]

Xenograft particles are manufactured in various sizes. The osteoconductive potential is influenced by the particle size, as small particles are associated with an increased surface area, which is beneficial for angiogenesis and cellular adhesion.[83] Pre-clinical (minipigs) and clinical studies have assessed the histomorphometric outcome of small or large particles in conjunction with MSFA.[95-100] A short-term pre-clinical study (minipigs) revealed no significant difference in the percentage of newly formed bone, BIC, bone-to-graft contact, and biodegradation, with large (1 to 2 mm) or small particles (0.25 to 1 mm).[95] A short-term clinical study disclosed improved angiogenesis, total bone volume, and new bone formation with larger particles (1 to 2 mm) compared with smaller particles (0.25 to 1 mm).[98] In contrast, similar short-term clinical studies have reported comparable bone formation and implant stability,[96,97,100] although the small particles (0.25 to 1 mm) disclosed a higher bone-to-graft contact compared with large particles (1 to 2 mm), indicating improved osteoconductive potential.[100] However, a systematic review and meta-analysis revealed no significant difference in bone regeneration, non-mineralized tissue, or residual xenograft with the use of small or large particles.[99]

Consequently, the osteoconductive potential of xenogenic bone substitutes are influenced by the particle size, although no significant difference in implant treatment outcome has been reported following ARA of the APM with different particle sizes.

The biologic origin of xenograft may theoretically influence the osteoconductive potential.[101-103] Short-term clinical studies assessing MSFA with xenograft of bovine or porcine origin revealed comparable bone regeneration, indicating that the origin of the xenograft does not seem to effect the osteoconductive potential following ARA of the APM.[101-103]

The porous structure of a grafting material is defined by the porosity, pore size, and pore interconnectivity. A higher porosity increases the surface area, which improves the osteoconductive potential by stimulating angiogenesis, cellular adhesion, osteogenic differentiation, and integration within the recipient bone.[79] The optimal porous structure is unknown, and the interaction between pore size and cellular activity is poorly understood. A systematic review involving in-vitro studies has shown large heterogenicity in porosity, pore size, and pore interconnectivity among the different xenografts with a pore size of 1.3 μm to 1000 μm.[79] However, in-vitro studies have shown that small pore sizes inhibit angiogenesis, cellular adhesion, and osteogenic differentiation, while pore sizes of >300 μm with a porosity between 36-80% is optimal for bone regeneration.[79,104-108]

Biodegradation of a grafting material is a naturally biological host mechanism to dissolve the foreign body by activating pro-inflammatory cytokines and phagocytosis. However, xenogenic bone substitutes are generally considered as a slow or non-resorbable grafting material and, therefore, tend to be surrounded by newly formed bone rather than being resorbed. The specific mechanism behind the biodegradation of xenografts is poorly understood and affected by the purification method, calcium content, and calcium-to-phosphate ratio.[55,84] Xenografts processed at low temperatures are more prone to biodegradability due to reduced density, less crystallinity, and lower calcium-to-

phosphate ratio compared with purification at higher temperatures.[84,91,108] Pre-clinical studies (minipigs) have shown the presence of multinucleated giant cells on the surface of DBBM particles, indicating biodegradation.[109,110] However, a clinical study showed that the DBBM particles were well integrated into lamellar bone without noticeable changes in particle size, 11 years after MSFA.[111] It is, therefore, still uncertain whether xenograft is defined as a slow or non-resorbable grafting material.

Alloplastic bone substitute

Alloplastic bone substitutes are synthetically manufactured and contain, therefore, no risk of disease transmission or tissue-related immunological reactions. Alloplastic bone substitutes are categorized as calcium phosphate, calcium sulfate, polymeric substitutes, or bioactive glass, and are fabricated as particulate, block, putty, paste, gel, and plaster.[112] The osteoconductive potential varies according to their composition and processing method, which influences the surface topography, particle size, pore size, porosity, crystallinity, and biodegradation.[113-116] Various chemical compositions and processing methods have been applied to develop an alloplastic bone substitute that resembles natural bone. However, the optimal biochemical composition of alloplastic bone substitutes and scaffold for facilitating angiogenesis, cellular adhesion, and osteogenic differentiation is unsolved.

The inorganic component of human bone is composed of hydroxyapatite, calcium, and phosphate. Synthetic-manufactured hydroxyapatite resembles natural or xenogenic derived hydroxyapatite. Hydroxyapatite and tricalcium phosphate are the most frequently used alloplastic bone substitutes, either alone or in combination, which is termed biphasic calcium phosphate (BCP).[112] The composition of hydroxyapatite and tricalcium phosphate affects the osteoconductive potential, exchange of Ca^{2+} ions, and biodegradation.[112] In this doctoral thesis, BCP composed of 20%

hydroxyapatite derived from red marine algae, and 80% tricalcium phosphate was used. BCP is, therefore, described in detail, while other alloplastic bone substitutes are not further described.

The ratio of hydroxyapatite and tricalcium phosphate affects the osteoconductive potential and biodegradation of BCP.[117] In-vitro studies have shown that cellular surface adhesion and osteogenic differentiation are reduced with a higher ratio of tricalcium phosphate.[118,119] However, a pre-clinical study (minipigs) disclosed improved bone regeneration with a higher ratio of tricalcium phosphate in the early healing period.[117] Hydroxyapatite is considered non-resorbable, while tricalcium phosphate is resorbed relatively fast.[117,120] The biodegradation can therefore be modified by changing the ratio of hydroxyapatite and tricalcium phosphate.[120] A pre-clinical study (minipigs) assessing different compositions of BCP revealed similar bone regeneration and biodegradation with a 20:80 ratio as compared with ABG, while a 60:40 or 80:20 ratio correspond to a xenogenic bone substitute.[120] Clinical studies assessing MSFA with a 70:30 ratio of hydroxyapatite and β-tricalcium phosphate revealed diminutive resorption of the augmented height, as evaluated by linear radiographic measurements after 36 and 72 months.[121,122]

The manufacturing method of BCP influences the crystal size, surface topography, and porosity. Synthetic-manufactured hydroxyapatite is prepared by sintering, and the crystal size increases with a higher sintering temperature, while the pore diameter and interconnectivity decrease.[123,124] A pre-clinical study (goat) revealed improved bone regeneration with a 60:40 BCP sintered at 1050°C or 1125°C compared with 1200°C.[125] An in-vitro study showed that most alloplastic bone substitute have a porosity of >100 µm, as evaluated by µCT-scan.[105]

The particle size and application method of BCP influences the osteoconductive potential. A pre-clinical study (dogs) revealed early bone formation with a BCP particle size >45 µm, while no bone formation was observed with a particle size <45 µm.[115] A clinical study assessing bilateral MSFA

with a 60:40 ratio of hydroxyapatite and β-tricalcium phosphate applied as particles or paste revealed a non-significantly higher percentage of newly formed bone with particles after six months.[126]

The osteoconductive potential of alloplastic bone substitutes is, therefore, influenced by to their composition and processing technique. However, no significant difference in implant treatment outcome has been reported following ARA of the APM with the different alloplastic bone substitutes.

Bone tissue engineering

In the last decades, advanced technologies have been invented to improve the osteogenic potential of the different bone grafting materials. Autologous bioactive substances, including coagulum, blood-derived growth factors, or MSCs, have been used, either alone or combined with a carrier/scaffold. Novel technologies for the acquisition, cellular isolation, and culturing of autologous bone marrow-derived or adipose tissue-derived MSCs as well as the manufacturing of recombinant growth factors have further expanded the possibilities of bone tissue engineering. However, autologous bioactive substances or recombinant growth factors are associated with increased cost, risk of donor site morbidity, and short-term degradation of the cells, which often hamper the clinical application.

Coagulum

A coagulum consists of platelets and fibrinogen, which form a fibrous mesh at the wound. Platelets contribute to bone regeneration by promoting angiogenesis, migration and proliferation of osteogenic cells, and establishing a chemotactic gradient for recruitment of MCSs. Platelets release various growth factors, including platelet-derived growth factor, vascular endothelial growth factor, insulin growth factor, epidermal growth factor, transforming growth factor-β, epithelial-cell growth factor,

and hepatocyte growth factor, which promote bone regeneration.[127] Platelet-derived growth factor and transforming growth factor-β contribute to the protein synthesis in osseous tissues and the proliferative stage of wound healing. Transforming growth factor-β has a chemotactic effect on osteoblastic cells and endothelial cells, inhibitory effects on osteoclasts, and initiates woven bone formation. Insulin growth factor increases the proliferation of osteoblasts and the expression of osteocalcin for matrix synthesis.[128] Pre-clinical (monkeys, dogs) and long-term clinical studies have demonstrated a high survival rate of suprastructures and implants, limited PIMBL, bone regeneration, and few surgical, biological, and technical complications following MSME and OMSFE with coagulum as grafting material.[129-145] However, RCTs comparing coagulum with alternate grafting materials in conjunction with MSME are missing. Moreover, the implant survival is significantly compromised following OMSFE with a coagulum if the RARH <5 mm, and the implant length is <6 mm.[134,135,144,145]

Autologous blood-derived growth factors

Platelet concentrates are autologous blood-derived products obtained after centrifugation of a blood sample. Autologous platelet-rich plasma, platelet-rich growth factor, and platelet-rich fibrin contain various growth factors, including platelet-derived growth factor, transforming growth factor-β, vascular endothelial growth factor, and interleukin.[146] The effect of platelet-rich fibrin on bone regeneration following MSFA remains questionable due to lack of well-designed RCTs.[147-149]

In this doctoral thesis, autologous blood-derived growth factors are not described further as they were not investigated either alone or in combination with other grafting materials.

Stem cells

MSCs are multipotent cells that differentiate as progenitor cells for osteoblasts, fibroblasts, chondroblasts, and pre-adipocytes. Autologous MSCs are mainly isolated from blood, bone marrow, or adipose tissue, and subsequently expanded in vitro. MSCs have the capacity to differentiate into specific cell types and thereby induce regeneration of damage tissue, depending on the molecular stimuli.[150] MSCs isolated from a blood sample has been compared with coagulum following MSFA revealing comparable radiographic ESBG and bone density (BD).[151]

Autologous bone marrow-derived MSCs isolated from the iliac crest or sternum are the most used MSCs in bone tissue engineering.[152] However, the frequency of bone marrow-derived MSCs are rather low, and the cells often lose their proliferative and differentiation capacity during cell expansion.[152] A pre-clinical study (minipigs) disclosed no significant difference in BD or BIC following MSFA with expanded autogenous osteoblast-like cells isolated from iliac cancellous bone and seeded on xenograft compared with xenograft.[153] Autologous adipose MSCs isolated from the subcutaneous tissue are used increasingly for bone tissue engineering purposes, as adipose tissue contains a high stem cell-to-volume ratio, and autologous adipose MSCs proliferate rapidly.[152] Moreover, autologous adipose MSCs attach very easily to a scaffold and differentiate toward the osteogenic lineage, which has been reported in pre-clinical (minipig) and clinical studies.[152,154,155] Pre-clinical (rabbit, canine) and clinical studies have shown improved bone regeneration following MSFA with autologous bone marrow-derived or adipose MSCs seeded on a scaffold compared with a scaffold alone,[156-162] which is in accordance with the conclusions of systematic reviews.[150,163,164]

Acquisition of autologous bone marrow-derived or adipose MSCs is associated with risk of donor site morbidity, and it is time consuming due to cellular isolation and culturing of the stem cells. Allogeneic MCSs seeded on a scaffold are, therefore, anticipated to simplify the surgical procedure,

shorten preparation time, and diminish donor site morbidity. A pre-clinical study (rabbit) has shown that cultured allogeneic bone marrow-derived MSCs seeded on a scaffold revealed comparable osteogenic potential as autologous bone marrow-derived MSCs in critical-sized defects.[165] Pre-clinical studies (rabbit, rats) have shown that allogeneic adipose tissue-derived MSCs (AAMSCs) seeded on a scaffold revealed improved bone regeneration in critical-sized defects compared with a scaffold.[166-168] However, the osteogenic potential of AAMSCs seeded on a scaffold compared with scaffold alone following MSFA or OMSFE have never previously been assessed in pre-clinical studies involving larger animals or RCTs in humans.

Growth factors

Bone morphogenic proteins and osteoinductive growth factors contribute to the regulation of cellular activities, including angiogenesis, as well as the proliferation, migration, and differentiation of osteogenic cells. Bone morphogenetic proteins, vascular endothelial growth factor, transforming growth factor, insulin-like growth factor, fibroblast growth factors, and platelet-derived growth factor are the most used growth factors for bone tissue engineering purposes and can be applied either directly or seeded on a scaffold. Selective growth factors seem to improve bone regeneration and accelerate the remodeling of particulate grafting materials, while recombinant human bone morphogenetic proteins significantly increase connective tissue formation following MSFA.[169] However, it has been reported that recombinant human bone morphogenetic proteins-2 facilitated comparable clinical and histomorphometric outcomes as compared with other grafting materials.[170]

In this doctoral thesis, bone morphogenic proteins or growth factors are not described further as they were not investigated either alone or in combination with other grafting materials.

Integration of a non-vascularized grafting material within the maxillary sinus

Integration of a non-vascularized grafting material within the MS involves a cascade of overlapping healing phases, including hemostasis, inflammatory, reparative, and the maturing phase.[171]

The healing process is initiated by hemostasis involving constriction of the blood vessel, activation of the coagulation cascade, platelet clot formation, and migration of granulocytes and macrophages. A coagulum is formed within the wound due to the adhesion and aggregation of the platelets combined with the polymerization of fibrin, which forms an extracellular matrix that stabilizes the wound and serves as a framework for recruited inflammatory cells and cytokines.

The inflammatory phase is initiated by platelet degradation and release of vasoactive substances causing vascular permeability. Neutrophils, monocytes, and macrophages cleanse the wound and release pro-inflammatory cytokines, chemotactic mediators, and growth factors for recruitment and activation of reparative cells that induce granulation tissue formation, which replace the extracellular matrix. The released growth factors and the oxygen gradient between the applied grafting material and recipient bone stimulate angiogenesis and capillary in-growth.

The reparative phase initiates the early stages of bone regeneration. Capillary in-growth within the grafting material ensures oxygen supply and nutritional diffusion, which stimulates the cells to synthesize and secrete osteoid. The adjacent bone walls are resorbed by osteoclasts, which release bone morphogenic proteins and other growth factors that induce osteoprogenitor cell proliferation and differentiation of MSCs into osteoblast. The grafting material slowly becomes integrated within the recipient bone as woven bone is formed.

The maturing phase involves the remodeling of immature woven bone into mature lamellar bone, where the grafting material slowly becomes well-integrated within the recipient bone. The maturing

phase can last several months, where the newly formed bone gradually transforms and adapts to its functional demands.

Successful integration of a grafting material within the MS, therefore, relies on several factors including rapid vascularization of the grafting material, morphology and osteogenic potential of the bone defect, characteristics of the grafting material, immobilization, and patient-related factors.

Vascularization of the grafting material

Vascularization of the grafting material arose through sprouting angiogenesis due to the presence of pro-angiogenic cells within the recipient bone. A well-vascularized recipient bone is, therefore, essential for inducing angiogenesis and early vascularization of the grafting material. The hypoxia of the grafting material activates pro-angiogenic cells within the recipient bone to secrete pro-angiogenic growth factors including, vascular endothelial growth factor, platelet derived endothelial cell growth factor, and platelet-derived growth factor, which initiate receptors on the endothelial cells in the pre-existing blood vessels to release endothelial cells.[172] The released endothelial cells proliferate and facilitate the sprouting of capillaries, which penetrate the grafting material from the recipient bone and ensure recruitment of progenitor cells, maintenance of metabolic activities, and diffusion exchange of nutrients and oxygen.[154,172] Moreover, angiogenesis contributes to the presence and proliferation of pre-osteoblasts and the synthesis of bone matrix within the grafting material.[173] The vascularization rate of the grafting material relies on various parameters, including the presence of pro-angiogenic cells, recipient bone, augmented volume, and biomechanical characteristics of the grafting material. ABG, coagulum, autologous bone marrow-derived or adipose tissue-derived MSCs contain pro-angiogenic cells and growth factors promoting angiogenesis, while xenogenic and alloplastic bone substitutes contain no angiogenic properties. Xenogenic and alloplastic bone

substitutes, therefore, rely on the recruitment and migration of pro-angiogenic cells from the recipient bone.[172] Seeding angiogenic growth factors or pro-angiogenic cells on a scaffold may, therefore, theoretically initiate and accelerate the activation of pro-angiogenic cells and angiogenesis.[174] Xenogenic or alloplastic bone substitutes are, therefore, often combined with ABG, coagulum, or autologous bone marrow-derived and adipose tissue-derived MSCs to induce pro-angiogenic cells and promote angiogenesis. However, the vitality of the seeded pro-angiogenic cells is crucial to achieve an effect on the angiogenesis. Clinical studies have demonstrated that angiogenesis precede bone regeneration, and better vascularization contributes to improved bone regeneration following MSFA.[152,154,175] Thus, the angiogenetic potential of the bone defect needs to be assessed individually to choose the appropriate surgical approach and grafting material for ARA of the APM.

The morphology and osteogenic potential of the bone defect

The bone quality of the APM is categorized as type III/IV bone, indicating that the alveolar ridge is composed mainly of cancellous bone with a thin cortical plate.[23] The morphology, architecture, and osteogenic potential of each bone defect are different and, therefore, no grafting material is suitable for all kinds of bone defects. The morphology and osteogenic potential of each bone defect, therefore, need to be assessed individually to choose the appropriate surgical approach and grafting material. An intimate contact between the applied grafting material and the bone defect is essential to achieve vascularization and integration of the grafting material within the recipient bone. ARA of the APM uses basically the principles of guided bone regeneration,[176-178] where the SM is elevated to create a cavity between the raised SM and the adjacent MS bone walls. Thus, the created cavity within the MS resembles a three-wall bone defect sealed by the SM. Pre-clinical (minipigs, dogs) studies have shown that bone regeneration following elevation of the SM originates from the adjacent MS bone

walls and progress towards the center of the applied grafting material.[179-181] The osteogenic potential of the RARH and adjacent MS bone walls is, therefore, essential for bone regeneration and integration of the grafting material within the recipient bone.

The osteogenic potential of the RARH and the adjacent MS bone walls have been assessed in clinical studies using radiographic and histomorphometric measurements.[182-187] Decreased RARH and increased width of the MS are associated with reduced bone regeneration.[183-187] Moreover, a wider MS and large lateromedial angle are negative correlated with bone regeneration,[183] and positively correlated with the biodegradation of the grafting material.[188] Correlation between the size of the lateral window and bone regeneration has been assessed by radiographic and histomorphometric measurements with inconclusive outcome.[189,190]

The osteogenic potential of the SM has been assessed in an in-vitro and pre-clinical (mice) study.[191,192] The SM contains mesenchymal osteoprogenitor cells capable of differentiating to the osteogenic lineage, indicating that the SM contributes to bone regeneration.[191,192] However, the osteogenic potential of the SM is disputable, as reported in a systematic review.[193]

Consequently, a wide MS and limited RARH are associated with reduced bone regeneration.

Characteristics of the grafting material

The ability of the grafting material to become vascularized, facilitate bone regeneration, integrate within the recipient bone, and biodegrade is influenced by its geometry and biomechanical characteristics.

The geometry is characterized by the particle size, surface topography, crystallinity, porosity, and interconnected porous structure, which define the osteoconductive properties of the grafting material.

Small particles increase the contact area, and pre-clinical studies (monkeys) have shown increased vascularization and biodegradation with small particles compared with large particles.[55,194,195] The surface topography affects protein absorption, cellular adhesion, osteogenic differentiation, and extracellular matrix production of osteoblasts and MSCs.[196-198] An in-vitro study has shown increased osteoblast cell proliferation by changing the surface topography,[199] but the ideal surface topography to achieve the best bone regenerative potential is unknown.[200] The crystallinity influences the density, diffusion, and biodegradation of the grafting material. The crystallinity gradually increases with higher sintering temperatures, causing reduced biodegradation, cellular adhesion, and protein absorption.[201] The porosity and interconnected porous structure affect the surface area, diffusion exchange of nutrients, angiogenesis, cellular migration, and surface adsorption of proteins. The ideal pore size and interconnectivity for inducing angiogenesis and bone regeneration is unknown. Small pores inhibit angiogenesis, diffusion exchange of nutrients, removal of waste products, and cell migration, whereas large pores decrease the surface area for cell adhesion.[104] A high degree of interconnectivity is essential for promoting angiogenesis, in-growth of bone, and integration of the grafting material within the recipient bone.[104] A structure like human cancellous bone with a porosity of 30-90% and an intermediate pore size of 200-500 μm has, therefore, been recommended.[105,202]

Consequently, the geometry and biomechanical characteristics of the grafting material influence the angiogenesis, bone regeneration, and integration of the grafting material within the recipient bone.

Immobilization of the grafting material

Immobilization is an important criterion for bone regeneration and integration of the grafting material within the recipient bone. The cavity between the raised SM and the adjacent MS bone walls enables the application of a particulate grafting material. However, soft tissue interference and displacement

of the grafting material through the created lateral window have been reported following MSFA.[203] The lateral window has, therefore, historically been covered by a non-fixated or fixated resorbable collagen barrier membrane to improve bone regeneration, stabilize the grafting material, hamper soft tissue interference, and prevent bone substitute particles from penetrating the buccal mucosa.[203] However, barrier membrane coverage of the lateral window may compromise the vascular supply to the grafting material and increase the risk of infection. The effect of barrier membrane coverage of the lateral window on bone regeneration within the MS has, therefore, been controversial, and no significant difference in the amount of vital bone formation has been reported in a systematic review, with or without barrier membrane coverage.[204]

Patient characteristics and surgical risk factors

Various patient characteristics and surgical risk factors have a significant impact on implant outcome. Smoking habits, alcohol consumption, gingival phenotype, bone degenerative diseases, radiotherapy, diabetes, and acute and chronic rhinosinusitis compromise the implant survival, bone regeneration, and frequency of surgical and biologic complications following ARA of the APM, as reported in systematic reviews and meta-analysis.[72-74] Moreover, vascularization of the MS decreases with age, edentulism, atrophy, radiotherapy, and metabolic bone diseases like osteoporosis.[205] Bleeding and SM perforation are the most common surgical complications.[206] The incidence of SM perforation varies between 11-56%.[206] A narrow MS, sinus septa, RARH <3.5 mm, and thin SM predispose for a higher perforation rate.[206,207] SM perforation is associated with a higher prevalence of sinusitis, infection, graft failure, compromised bone regeneration, and implant loss.[207-209]

Purpose of the studies

The objective of this doctoral thesis is to address the appropriate surgical approach and grafting material for ARA of the APM in conjunction with simultaneous implant placement, as evaluated by clinical, radiographic, histologic, and patient-reported outcome measures (PROMs).

Outcome measures:

- Survival of suprastructures and implants
- Implant stability quotient
- Health status of the peri-implant tissue
- Peri-implant marginal bone loss
- Bone regeneration
- Surgical, biological, and technical complications
- Bone density
- Patient-reported outcome measures

Summary of used methods

Systematic review and meta-analysis (I-IV, VI-VIII)

The systematic reviews (I-IV, VI-VIII) were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[217] The material and methods used were meticulous describe in the protocols and registered in PROSPERO. The focus questions were developed according to Patient, Intervention, Comparison, and Outcome (PICO). The search strategies were conducted in collaboration with a librarian and utilized a combination of Medical

subject heading (MeSH) and free text terms. The search strategy incorporated examinations of electronic databases, supplemented by a hand-search of relevant journals. A MEDLINE (PubMed), Embase, and Cochrane Library search was conducted. Grey literature, unpublished literature, and other databases like Scopus, Google Scholar, and Research Gate were not included in the search strategy. The level of authors agreement was assessed by Cohen's kappa coefficient (VIII).[216] Data were extracted using a specific data-collection form ensuring systematic registration of the outcome measures. The quality and risk of bias assessment was performed according to a none validated methodological quality rating systems and categorized as low, moderate, or high risk of bias (I-IV, VI),[210-214] or Cochrane Collaboration's risk of bias tool of RCTs[218,219] (VII, VIII).[215,216]

Meta-analyses were conducted if it was possible to combine data from multiple studies where similar effects were measured (II-IV, VI-VIII).[211-213,214-216] Forest plots were fabricated to graphically illustrate the estimated results and heterogeneity from the included studies addressing the same question (II-IV, VI-VIII).[211-213,214-216] Funnel plots were produced for assessment of publication bias, where larger studies with higher power are placed towards the top (smaller standard errors), while lower powered studies are placed towards the bottom (VII, VIII).[215,216]

Retrospective study (V)

The 10-year implant outcome and PROMs were retrospectively assessed following MSFA with ABG from the mandibular ramus in conjunction with simultaneous or delayed implant placement (V).[220] Patient demographic as well as clinical and radiographic data were analyzed from in-hospital records. Subjective assessment of the peri-implant soft tissue, implant crown, implant function, and total implant outcome was assessed by questionnaire using VAS. Professional assessment of the esthetic

outcome was performed using the pink esthetic score and white esthetic score.[221,222] Two-dimensional linear changes of the grafting material over time were measured on panoramic radiographs.

Pre-clinical randomized controlled trial (XIV, XVI, XX)

Female Göttingen minipigs (Ellegaard Göttingen Minipigs A/S, Dalmose, Denmark) with a mean age of 18 months and 30 kilos were used (XIV, XVI, XX).[223-225] The studies were conducted in accordance with institutional and national standards as well as ARRIVE guidelines for animal studies. The animals were kept in cages with 2-3 minipigs and fed with a standardized laboratory diet (Altromin 9023, Altromin International Gmbh, Lage, Germany) and water ad libitum. Anesthesia and drug administration were performed according to a previous described procedure.[68,181]

Randomized controlled clinical trial (IX-XIII, XV, XVII-XIX)

Study protocols were approved by the regional research ethics committee, registered in ClinicalTrials, and conducted in agreement with guidelines for reporting RCTs (CONSORT) (http://www.consort-statement.org/) (IX-XIII, XV, XVII-XIX).[226-234] Patients were recruited by public invitation through Facebook or admitted to the hospitals. Candidates were screened for inclusion and exclusion criteria. Healthy adult patients with a missing posterior maxillary tooth were offered to participate in the studies if they met the inclusion criteria. Included patients received written and oral information about the study and signed an informed consent form before initiating the study.

Surgical procedure

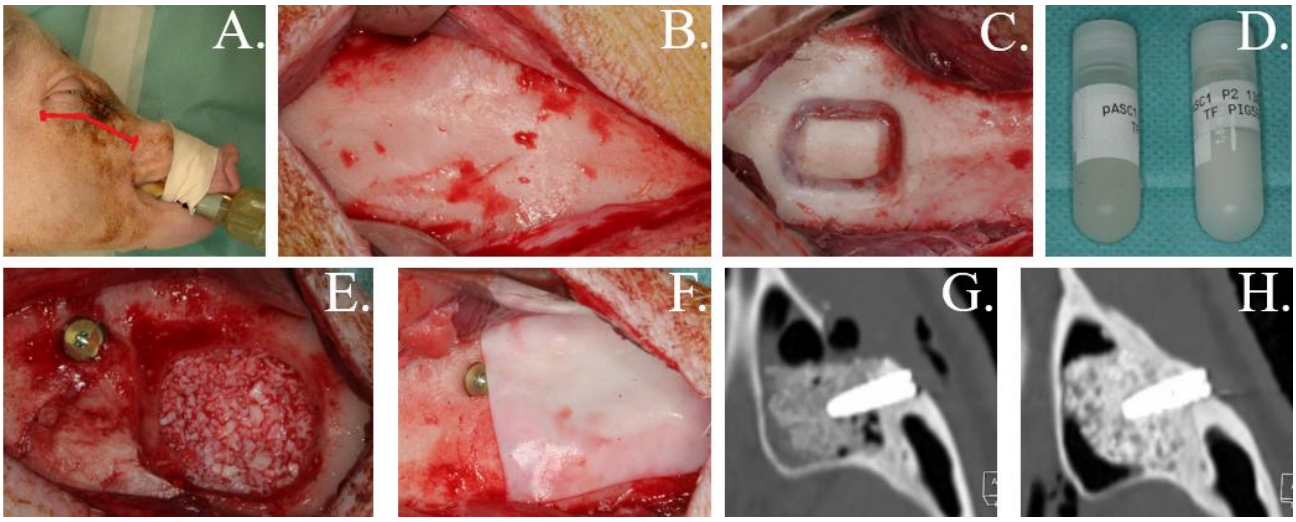
Pre-clinical randomized controlled trial (XIV, XVI, XX)

Surgeries were performed in general anesthesia with an orotracheal tube. The MS wall was exposed through a skin incision below the lower eyelid, and a lateral bony window to the MS was created with burrs before the SM was elevated. The MS wall posteriorly to the created window was reduced to a thickness of 5 mm and an implant bed was successively prepared. Simultaneous implant placement was performed with 4.0 x 15 mm implants (Brånemark, RP, TiUnite (XVI);[224] NobelParallel CC, TiUltra RP (XIV, XX).[223,225] The implants were mounted with a cover screw.

Bilateral MSFA was performed in 40 minipigs with ABG from the iliac crest or the mandible combined with deproteinized bovine bone mineral (DBBM) (Bio-Oss, 1-2 mm, Geistlich Pharma AG, Wolhusen, Switzerland) in different ratios (100:0, 75:25, 50:50, 25:75, 0:100).[224] A standardized graft volume of 5 cm^3 was applied in each MS as estimated by stainless-steel cups with volumes of 5, 3.75, 2.5, and 1.25 cm^3. The grafting material was soaked in autogenous blood and stored at room temperature, before being packed around the exposed implant surface within the MS. The created window was covered by a resorbable collagen barrier membrane (Bio-Gide, 25 x 25mm, Geistlich Pharma AG, Wolhusen, Switzerland), before periosteum and skin were sutured in layers (XVI).

Bilateral MSFA was performed in 18 minipigs with AAMSCs seeded on DBBM and compared with excipient on DBBM.[223,225] Abdominal adipose tissue (50 ml) was aspirated from a non-familiar related minipig donor for isolation and culturing of AAMSCs. Aliquots of AAMSCs and excipient were fabricated with identical appearance and quantity. The aliquots were randomly assigned label A or B. Aliquot A was always applied in the right MS and aliquot B in the left MS. Aliquot A or B was mixed with standardized volume of 2 g DBBM (Creoss, vival, L, 1.0-2.0, Nobel Biocare, Gothenburg, Sweden). The entire graft was packed around the exposed implant surface securing identical grafting

material quantities within each MS. The window was covered by a resorbable collagen barrier membrane (Creos, xenoprotect, 30-40 mm, Nobel Biocare, Sweden), before suturing (XIV, XX).



MSFA with AAMSCs seeded on DBBM compared with DBBM. A-C: The MS wall was exposed through a skin incision. A window to the MS was created. D: Aliquots of AAMSCs and excipient with identical appearance and quantity. E,F: The implant and grafting material was covered by a collagen membrane. G,H:CT-scan after surgery and euthanasia.

Retrospective study (V)

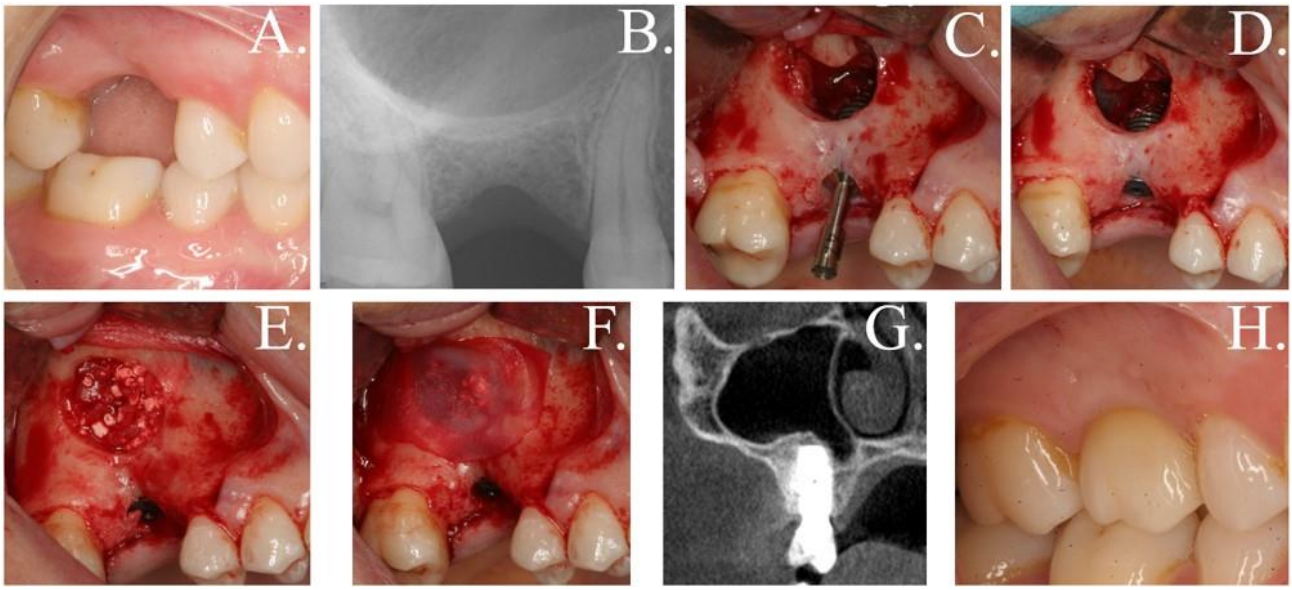
MSFA was performed under local or general anesthesia using the method previously described.[220] The technique for harvesting autogenous bone blocks from the mandibular ramus has previously been described.[235] A non-standardized amount of ABG was applied in each MS. Simultaneous implant placement was performed if the RARH was >5 mm and primary implant stability was achievable (V).

Randomized controlled clinical trial (IX-XIII, XV, XVII-XIX)

MSFA was performed under local anesthesia using the method previously described.

MSFA and simultaneous implant placement (OsseoSpeed EV, Astra Tech Implant System, straight, 13 mm, diameter 3.6, 4.2, 4.8) was performed in 60 patients with a RARH at the implant site

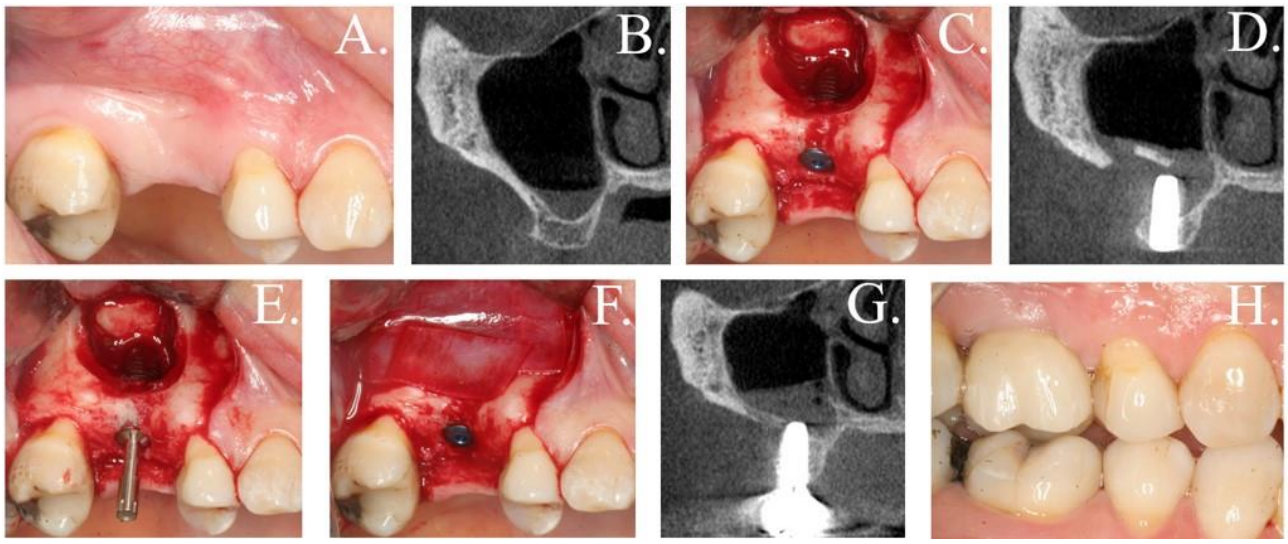
≥3 mm and ≤7 mm.[227,233,234] Included patients were randomly assigned to ABG, 1:1 ratio of ABG and deproteinized porcine bone mineral (DPBM), or 1:1 ratio of ABG and biphasic bone graft material (BBGM). Patients were blinded to their allocation group. Customized stainless-steel cups (1.0 cm^3) standardize the amount of ABG. The different ratios were 2.0 cm^3 ABG, 1.0 cm^3 ABG and 1 mL DPBM (Symbios Xenograft Granules, 1.0-2.0 mm, Dentsply Sirona, Implants, Mölndal, Sweden), and 1.0 cm^3 ABG and 1 mL BBGM (Symbios Biphasic Bone Graft Material, 1.0-2.0 mm, Dentsply Sirona Implants, Mölndal, Sweden). The different compositions were soaked in autogenous blood from the surgical site and stored at room temperature until use. The entire graft was packed around the exposed implant surface securing identical grafting material quantities within each MS. The window was covered by a resorbable collagen barrier membrane (Symbios pre-hydrated membrane, 20 mm × 30 mm, Dentsply Sirona Implants, Mölndal, Sweden), before suturing. No provisional restoration was used during healing. Healing abutment connection was performed after six months, before the prosthetic rehabilitation was finalized (X, XVIII, XIX).



MSFA. A, B: Partial edentulous posterior maxilla with a RARH of 4 mm. C,D: A window to the MS is created. The SM is elevated. The ISQ value is determined. E,F: 1:1 ratio ABG and BBGM is applied. The window is covered by a collagen membrane. G: CBCT-scan showing ESBG, after 1-year of FIL. H: Prosthetic rehabilitation after 1-year of FIL.

MSME was performed in local anesthesia using the method previously described.

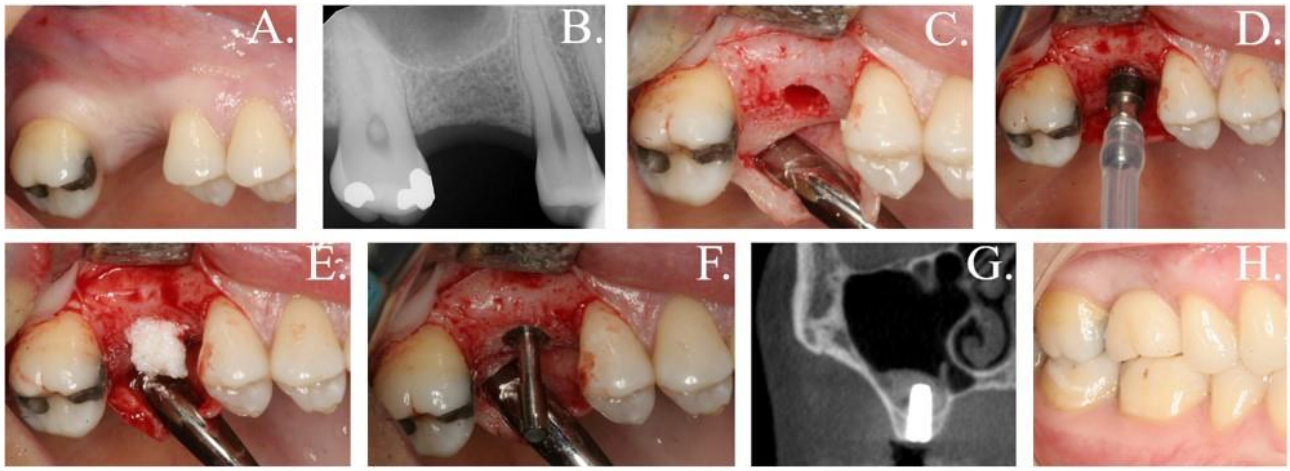
MSME and simultaneous implant placement (OsseoSpeed EV, Astra Tech Implant System, straight, 13 mm, diameter 3.6, 4.2, 4.8) was performed in 40 patients with a RARH at the implant site ≥4 mm and ≤7 mm.[228,231,232] Included patients were randomly assigned to coagulum or a 1:1 ratio of ABG and DPBM. Patients were blinded to their allocation group. In the group assigned to coagulum, autogenous blood (2 ml) was aspirated from the surgical site and injected underneath the SM around the exposed implant surface. The amount of ABG was standardized by customized stainless-steel cups (1.0 cm^3). The grafting material consisted of 1.0 cm^3 ABG and 1 mL DPBM (Symbios Xenograft Granules, 1.0-2.0 mm, Dentsply Sirona, Implants, Mölndal, Sweden), and was soaked in autogenous blood from the surgical site and stored at room temperature until use. The entire graft was packed around the exposed implant surface securing equal quantities of the grafting material within each MS. The created window was covered by a resorbable collagen barrier membrane (Symbios pre-hydrated membrane, 20 mm × 30 mm, Dentsply Sirona Implants, Mölndal, Sweden), before suturing the mucosa. No provisional restoration was used during the healing period. Healing abutment connection was performed after six months, before the prosthetic rehabilitation was finalized (XI, XV, XVII).



MSME. A, B: Partial edentulous posterior maxilla with a RARH of 4 mm. C-F: A window to the MS is created. The SM is elevated. The ISQ value is determined. The cavity is filled with autogenous blood (2 ml) The window is covered by a collagen membrane. G: CBCT-scan showing ESBG, after 1-year of FIL. H: Prosthetic rehabilitation after 1-year of FIL.

OMSFE was performed in local anesthesia using the method previously described in this thesis.

OMSFE and simultaneous implant placement (OsseoSpeed EV, Astra Tech Implant System, straight, 13 mm, diameter 3.6, 4.2, 4.8) was performed in 40 patients with a RARH at the implant site of ≥6 mm and ≤10 mm.[226,229,230] Included patients were randomly assigned to DBBM (Bio-Oss collagen 250 mg, 0.4-0.5 cm^3, Geistlich Pharma AG, Wolhusen, Switzerland) or no grafting material. DBBM was soaked in saline and stored at room temperature until use. Patients were blinded to their allocation group. The MS floor was raised to the planned implant length using calibrated osteotomes combined with piezoelectric surgery and hydraulic pressure technique (Sinus physiolift II, Mectron, Carasco, Italy). No provisional restoration was used during healing. Healing abutment connection was performed after six months, before the prosthetic rehabilitation was finalized (IX, XII, XIII).



OMSFE. A, B: Partial edentulous posterior maxilla with a RARH of 5 mm. C-F: Preparation of the implant bed, which is ended 1-2 mm beneath the MF floor. The SM including the original MS floor is elevated to the planned implant length using hydraulic pressure technique. Bio-Oss collagen sponge is applied through the implant site underneath the SM. The ISQ is determined. G: CBCT-scan showing ESBG, after 1-year of FIL. H: Prosthetic rehabilitation after 1-year of FIL.

Bone grafting materials

Autogenous bone graft

Pre-clinical randomized controlled trial (XVI)

A cortico-cancellous autogenous bone block involving the entire posterior iliac crest, or a cortical mandibular bone block from the lateral and inferior mandibular border was harvested through a skin incision, and particulated by a bone mill (Roswitha Quétin DentalProdukte, Leimen, Germany) with 3 mm perforations to obtain ABG particles with a size of 0.5-2mm^3 (XVI).[224]

Retrospective study (V)

The cortical plate of the ascending mandibular ramus was harvested and particulated using a bone mill (Roswitha Quétin DentalProdukte, Leimen, Germany) with 3 mm perforations to obtain ABG particles with a size of 0.5-2mm^3 (V).[220]

Randomized controlled clinical trial (X, XI, XV, XVII-XIX)

Cortical ABG particles were harvested from the zygomatic buttress with a cortical bone collector (Curved SafeScraper, Meta, Reggio Emilia, Italy).[227,228,231-234] Cortical ABG particles obtained with a manual bone scraper are oblong or quadrangular shape with a length of 900-1700 µm and a thickness of 100 µm.[236] The particle size is 200-1100 µm, and the cell viability varies between 45-72%.[236,237]

Xenogenic bone substitute

Pre-clinical randomized controlled trial (XIV, XVI, XX)

DBBM (Bio-Oss®) with a particle size of 1000-2000 µm was used (XVI).[224] Bio-Oss originates from bovine femoral heads from registered slaughterhouses in Australia and New Zealand. Bio-Oss is classified of having a negligible risk of bovine spongiform encephalopathy according to the World Organization for Animal Health. Purification of Bio-Oss implies thermal treatment with gradual heating up to 350°C, followed by a chemical purification using a strongly alkaline agent, sodium hydroxide. The pore size varies between 455-667 µm with a porosity of 58-81%.[238-241]

DBBM (Creos) with a particle size of 1000-2000 µm was used (XIV, XX).[223,225] Creos origin from bovine pelvic and femur bone. Purification of Creos implies alkaline treatment before heat treatment. The calcium phosphate ratio resembles human bone with a low crystalline structure. The pore size varies between 60-100 µm with a porosity of 50-90%.

The manufacturer provides the above product information, and it has not been possible to verify this information in either in-vitro, pre-clinical, or clinical studies.

Randomized controlled clinical trial (IX-XIII, XV, XVII-XIX)

DPBM (Symbios xenograft) with a particle size of 1000-2000 µm was used (X, XI, XV, XV-XIX).[227,228,231-234] Symbios xenograft origin from porcine. The porosity varies between 88-95%.

The above product information is provided by the manufacturer, and it has not been possible to verify these information's in either in-vitro, pre-clinical, or clinical studies. However, Symbios xenograft (250-1000 µm) combine with ABG in an 80:20 ratio has been compared with 80:20 ratio of Bio-Oss (250-1000 µm) and ABG in conjunction with MSFA revealing no significant difference is in histologic, histomorphometrically, or immunohistochemical outcome.[103]

Bio-Oss collagen with a size of 250 mg was used (IX, XII, XIII).[226,229,230] Bio-Oss collagen consist of 90% DBBM particles which are embedded in a 10% collagen matrix of porcine origin and is available in four different block sizes. An in-vitro study revealed an average pore size of 65.1 µm, and a porosity of 50.2 µm, as evaluated by µCT-scan.[242]

BBGM (Symbios Biphasic Bone Graft Material) with a particle size of 1000-2000 µm was used (X, XVIII, XIX). Symbios Biphasic Bone Graft Material is a resorbable inorganic bone-forming material of plant origin derived from red algae consisting of 20% hydroxyapatite and 80% β-tricalcium phosphate.

The manufacturer provides the above product information, and it has not been possible to verify this information in either in-vitro, pre-clinical, or clinical studies.

Observation periods

Pre-clinical randomized controlled trial (XIV, XVI, XX)

Histomorphometric and radiographic outcomes were assessed after one month, two months, and four months (XIV, XX).[223,225] Histomorphometric outcomes were assessed after 12 weeks (XVI).[224]

Retrospective study (V)

Clinical, radiographic, and PROMs were assessed after 10-years (V).[220]

Randomized controlled clinical trial (IX-XIII, XV, XVII-XIX)

Clinical, radiographic, and PROMs were assessed at different time points, including enrolment (T0), implant placement in conjunction with MSFA, MSME, or OMSFE (T1), one week (T2) and one month (T3) after implant placement, healing abutment connection (T4), immediately after delivery of the prosthetic rehabilitation (T5), and after 1-year of FIL (T6) (IX-XIII, XV, XVII-XIX).[226-234]

Clinical outcomes

Survival of suprastructures (XII, XV, XVIII)

Failure of suprastructures was defined as loss due to a mechanical and/or biological complication at T5 and T6.[229,231,233]

Survival of implants (XII, XV, XVIII)

Failure of implants was defined as loss, due to mobility, of previously clinically osseointegrated implants or removal of non-mobile implants due to progressive PIMBL or infection at T4-T6.[229,231,233]

Implant stability quotient (XII, XV, XVIII)

ISQ was assessed by resonance frequency analysis (Penguin; Integration Diagnostics Sweden AB, Gothenburg, Sweden), at T1 and T4. Short magnetic pulses were sent from the measuring instrument to a MulTipeg, which was mounted on the implant. The magnetic pulses interact with a magnet inside the MulTipeg, causing vibrations. The measuring instrument collects the alternating magnetic field from the vibrating magnet and calculates the ISQ value. The ISQ measurement was repeated until the same value was recorded twice, which was taken as the authentic value.[229,231,233]

Health status of the peri-implant tissue (XII, XV, XVIII)

The health status of the peri-implant tissue was assessed by papilla morphology, plaque index, gingival index, and probing pocket immediately at T5 and T6.[243,244] The registrations were measured to the nearest millimeter, and an average score was estimated based on three facial and oral measurements, respectively.[229,231,233]

Surgical, biological, and technical complications (IX-XII, XV, XVIII)

Surgical, biological, and technical complications were registered at T1-T6.[226-229,231,233] Surgical complications were defined as intra- and early postoperative complications. Biological complications imply disturbances in the implant function due to a biological process affecting the peri-implant

tissue, while technical complications represent a mechanical damage of the implant components or suprastructures.[245]

Radiographic assessment

Peri-implant marginal bone (XII, XV, XVIII)

PIMBL was assessed using linear measurements on digital peri-apical radiographs at T1, T4-T6 (XII, XV, XVIII).[229,231,233] Intraoral radiographs were obtained with a photostimulable phosphor system (Digora FMX; Soredex Orion Corporation, Helsinki, Finland). Reference points were the coronal margin of the implant shoulder and the most coronal point of BIC as measured by ImageJ (National Institutes of Health, Bethesda, MD, USA).[246] Correction of magnification and calibration were based on the distance of the micro-threaded portion of the implant (3.5 mm), or the implant length (13 mm).

Three-dimensional radiographic assessment

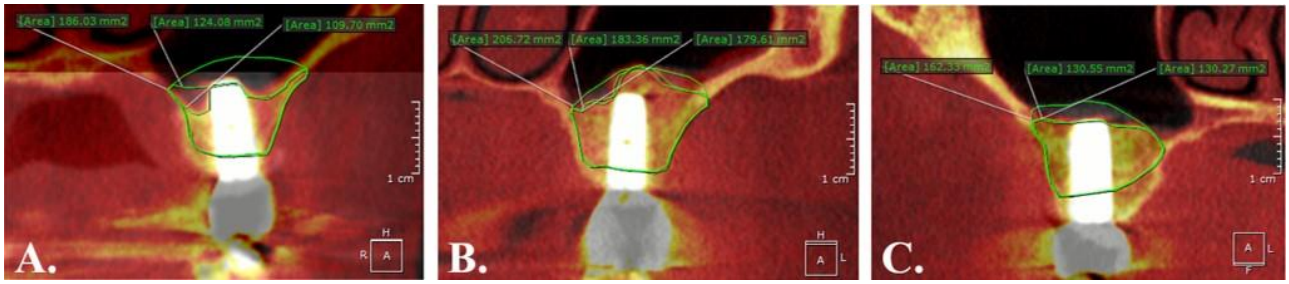
Pre-clinical randomized controlled trial (XIV)

Three-dimensional volumetric changes of the grafting material were assessed by CT-scans obtained immediately after MSFA and compared with CT-scans obtained after euthanasia at one month, two months, and four months, respectively (XIV).[223] CT-volumes were generated using OnDemand3D software. The axial, coronal, and sagittal planes were adjusted according to the center of the longitudinal implant axis. The original MS floor and circumference of the augmented area immediately after MSFA were manually outlined (mm^2) and superimposed with the identical CT-scan image obtained after euthanasia. Volumetric changes of the grafting material (mm^3) were

calculated by subtracting of the measured volumes after euthanasia from the volume immediately after MSFA.

Randomized controlled clinical trial (XIII, XVII, XIX)

Three-dimensional assessment of volumetric changes was estimated by CBCT-scans obtained at T0, T1, T5, and T6 using a similar method as described for the pre-clinical study (XIII, XVII, XIX).[230,232,234] The IPL at T1 and RARH at T0 were correlated with radiographic ESBG at T1, T5, and T6.



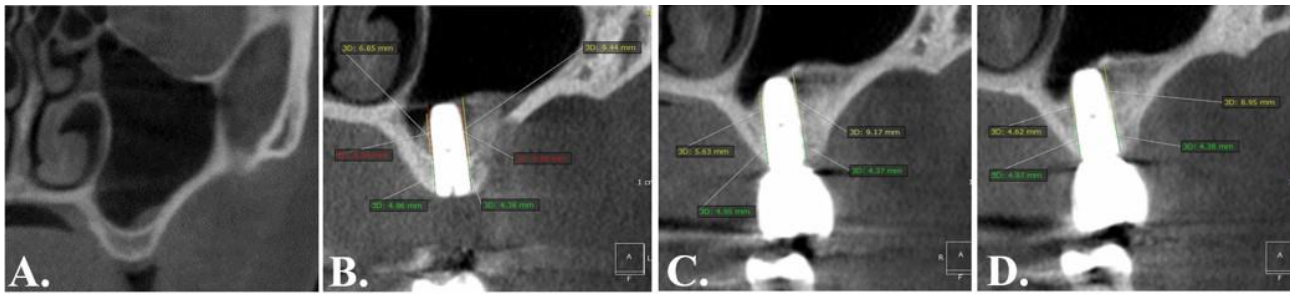
Three-dimensional assessment of volumetric changes of the grafting material. A: ABG. B: 1:1 mixture of ABG and DPBM. C: 1:1 mixture of ABG and BBGM. CBCT-scan obtained immediately after MSFA are superimposed with the scan taken after delivery of the prosthetic rehabilitation, and 1-year of FIL. The original border of the MS and circumference of the augmented area are outlined (mm^2) before the volume of the grafting material is calculated, at the different time periods.

Two-dimensional radiographic assessment

Randomized controlled clinical trial (XIII, XVII, XIX)

Two-dimensional assessment of height changes was estimated by coronal CBCT-scan images using linear measurements of the RARH, IPL, and grafting material (XIII, XVII, XIX).[230,232,234] The RARH at the planned implant site was measured at T0. The RARH was defined by a perpendicular line from the center of the alveolar crest to the original MS floor. The RARH corresponding to the mesial and distal implant surfaces were measured at T1. The IPL corresponding to the facial and oral implant

surfaces within the MS was measured at T1 based on the known implant length (13 mm). Two-dimensional linear measurements at the longitudinal facial and oral axis of the implants from the MS floor to the apex of the implant were performed and defined as the IPL within the MS at T1. The height of the grafting material corresponding to the facial and oral implant surfaces was measured at T1, T5, and T6. Two-dimensional linear measurements at the longitudinal facial and oral surface of the implants from the MS floor to the highest point of the grafting material were performed and defined as the height of the grafting material at T1, T5, and T6. The correlation between the IPL at T1 and the height of the grafting material at T1, T5, and T6 was estimated using two-dimensional coronal CBCT sections. Bone covering the facial and oral implant surfaces within the MS were measured using linear measurements from the MS floor to the most apical part of the bone covering the implant surface at T1, T5, and T6 and correlated with the IPL at T1.



Two-dimensional linear measurements on the facial and oral implant surface of the RARH (green lines), grafting material (yellow lines), and IPL (red lines) using coronal CBCT scans. A: Enrolment, B: Immediately after MSFA with 1:1 ABG and DPBM. C: Delivery of the prosthetic rehabilitation. D: 1-year of FIL.

Bone density

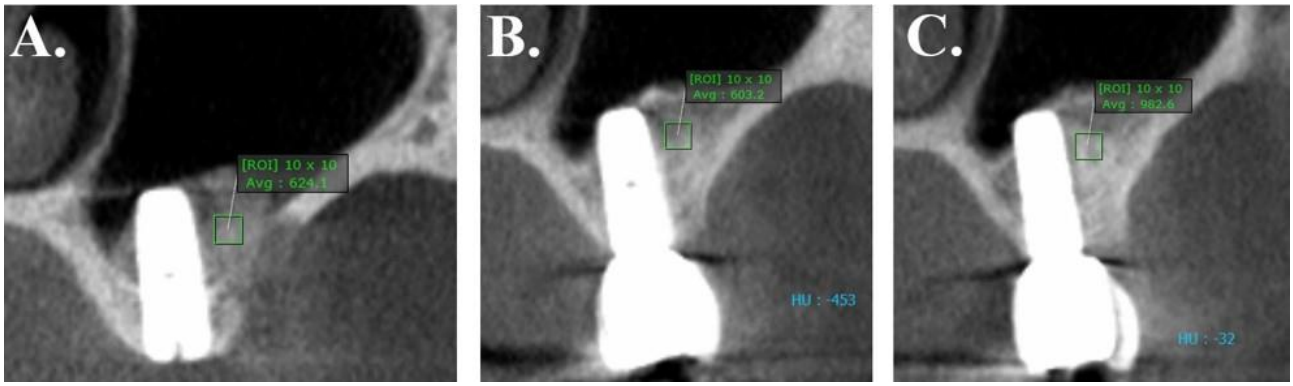
Pre-clinical randomized controlled trial (XIV)

BD of the grafting material was assessed by Hounsfield unit (HU) on two-dimensional coronal CT-scans images (XIV).[223] The BD after MSFA was used as a reference and matched with the BD at one month, two months, and four months, respectively. BD was measured on 11 sections, five sequential

CT-scan images on each side of the longitudinal implant axis. A region of interest (ROI) (15 x 15 mm) was randomly outlined on each CT image within the periphery of the grafting material. The HU values within the square were automatically displayed.

Randomized controlled clinical trials (XVII, XIX)

BD of the grafting material was measured using grayscale density on two-dimensional coronal CBCT images at T1, T5, and T6 (XVII, XIX).[232,234] The BD at T1 was used as reference and matched with BD at T5 and T6. BD was measured on 11 sections, five on each side of the longitudinal implant axis. A standardized 10 x 10 square was created and randomly positioned within the graft using OnDemand software. The grayscale density values within the square were automatically displayed.



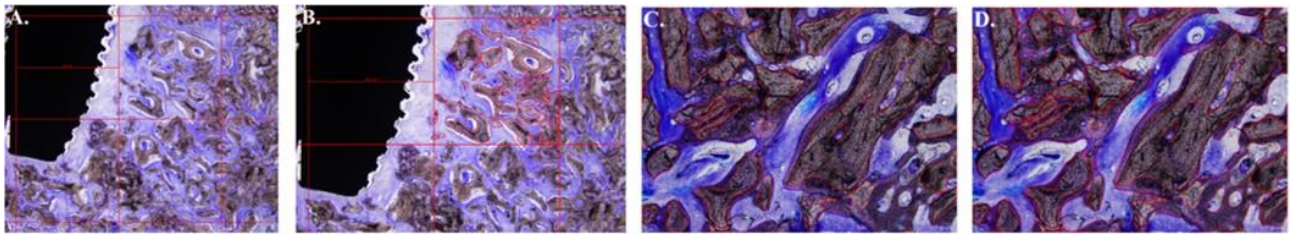
Coronal CBCT. MSFA with 1:1 ABG and DPBM. A standardized 10 x 10 square was created and randomly positioned within the grafting material. A: Immediately after MSFA. B: Completion of prosthetic rehabilitation. C: 1-year of FIL.

Histomorphometric assessment

Pre-clinical randomized controlled trials (XVI, XX)

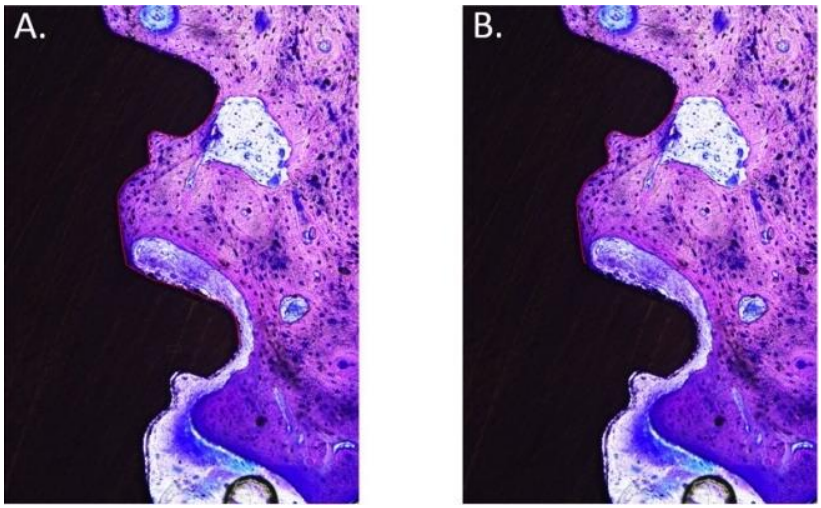
Percentage of bone, non-mineralized tissue, and residual grafting material were assessed by histomorphometric analysis (XVI, XX).[225,232] Quantitative histomorphometry was performed manually using an optical light microscopy (Nikon Eclipse E600) and Nikon NIS-elements computer

software. High-resolution photographs of the histologic sections were uploaded in the software with the most applicable magnification. In each histologic section, a standardized grid containing uniform squares was automatically generated by the computer and randomly positioned on the sections. In most of the histologic sections, solely one square matched the augmented area between the original MS floor and the apical part of the implant without including the implant or the recipient bone. The percentage of bone, non-mineralized tissue, and residual grafting material were estimated within the selected square, which was defined as the ROI. The total area within the ROI was calculated before non-mineralized tissue and residual grafting material particles were manually outlined on the computer screen. The software automatically calculated the total area of non-mineralized tissue and residual grafting material. The percentage of bone was estimated by subtracting the area of non-mineralized tissue and residual grafting material from the total area within the ROI.



A: Standardized grid containing 400 x 400 µm squares randomly positioned on the histologic sections (x1 magnification). B: Bone and residual grafting material outlined (x1 magnification). C: ROI was magnified (x4) and residual grafting material was outlined. D: Bone was outlined before the total area of non-mineralized tissue was calculated.

The external implant threads were used to assess BIC. The implant surface within the specimens was magnified (x20). The total length of each implant thread´s was outlined and measured. The length of the bone in contact with the implant surface within the threads was outlined and measured. The percentage of BIC was calculated by dividing the length of the bone in contact with the total length of the implant threads.



A: The total length of the external implant thread outlined and measured (red line). B: The length of bone in contact with the implant surface within the implant threads outlined and measured (red line).

Patient-reported outcome measures

Retrospective study (V)

Patient satisfaction with the peri-implant soft tissue, prosthetic solution, implant function, and implant outcome was assessed by a validated questionnaire using VAS after 10-year (V).[220]

Randomized controlled clinical trials (IX-XII, XV, XVIII)

PROMs including patient´s perception of recovery, OHQoL, and satisfaction with the treatment outcome were assessed at T2, T3, T5, and T6 (IX-XII, XV, XVIII).[226-229,231,233]

Patient´s perception of recovery, including pain, social and working isolation, physical appearance, eating and speaking ability, diet variations, sleep impairment, and discomfort, were assessed by validated questionnaire and visual analogue scale (VAS) at T2 and T3.[226,228]

OHQoL was assessed by The Oral Health Impact Profile-14 (OHIP-14) questionnaire at T0, T5, T6 (Study IX-XII, XV, XVIII).[226-229,231,233] OHIP-14 is arranged in seven conceptual dimensions

including functional limitation, physical discomfort, psychological discomfort, physical disability, psychological disability, social disability, and handicap.[247,248] OHIP-14 questionnaire consists of 14 items, as two items measure each dimension. The response format is: Very often = 4; fairly often or many times = 3; occasionally = 2; hardly ever or nearly never = 1; never/I do not know = 0. OHIP-14 scale ranged from 0 to 56 and dimension score ranged from 0 to 8. The values of the 14 items and each dimension are summed to calculate the OHIP-14 severity score. Higher scores indicate poorer OHQoL.[226-229,231,233] OHIP-14 expresses the patient's overall oral impairment and does not take the surgical intervention into account. OHIP-14 questionnaire should, therefore, be supplemented with additional OHQoL questionnaires to interpret patient's perception of the treatment and recovery as well as the social impact of oral disorders on their generally well-being (XVIII).[233]

Satisfaction with the peri-implant soft tissue, prosthetic solution, implant function, and implant outcome was assessed by validated questionnaires using VAS at T5 and T6.[229,231,233]

Results

Paper I (systematic review)

The aim was to compare implant outcomes following MSME and simultaneous implant placement with or without a grafting material.[210] Thirteen studies were included, involving two short-term RCTs, and 11 non-comparative studies. All studies were considered at high risk of bias. MSME without a grafting material revealed bone regeneration and high implant survival, comparable with a grafting material. However, long-term RCTs assessing clinical, radiographic, and PROMs are lacking.[210]

Paper II (systematic review and meta-analysis)

The aim was to test the hypothesis of no difference in long-term (≥5 years) implant outcomes following MSFA with ABG compared with ABG mixed with bone substitutes or bone substitutes alone.[211] Nine studies were included, involving one retrospective comparative study and eight non-comparative studies. Two studies were considered low risk of bias, and seven by high risk of bias. High survival of suprastructures and implants, limited PIMBL, high ISQ value, low frequency of complications, and high patient satisfaction were disclosed, regardless of the grafting material. Long-term RCTs comparing ABG with other grafting materials were not identified.[211]

Paper III (systematic review and meta-analysis)

The aim was to test the hypothesis of no difference in long-term (≥5 years) implant outcomes following OMSFE with or without a grafting material.[212] Eight studies were included, involving one RCT and seven non-comparative studies. Six studies were considered at moderate risk of bias, and two at high risk of bias. High survival of suprastructures and implants, limited PIMBL, bone regeneration, and low frequency of complications was disclosed, with or without a grafting material. Long-term RCTs were missing, and PROMs have never been assessed in long-term studies.[212]

Paper IV (systematic review and meta-analysis)

The aim was to test the hypotheses of no differences in implant outcome following MSFA with alloplastic bone substitutes compared with other grafting materials.[213] Five RCTs with low risk of bias were included. Alloplastic bone substitutes disclosed high survival rate of suprastructures and implants with no significant difference compared with ABG or xenogenic bone substitutes.

Alloplastic bone substitutes demonstrated significantly less bone regeneration compared with ABG, whereas no significant difference was revealed as compared with xenogenic bone substitutes.[213]

Paper V (retrospective study)

The aim was to assess the 10-year esthetic implant outcome and PROMs following MSFA with ABG from the mandibular ramus.[220] The 10-year survival of suprastructures and implants was 84% and 100%, respectively. Patients were highly satisfied with the esthetic implant outcome, as expressed by VAS-scores higher than 90 for all parameters. Mean pink and white esthetic scores were 9 and 8, after 10-years. The augmented height was reduced by 6.9% and 14.9% at 1-year and 10-years, respectively.[220]

Paper VI (systematic review and meta-analysis)

The aim was to test the hypothesis of no difference in implant outcome following MSFA with or without barrier membrane coverage of the lateral window.[214] Six RCTs with a low to high risk of bias and one controlled trial with a high risk of bias were included. There was no significant difference in any of the outcome measures. However, barrier membrane coverage of the lateral window non-significantly improved bone formation and diminished proliferation of non-mineralized tissue.[214]

Paper VII (systematic review and meta-analysis)

The aim was to test the hypothesis of no difference in histomorphometric outcome following MSFA with ABG compared with other grafting materials.[215] Sixteen RCTs with unclear risk of bias were included. The included studies were characterized by unclear risk of bias and methodological

confounding factors. Descriptive statistics combined with meta-analysis revealed that ABG facilitate improved histomorphometric outcomes compared with other grafting materials. Similar BIC values were reported when ABG was compared with either coagulum or mixtures of ABG and xenograft.[215]

Paper VIII (systematic review and meta-analysis)

The aim was to test the hypothesis of no difference in volumetric stability following MSFA with ABG compared with other grafting materials using three-dimensional radiographic measurements.[216] Four short-term RCTs with unclear risk of bias were included. Volumetric reduction is inevitable following MSFA, regardless of the grafting material. ABG, allogenic bone graft, and alloplastic bone substitutes reveal significant volumetric reduction during the early healing period, while the volumetric stability was improved by combining ABG and xenograft. Correlation between volumetric grafting material changes and predictive parameters were not assessed in the included studies.[216]

Paper IX (randomized controlled clinical trial)

The aim was to assess the patient's perception of recovery following OMSFE with Bio-Oss collagen (test) compared with no grafting material (control).[226] Forty patients were included and randomly allocated to test or control. The patient´s perception of recovery was assessed by questionnaires and VAS, evaluating pain, social and working isolation, physical appearance, duration and quality of life alterations, eating and speaking ability, diet variations, and sleep impairment at T2 and T3. OHQoL was evaluated by OHIP-14, and the correlation between impaired OHQoL at enrollment and age, gender, and recovery was assessed. OMSFE was associated with high patient satisfaction, limited postoperative discomfort, and willingness to undergo similar surgery. Influence on the patient's daily life activities was minimal and limited to the first postoperative days. Most patients return to work

and their routine daily activities within 0-2 days. The number of days with pain, eating difficulties, and sleep disturbances was significantly higher in test than control. Impaired OHQoL, gender, or younger age did not predispose for delayed recovery or prolonged postoperative discomfort.[226]

Paper X (randomized controlled clinical trial)

The aim was to assess patient's perception of recovery following MSFA with ABG (control) compared with 1:1 ratio of ABG and DPBM (Test I) or BBGM (test II).[227] Sixty patients were included and randomly allocated to test or control. The patient´s perception of recovery was assessed by questionnaires and VAS, evaluating pain, social and working isolation, physical appearance, duration and quality of life alterations, eating and speaking ability, diet variations, and sleep impairment at T2 and T3. OHQoL was evaluated by OHIP-14, and the correlations between impaired OHQoL at enrollment and age, gender, and recovery were assessed. High satisfaction and willingness to undergo similar surgery were reported in all groups. The average numbers of days with pain or sick leave were 3.5 and 0.5, with no significant difference between test groups and control. No significant difference in eating and speaking ability, physical appearance, work performance, and sleep impairment were observed between the test groups and the control. Impaired OHQoL, gender, or younger age did not predispose for delayed recovery or prolonged postoperative discomfort.[227]

Paper XI (randomized controlled clinical trial)

The aim was to assess the patient's perception of recovery following MSME with coagulum (test) compared with MSFA using a 1:1 ratio of ABG and DPBM (control).[228] Forty patients were included and randomly allocated to test or control. The patient´s perception of recovery was assessed by questionnaires and VAS evaluating pain, social and working isolation, physical appearance, duration

and quality of life alterations, eating and speaking ability, diet variations, and sleep impairment at T2 and T3. OHQoL was evaluated by OHIP-14, and the correlations between impaired OHQoL at enrollment and age, gender, or recovery were assessed. High satisfaction and willingness to undergo similar were reported in test and control. MSME revealed 2.1 fewer days of pain and 1.2 days of sick leave compared with MSFA. No significant difference was observed in eating and speaking ability, physical appearance, work performance, and sleep impairment between test and control. Impaired OHQoL, gender, or younger age did not predispose for delayed recovery or prolonged postoperative discomfort.[228]

Paper XII (randomized controlled clinical trial)

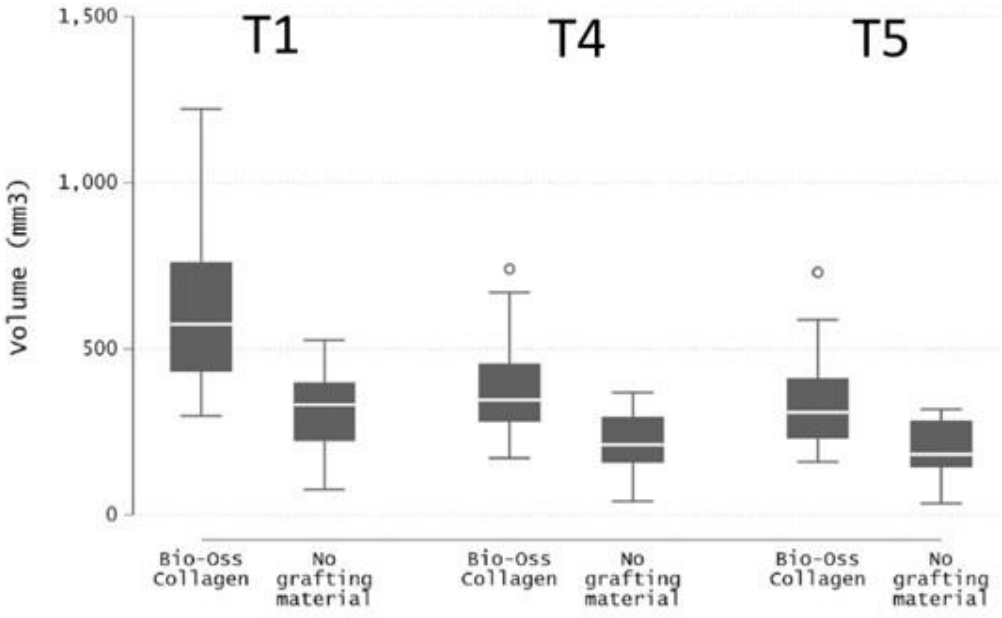
The aim was to test the hypothesis of no difference in implant outcome and PROMs following OMSFE with Bio-Oss Collagen (test) compared with no grafting material (control) at T6.[229] Forty patients were included and randomly allocated to test or control. Implant outcome was assessed by clinical parameters. OHQoL was assessed by OHIP-14. Patient satisfaction with the peri-implant tissue, implant crown, implant function, and total implant treatment outcome were assessed by questionnaire and VAS. All patients attended the 1-year examination. All suprastructures and implants were well-functioning, limited PIMBL, high ISQ, few biological and technical complications, improvement in OHQoL, and high patient satisfaction with the final prosthetic rehabilitation and peri-implant tissue were reported in test and control, as expressed by VAS-scores higher than 88 for all parameters.[229]

Dimension	Variables (0 = no; 100 = yes)	OMSFE with Bio-Oss Collagen VAS score, mean ± SD $n = 20$		OMSFE with no grafting material VAS score, mean ± SD $n = 20$		P-value[a]	
		T3	T4	T3	T4	T3	T4
Peri-implant soft tissue	Satisfied with the look of the peri-implant soft tissue?	97.7 ± 4.7	99.0 ± 1.4	97.4 ± 3.7	96.4 ± 10.6	0.852	0.274
	Satisfied with the shape of the peri-implant soft tissue?	97.1 ± 6.3	99.0 ± 1.3	97.0 ± 5.4	98.5 ± 2.9	0.979	0.483
	Satisfied with the colour of the peri-implant soft tissue?	96.3 ± 10.0	99.0 ± 1.3	96.6 ± 5.1	97.0 ± 6.2	0.921	0.147
	Average score	97.0 ± 6.3	99.0 ± 1.3	97.0 ± 4.0	97.3 ± 4.4	0.992	0.098
Prosthetic solution	Satisfied with the look of the implant crown?	98.4 ± 4.2	99.0 ± 1.4	96.0 ± 10.1	97.5 ± 6.9	0.324	0.332
	Satisfied with the shape of the implant crown?	95.3 ± 8.9	97.5 ± 4.4	93.9 ± 11.7	91.8 ± 15.8	0.661	0.122
	Satisfied with the colour of the implant crown?	95.4 ± 9.1	97.5 ± 4.8	88.0 ± 20.3	92.0 ± 16.0	0.143	0.154
	Average score	96.4 ± 6.9	98.0 ± 3.3	92.6 ± 12.2	93.8 ± 12.1	0.234	0.135
Implant function	Satisfied with the function of implant?	96.2 ± 8.0	98.5 ± 2.7	92.5 ± 13.5	95.5 ± 7.6	0.298	0.107
	Experienced problems with the implant, when you speak?	97.8 ± 4.6	99.0 ± 1.7	97.5 ± 3.3	96.2 ± 11.5	0.844	0.287
	Experienced problems with the implant, when you eat?	98.2 ± 3.8	98.7 ± 1.9	98.3 ± 2.5	99.0 ± 1.9	0.883	0.510
	Experienced problems with implant, when tooth brushing?	95.8 ± 9.1	99.3 ± 1.2	98.5 ± 2.7	98.8 ± 1.8	0.222	0.407
	Average score	97.0 ± 5.2	98.8 ± 1.6	96.7 ± 4.8	97.4 ± 3.8	0.858	0.127
Treatment	Satisfied with the implant treatment outcome in general?	97.7 ± 5.2	98.3 ± 3.9	96.8 ± 8.1	97.8 ± 5.5	0.678	0.690

Subjective assessment of implant treatment outcome as evaluated by self-administrated questionnaire and VAS (0-100). T3, immediately after delivery of the prosthetic rehabilitation; T4, 1-year after FIL.

Paper XIII (randomized controlled clinical trial)

The aim was to assess radiographic ESBG after OMSFE with Bio-Oss Collagen (test) compared with no grafting material (control) by two- and three-dimensional methods at T6.[230] Forty patients were included and randomly allocated to test or control. CBCT-scans were obtained at T0, T1, T5, and T6. ESBG was significantly higher in test compared with control at all-time points. A gradual decrease in ESBG was observed over time, diminishing the difference between test and control. The average two-dimensional ESBG at the facial and oral implant surface was 5.5 mm and 5.7 mm at T6. Corresponding measurements in control were 4.4 mm and 4.1 mm. ESBG was positively correlated with IPL and negatively with the RARH.[230]



Three-dimensional radiographic assessment of ESBG after OMSFE with Bio-Oss Collagen or no grafting material, immediately after surgery (T1), delivery of the prosthetic rehabilitation (T4), and at 1-year of FIL (T5).

Paper XIV (pre-clinical randomized controlled trial)

The aim was to test the hypothesis of no difference in radiographic outcome following MSFA with AAMSCs seeded on DBBM (test) compared with excipient on DBBM (control).[223] Eighteen minipigs were randomly assigned into three groups of six animals and euthanized after one month, two months, and four months, respectively. Each MS was randomly allocated to test or control, with equal graft volumes. CT-scans after MSFA and euthanasia were compared to estimate volume changes of the grafting material and BD by three-dimensional measurements and HU, respectively. There was no difference in any of the radiographic outcomes between test or control at the different observation periods. BD was higher in both groups at four months compared with one or two months. Thus, AAMSCs seeded on DBBM seem not to improve the radiographic outcome compared with excipient on DBBM.[223]

Paper XV (randomized controlled clinical trial)

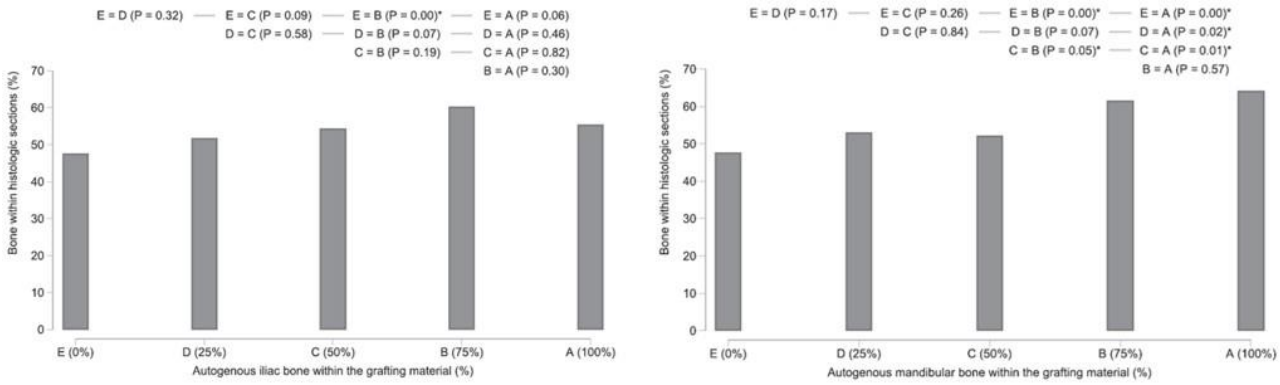
The aim was to test the hypothesis of no difference in implant outcome and PROMs following MSME with coagulum (test) compared with MSFA and 1:1 ratio of ABG and DPBM (control) at T6.[231] Forty patients were included and randomly allocated to test or control. Implant outcome was assessed by clinical parameters. OHQoL was assessed by OHIP-14. Patient satisfaction with the peri-implant tissue, implant crown, implant function, and total implant outcome were assessed by questionnaire and VAS. Two patients did not attend the 1-year examination. All suprastructures and implants were well-functioning at T6. A significant increase in ISQ was observed from T1 to T4 in test and control. Limited PIMBL, few biological and technical complications, improvement in OHQoL, and high patient satisfaction with the final prosthetic rehabilitation and peri-implant tissue were reported in test and control, as expressed by VAS-scores higher than 90 for all parameters.[231]

		MSME with coagulum, mean ± SD		MSFA with 1:1 autogenous bone graft and DPBM, mean ± SD		*P*-value	
Dimension	Variables (0 = no; 100 = yes)	T4	T5	T4	T5	T4	T5
Peri-implant soft tissue	Satisfied with the look of the peri-implant soft tissue?	98.9 ± 1.7	98.8 ± 1.8	97.6 ± 3.4	94.2 ± 20.3	0.148	0.328
	Satisfied with the shape of the peri-implant soft tissue?	97.1 ± 8.4	96.2 ± 11.8	97.4 ± 3.1	97.6 ± 3.5	0.884	0.631
	Satisfied with the color of the peri-implant soft tissue?	99.1 ± 1.6	97.1 ± 6.6	95.0 ± 7.0	92.5 ± 21.7	0.020*	0.385
	Average score	98.4 ± 3.4	97.4 ± 5.1	96.7 ± 3.6	94.7 ± 14.4	0.149	0.460
Prosthetic solution	Satisfied with the look of the implant crown?	96.5 ± 9.0	96.2 ± 12.5	97.6 ± 3.3	98.3 ± 2.6	0.602	0.488
	Satisfied with the shape of the implant crown?	94.9 ± 13.0	95.0 ± 10.2	92.7 ± 16.2	97.1 ± 6.4	0.637	0.462
	Satisfied with the color of the implant crown?	95.9 ± 8.6	93.9 ± 11.1	90.4 ± 17.5	95.8 ± 6.4	0.222	0.512
	Average score	95.8 ± 7.6	95.0 ± 9.1	93.6 ± 11.6	97.1 ± 4.0	0.485	0.381
Implant function	Satisfied with the function of implant?	98.5 ± 2.5	96.5 ± 6.3	96.5 ± 5.0	98.5 ± 2.0	0.131	0.195
	Experienced problems with implant, when you speak?	95.9 ± 12.9	98.1 ± 2.7	97.2 ± 3.9	92.7 ± 22.1	0.680	0.299
	Experienced problems with implant, when you eat?	99.0 ± 2.0	98.6 ± 2.1	97.0 ± 3.8	98.9 ± 1.6	0.047*	0.547
	Experienced problems with implant, when tooth brushing?	95.4 ± 12.2	97.9 ± 4.6	97.5 ± 3.1	92.6 ± 22.7	0.464	0.320
	Average score	97.2 ± 6.2	97.8 ± 3.0	97.0 ± 3.5	95.7 ± 11.1	0.921	0.431
Treatment	Satisfied with the implant treatment outcome in general?	98.9 ± 2.0	97.1 ± 5.6	96.0 ± 4.9	96.2 ± 7.9	0.022*	0.671

Subjective assessment of the implant outcome as evaluated by self-administrated questionnaire and VAS (0-100). T4, immediately after delivery of the prosthetic rehabilitation; T5, 1-year after FIL.

Paper XVI (pre-clinical randomized controlled trial)

The aim was to test the hypothesis of no difference in bone regeneration following bilateral MSFA with different ratios of ABG (iliac, mandibular) and DBBM, after 12 weeks.[224] Forty minipigs were randomly allocated to MSFA with different ratios of ABG and DBBM (100,0; 75,25; 50,50; 25,75; 0,100). A higher percentage of bone within the augmented area was observed, with a higher ratio of ABG, regardless of the origin of ABG (iliac, mandible).[224]

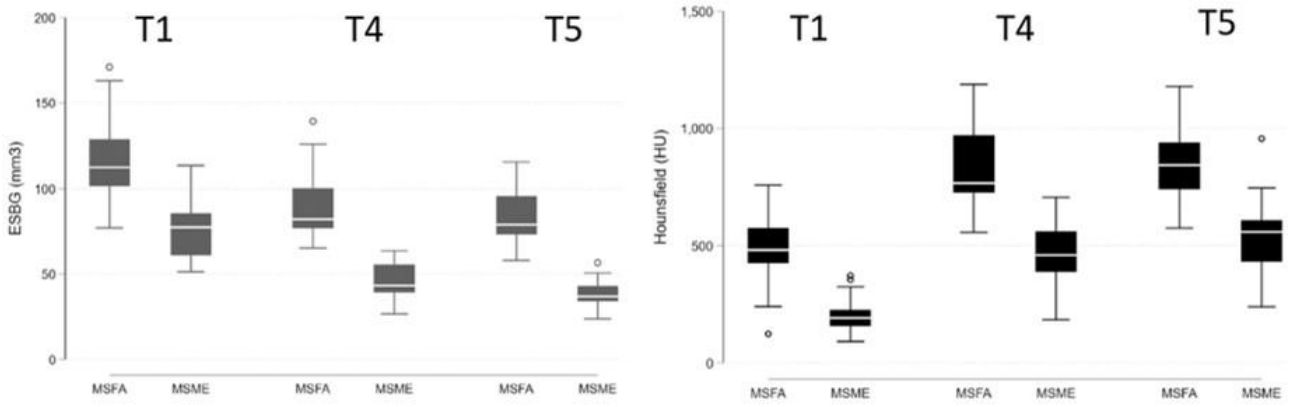


Mean percentage of bone in the augmented area after MSFA with different ratios of ABG (iliac, mandible) and DBBM.

Paper XVII (randomized controlled clinical trial)

The aim was to assess radiographic ESBG following MSME without graft (test) compared with MSFA and 1:1 ratio of ABG and DPBM (control) by two- and three-dimensional methods at T6.[232] Forty patients were included and randomly allocated to test or control. CBCT-scans were obtained at T0, T1, T5, and T6. ESBG and BD were significantly higher in control compared with test at all-time points. A gradual decrease in ESBG, and an increase in BD were observed over time in test and control. Test, the average two-dimensional ESBG at the facial and oral implant surface was 9.4 mm and 7.2 mm at T6. Control, corresponding measures were 6.2 mm and 4.1 mm. A non-significant positive correlation between ESBG and IPL and non-significant negative correlation with the RARH

was observed. The lower ESBG and BD in control did not negatively affect the ISQ values or implant outcome compared with the test at T6.[232]



Three-dimensional radiographic assessment of ESBG and BD after MSME without a graft compared with MSFA and 1:1 ABG and DPBM, immediately after surgery (T1), delivery of the prosthetic rehabilitation (T4), and at 1-year of FIL (T5).

Paper XVIII (randomized controlled clinical trial)

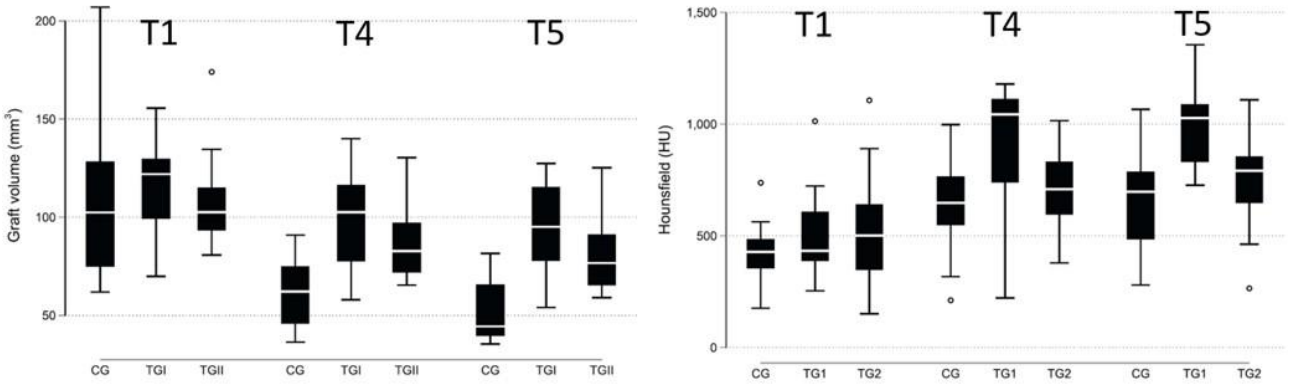
The aim was to test the hypothesis of no difference in implant outcome and PROMs following MSFA with ABG (control) compared with 1:1 ratio of ABG and DPBM (test I) or BBGM (test II) at T6.[233] Sixty patients were included and randomly allocated to control or test groups. Implant outcome was assessed by clinical parameters. OHQoL was assessed by OHIP-14. Patient satisfaction with the peri-implant tissue, implant crown, implant function, and total implant treatment outcome were assessed by questionnaire and VAS. Seven patients did not attend the 1-year examination. All suprastructures and implants were well-functioning at T6. A significant increase in ISQ from T1 to T4 was observed in all groups. Limited PIMBL, few biological and technical complications, improvement in OHQoL, and high patient satisfaction with the final prosthetic rehabilitation and peri-implant tissue were reported in all groups, as expressed by mean VAS-scores higher than 88 for all parameters.[233]

	(A)		(B)		(C)							
	MSFA with ABG		MSFA with 1:1 ABG and APBM		MSFA with 1:1 ABG and BBGM		*p*-Value					
	Mean ± SD		Mean ± SD		Mean ± SD		T3			T4		
Question	T3	T4	T3	T4	T3	T4	A vs. B	A vs. C	B vs. C	A vs. B	A vs. C	B vs. C
Q1	94.8 ± 10.1	93.3 ± 13.5	96.7 ± 6.3	97.8 ± 5.4	96.8 ± 6.9	97.7 ± 4.6	1.00	1.00	1.00	.66	1.00	.57
Q2	94.1 ± 11.4	94.3 ± 13.2	97.2 ± 5.0	93.4 ± 19.5	92.3 ± 18.0	91.1 ± 20.1	.81	.75	1.00	1.00	1.00	1.00
Q3	90.7 ± 16.3	94.6 ± 12.1	97.0 ± 5.4	95.6 ± 11.3	90.3 ± 20.0	93.3 ± 18.4	.33	.45	1.00	1.00	1.00	1.00
Average	93.2 ± 12.8	94.1 ± 12.7	97.0 ± 5.5	95.6 ± 13.2	93.2 ± 16.0	94.0 ± 15.9	.69	.96	1.00	1.00	1.00	1.00
Q4	93.9 ± 11.1	95.4 ± 11.9	97.2 ± 6.0	88.9 ± 26.7	95.2 ± 9.5	95.7 ± 7.7	.63	1.00	1.00	1.00	0.87	1.00
Q5	92.2 ± 12.6	93.4 ± 19.7	88.8 ± 23.7	91.6 ± 20.2	94.8 ± 7.5	95.9 ± 6.6	1.00	.87	1.00	1.00	1.00	1.00
Q6	90.1 ± 12.7	93.1 ± 19.3	88.8 ± 23.9	90.3 ± 23.5	95.7 ± 6.5	92.6 ± 12.4	1.00	.66	.27	1.00	1.00	1.00
Average	92.1 ± 12.0	94.0 ± 17.1	91.6 ± 19.8	90.3 ± 23.1	95.2 ± 7.8	94.8 ± 9.2	1.00	1.00	1.00	1.00	1.00	1.00
Q7	94.8 ± 8.3	95.2 ± 12.2	94.0 ± 11.7	92.1 ± 17.9	95.3 ± 7.0	97.3 ± 4.9	1.00	1.00	1.00	1.00	.69	1.00
Q8	96.4 ± 7.8	95.6 ± 8.7	97.4 ± 6.9	95.8 ± 11.8	96.5 ± 7.7	97.5 ± 5.2	1.00	1.00	1.00	1.00	1.00	1.00
Q9	96.5 ± 6.6	96.9 ± 5.1	98.0 ± 4.0	98.7 ± 2.1	97.4 ± 6.6	98.5 ± 3.2	1.00	1.00	1.00	.57	1.00	.78
Q10	96.6 ± 5.6	97.4 ± 4.4	98.7 ± 2.7	97.4 ± 6.0	97.2 ± 5.8	97.6 ± 6.8	.52	.99	1.00	1.00	1.00	1.00
Average	96.1 ± 7.0	96.3 ± 8.1	97.0 ± 7.3	96.0 ± 11.2	96.6 ± 6.7	97.7 ± 5.1	1.00	1.00	1.00	1.00	1.00	1.00
Q11	95.4 ± 7.4	97.2 ± 5.1	98.8 ± 2.5	98.3 ± 3.2	96.3 ± 6.0	97.2 ± 7.0	.21	.30	1.00	1.00	1.00	1.00

Subjective assessment of the implant outcome as evaluated by self-administrated questionnaire and VAS (0-100). T3, immediately after delivery of the prosthetic rehabilitation; T4, 1-year after FIL.

Paper XIX (randomized controlled clinical trial)

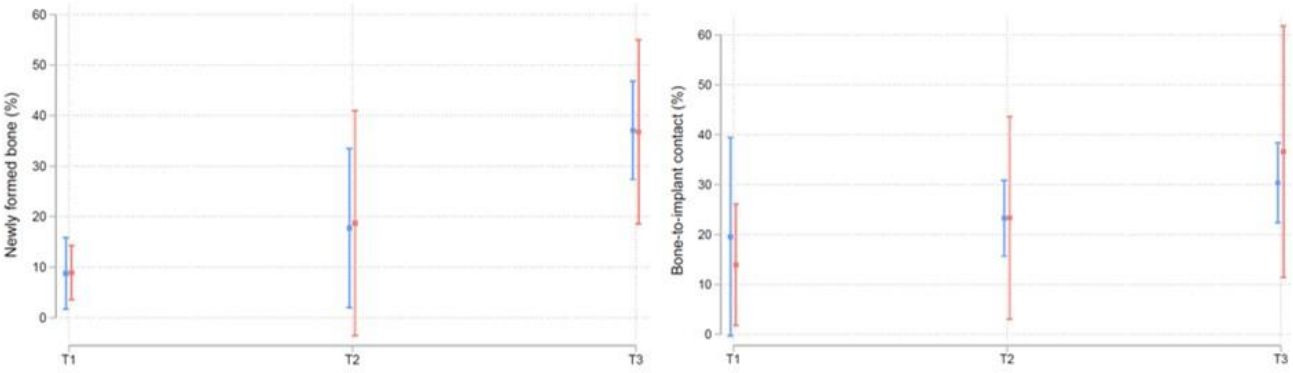
The aim was to assess radiographic ESBG following MSFA with ABG (control) compared with 1:1 ratio of ABG and DPBM (test I) or BBGM (test II) by two- and three-dimensional methods at T6.[234] Sixty patients were included and randomly allocated to control or test groups. CBCT-scans were obtained at T0, T1, T5, and T6. A gradual decrease in ESBG and an increase in BD were observed over time in all groups. Test I disclosed significantly higher ESBG and BD as compared with control and test II. Test I, the average two-dimensional ESBG was 9.1 mm and 8.4 mm at the facial and oral implant surface at T6. Corresponding measurements were 8.1 mm and 6.1 mm for test II, and 6.3 and 6.5 for control. No significant correlation between ESBG and IPL or RARH was observed in the groups. The lower ESBG and BD in control did not negatively affect ISQ or implant outcome compared with test I or II at T6.[234]



Three-dimensional radiographic assessment of ESBG and BD after MSFA with ABG (CG), 1:1 ratio ABG and DPBM (TGI), and 1:1 ratio ABG and BBGM, immediately after surgery (T1), delivery of the prosthetic rehabilitation (T4), and at 1-year of FIL (T5).

Paper XX (pre-clinical randomized controlled trial)

The aim was to test the hypothesis of no difference in histomorphometric outcome after MSFA with AAMSCs seeded on DBBM (test) compared with excipient on DBBM (control).[225] Eighteen minipigs were allocated into three groups of six animals and euthanized after one month, two months, and four months, respectively. Each MS was randomly assigned to test or control with identical graft volume. The percentage of newly formed bone, non-mineralized tissue, residual DBBM, and BIC was analyzed in a randomly selected ROI. The percentage of newly formed bone was significantly higher at four months compared with one month or two months in both test and control, while no significant difference in BIC was disclosed between the different time points. Test, mean percentage of newly formed bone was 8.8, 17.7, and 37.1 at one month, two months, and four months. Control, corresponding values were 8.9, 18.7, and 36.8. There were no significant differences in any of the outcome measures between test and control at any of the time points. Thus, adding AASCs to DBBM did not improve bone regeneration or BIC compared with DBBM alone in conjunction with MSFA.[225]



Mean percentage of newly formed bone and BIC after MSFA with AAMSCs seeded on DBBM (blue) compared with excipient seeded on DBBM (red), after one month (T1), two months (T2), and four months (T3), respectively.

Discussion, limitations, and interpretation of the results

The included studies within this doctoral thesis demonstrate that ARA of the APM is associated with a high survival rate of suprastructures and implants, limited PIMBL, ESBG, few surgical, biological, and technical complications, and high patient satisfaction, regardless of the surgical approach and grafting material. Similar conclusions have previously been reported in systematic reviews and meta-analyses.[134,134,249-69] However, the included studies within these systematic reviews reveal that the previous knowledge about implant-supported prosthetic rehabilitation of the APM is based on a few RCTs using heterogeneous assessment methods, and PROMs were seldom assessed. The systematic reviews, pre-clinical, and clinical studies within this doctoral thesis were conducted by standardized and validated assessment methods of clinical, radiographic, histologic, and PROMs with the intention of contributing new knowledge for evidence-based guidelines about implant-supported prosthetic rehabilitation of the APM. The overall conclusion of this doctoral thesis is that the surgical approach and grafting material should be individualized and determined by the planned implant length and RARH due to the different osteogenic and osteoconductive potential of the various grafting materials. However, the conclusions of this doctoral thesis should be interpreted with caution due to the small patient samples and short-term observation periods.

Study design

Pre-clinical and clinical studies are defined as primary medical research, whereas secondary research summarizes the existing knowledge in literature reviews, systematic reviews, and meta-analyses.[270] High level of evidence is required for providing evidence-based treatment guidelines and clinical recommendations. The level of scientific evidence is categorized in the hierarchy of evidence based on the design and quality of the study.[271] Systematic reviews combined with meta-analysis of well-designed RCTs are categorized as the highest level of evidence. RCTs are the most reliable evidence of the effectiveness of a surgical intervention due to the random allocation and low risk of bias. In-vitro studies and pre-clinical studies are located at the bottom of the hierarchy of evidence due to disputable translational reliability and predictive value for human outcomes.[272]

A systematic review is a transparent and reproducible research method to systematically answer a well-defined focus question using a detailed and comprehensive search strategy of published and unpublished primary research to identify and critically evaluate the existing scientific knowledge.[273] PRISMA statement guidelines and PICO template are normally used for composing a systematic review with a clinical relevant focus question.[217] GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) is a transparent framework for grading the quality of evidence obtained by systematic reviews, which is used to provide clinical recommendations.[274] Systematic reviews are frequently combined with a meta-analysis, which is a statistical method to analyze and quantitatively combine the data withdrawal from the comparable studies of the systematic review.[275] A meta-analysis reduces the risk of bias by utilizing a methodological approach and provides a precise estimate of the effect size, and increases the generalizability of the results.[218,219] The estimate results obtained from RCTs in a meta-analysis are often graphically presented in a forest

plot visualizing the pooled effect estimate and heterogeneity of the included results. The strength of evidence of a systematic review and meta-analysis is associated with the quality of the included studies. Thus, studies with biased outcomes lead to inaccurate qualitative or quantitative synthesis of results, and quantitative synthesis of results from heterogeneous studies leads to biased results.[271] The systematic reviews and meta-analysis of this doctoral thesis revealed that long-term RCTs assessing MSFA with ABG or MSME with coagulum are lacking.[210,211] Moreover, most of the included studies within the systematic reviews demonstrated a high risk of bias and confounding factors due to the study design, heterogeneous assessment methods, and short-term observation period.[210-213, 214-216]

RCTs are prospective studies that assess the effectiveness of an intervention through comparison with a control.[276] Eligible participants are enrolled and randomly allocated to test intervention or control, which is usually the conventional treatment approach. Randomization leads to an equal distribution of confounding factors between the test and control. Allocation concealment reduces selection bias, and blinding of the surgeon, patient, as well as the data analyzer reduces observation bias. Blinding is an important methodologic parameter of RCTs to diminish bias and improve the study´s validity.[277] Blinding of the surgeon to the surgical intervention is often difficult. In the pre-clinical studies (XIV, XX), blinding of the surgeon was performed by using aliquots of AAMSCs and excipient with identical appearance and quantity.[223,225] In the clinical studies (IX-XIII, XV, XVII-XIX), solely patients were blind to their allocation group.[226-234] Attrition bias occurs if loss to follow-up or drop-out rates are unbalanced between test and control.[277] In the pre-clinical studies (XIV, XX), and clinical studies (IX-XIII, XV, XVII-XIX), an equal distribution of losses to follow-up or drop-out occurred.[223,225-234] Primary outcome measure addresses the most important outcome of the study, while secondary outcome refers to less important outcomes. According to the CONSORT statement, it is necessary to distinguish between primary and secondary outcomes, as the primary outcome is

directly related to the study´s objective and serves as the basis for sample size calculation. Moreover, the primary outcome reflects the most important study result with the highest importance for healthcare professionals and patients.[278] Implant survival and PIMBL are the most frequently used primary outcomes following ARA of the APM, while ISQ, health status of the peri-implant tissue, bone regeneration, complications, BD, and PROMs are often used as secondary outcomes.[279] However, secondary outcomes are important parameters, which could have a significant influence on the primary outcome, although they do not necessarily exhibit a change in the final implant outcome. Moreover, a resent published consensus report with the intention of improving evidence-informed implant dentistry and quality of care suggested that surgical morbidity and complications, peri-implant tissue health status, intervention-related adverse events, complication-free survival, and overall patient satisfaction and comfort should be mandatory outcome domains.[280] The primary outcome of the pre-clinical and clinical studies was implant survival (IX),[226] PIMBL (X-XIII, XV, XVII-XIX),[227-234] volumetric changes of the grafting material (XIV, XX).[223,225] and percentage of bone (XVI).[224]

Pre-clinical studies using animals are a valuable experimental model within bone regeneration for assessing new grafting materials prior to a clinical trial. Pre-clinical studies enable the use of specific research methods, including repeated CT-scans, implant retrieval, and histomorphometric analyses of bone biopsies. However, the validity of pre-clinical studies and translation of data derived from animals into clinical recommendations is associated with caveats due to obvious genetic disparities.[225] It is, therefore, essential that the experimental model and species contain biological, anatomical, functional, and genetic similarities to humans. Rabbits, dogs, sheep, rhesus monkeys, chimpanzees, and minipigs have previously been used in pre-clinical studies assessing ARA of the APM.[181,225,256] Minipigs are considered an appropriate pre-clinical model for histomorphometric assessment of bone

regeneration due to close similarity to the human skeleton in terms of anatomy, comparable size of the MS, physiology, healing pattern, bone apposition rate, and trabecular thickness.[281,282] In the preclinical studies (XIV, XVI, XX), radiographic and histomorphometric assessments of bone regeneration were performed in minipigs following MSFA with ABG, DBBM, and AAMSCs.[223-225] However, bone regeneration and volumetric changes of the grafting material within the MS of a minipig may be affected by different physiology, like increased dynamic pressure changes during respiration and grunt. The translational reliability of the results to humans is, therefore, debatable.

Surgical procedures

The required implant length, diameter, and number of implants for an implant-supported prosthetic rehabilitation of the APM is unknown and influenced by the remaining dentition, number of missing teeth, bruxism, and occluding dentition.[28] An implant length of 8-12 mm is generally considered as sufficient for implant-supported prosthetic rehabilitation of the posterior maxilla, and implant length of ≥10 mm is recommended following MSME and coagulum.[28,130] ARA is, therefore, necessary when the RARH is <8 mm. However, the appropriate surgical approach and grafting material for ARA of the APM lacks consensus.[28] It has been advocated that MSFA and MSME applying the lateral window technique should be used, when the RARH <5 mm, and OMSFE when RARH is >5 mm.[28,283] MSME and OMSFE necessitates simultaneous implant placement to maintain the raised SM with the original MS floor within its elevated position. However, the required RARH of the APM to achieve primary implant stability is disputable.[28,283] The RARH, therefore, defines the surgical technique and whether simultaneous implant placement is possible. In the preclinical studies (XIV, XVI, XX), the RARH was reduced to 5 mm and an implant length of 15 mm was inserted in conjunction with MSFA, thus 10 mm of the implant length was exposed within the MS.[223-225] In all the clinical studies (IX-

XIII, XV, XVII-XIX), an implant length of 13 mm was chosen.[226-234] The RARH at the implant site was either ≥3 mm and ≤7 mm (X, XVIII, XIX),[227,233,234] ≥4 mm and ≤7 mm (XI, XV, XVII),[228,231,232] or ≥6 mm and ≤10 mm (IX, XII, XIII)[226,229,230] following MSFA, MSME, or OMSFE, respectively.[226-234] Thus, primary implant stability was achievable when the RARH of the APM is ≥3 mm, allowing simultaneous implant placement.

Bone grafting materials

ABG is generally considered as the preferred grafting material for ARA of the APM due to its osteogenic, osteoinductive, and osteoconductive properties. AGB has, therefore, historically been used as a reference for the assessment of new grafting materials. However, ABG has never been compared with other grafting materials in long-term RCTs following MSFA or OMSFE (II, III).[211,212] A pre-clinical study (minipigs) has demonstrated that the early BIC formation in conjunction with MSFA was higher with ABG or different ratios of ABG and DBBM compared with DBBM alone.[181] Systematic reviews have demonstrated that ABG generates the highest short-term amount of bone regeneration compared with other grafting materials following MSFA,[284,285] which are in accordance with the systematic review (VII), and pre-clinical study (XVI) within this doctoral thesis.[215,224] The retrospective study (V) revealed high long-term implant survival and patient satisfaction following MSFA with particulate ABG from the ascending mandibular ramus.[220] Thus, ARA of the APM with ABG is a predictable treatment modality with a successful long-term implant treatment outcome. However, harvesting of ABG is associated with the risk of donor site morbidity, prolonged treatment time, and the possibility of injury to adjacent vital anatomic structures.[235,286-290] Moreover, a pre-clinical study (minipigs) has demonstrated a 65% volumetric reduction of ABG, 12 weeks following MSFA.[68] The graft volume was significantly better preserved after combining ABG and DBBM, and

the volumetric reduction was significantly influenced by the ratio of ABG and DBBM.[68] Systematic reviews have demonstrated that ABG is associated with the highest volumetric reduction compared with other grafting materials following MSFA,[291,292] which are in accordance with the systematic review (VIII), and clinical study (XIX) within this doctoral thesis.[216,234] The retrospective study (V) revealed that the average two-dimensional linear reduction of the augmented following MSFA with ABG from the mandibular ramus was 6.9% and 14.9%, after 1-year and 10-years, respectively.[220]

Xenogenic bone substitutes alone, or in combination with ABG or other bone substitutes are used increasingly for ARA of the APM.[255,293] Xenografts possess solely osteoconductive properties, and a prolonged healing period has, therefore, been advocated when used alone for ARA of the APM.[253] A pre-clinical study (minipigs) showed that the BIC formation arose later with DBBM compared with different ratios of ABG and DBBM following MSFA.[181] However, DBBM mixed with diminutive quantities of ABG revealed comparable BIC as compared with ABG.[181] Xenografts are generally considered a slow or non-resorbable bone substitute. However, the biodegradability is influenced by the biomechanical characteristics of the xenograft. A pre-clinical study (minipigs) revealed a diminutive reduction of the augmented area following MSFA with DBBM alone,[181] which is in accordance with the pre-clinical study within this doctoral thesis (XIV).[223] The clinical studies of this doctoral thesis revealed significantly improved stability of the augmented volume following MSFA with 1:1 ratio of ABG and DBBM compared with ABG, 1:1 ratio with ABG and BBGM, or coagulum (XVII, XIX) after 1-year of FIL.[232,234]

Alloplastic bone substitutes alone or combined with ABG or other bone substitutes are used increasingly for ARA of the APM. Alloplastic bone substitutes possess solely osteoconductive properties, and their biomechanical characteristics are associated with their manufacturing method and chemical structure. A meta-analysis revealed comparable bone regeneration between alloplastic

bone substitute and xenogenic bone substitute,[294] which is in accordance with the systematic review within this doctoral thesis (IV).[213] However, the amount of bone regeneration with alloplastic or xenogenic bone substitutes was significantly less as compared with ABG (IV).[213] In the clinical study, 1:1 ABG and BBGM revealed significantly better stability of the augmented volume as compared with ABG, but significantly worse compared with 1:1 ABG and DBBM immediately after prosthetic rehabilitation, and 1-year of FIL, respectively (XIX).[234]

Coagulum has been used as grafting material in conjunction with MSME and OMSFE. MSME with coagulum has never been compared with ABG or other bone substitutes in a RCT. A long-term study reported high implant survival and an average radiographic ESBG of 4 mm following MSME with coagulum.[295] The systematic review included within this doctoral thesis disclosed comparable short-term implant survival and radiographic ESBG with coagulum compared with ABG or allogenic mineralized bone (I).[210] The clinical study revealed comparable implant outcome but significantly less radiographic ESBG with coagulum compared with 1:1 ABG and DPBM (XV, XVII).[231,232] OMSFE with or without a grafting material has been assessed in several RCTs and systematic reviews combined with meta-analyses revealing comparable implant outcomes,[264,269] which are in accordance with the results of the systematic review within this doctoral thesis (III).[212] Application of a grafting material in conjunction with OMSFE seems to improve radiographic ESBG, which is in accordance with the results of the clinical study within this doctoral thesis (XIII).[230] A systematic review reported that radiographic ESBG was 4.2 mm and 3 mm, 3-years following OMSFE with or without a grafting material, respectively,[296] and a long-term retrospective study reported an ESBG of 2.6 mm, 10-years following OMSFE without a grafting material.[140] A RARA ≤4 mm and placement of implants with a length ≤6 mm significantly decreased implant survival following OMSFE with or without a grafting material.[140,145]

AAMSCs have never been assessed in pre-clinical studies involving larger animals or clinical studies. In the pre-clinical studies (XIV, XX), no beneficial effect on radiographic or histologic outcome was achieved following MSFA with AAMSCs seeded on DBBM compared with excipient on DBBM.[223,225] These results are in accordance with a previous pre-clinical study (minipigs) revealing no significant difference in BD or BIC following MSFA with expanded autologous osteoblast-like cells isolated from iliac cancellous bone and seeded on DBBM compared with DBBM.[297] A possible explanation for the missing effect of autologous and allogenic MCSs within the MS is that upon being seeded onto the DBBM and transplanted into the animals, the stem cells reacted to the hypoxic microenvironment within the matrix and lost their viability, proliferative capacity, and functionality before angiogenesis had formed to sustain the transplanted cells with sufficient nutrition and oxygen.

ABG is associated with the highest bone regeneration and least stability of the augmented volume. Xenogenic bone substitutes combined with diminutive quantities of ABG revealed comparable BIC and improved stability of the augmented volume as compared with ABG. Alloplastic bone substitutes revealed comparable bone regeneration as compared with xenogenic bone substitutes. The volumetric stability of alloplastic bone substitute is enhanced as compared with ABG, but inferior when compared with xenogenic bone substitutes. Coagulum is associated with diminutive radiographic ESBG and substantial reduction of the augmented volume. AAMSCs seeded on DBBM seem not to improve the histomorphometric or radiographic outcome compared with DBBM. However, the necessary ESBG and augmented volume for a long-term successful implant outcome following implant-supported prosthetic rehabilitation of the APM is unknown. Moreover, the difference in ESBG and volumetric stability of the grafting materials did not affect the clinical implant outcome.

Assessment methods

Survival of suprastructures and implants

Various success criteria have been proposed for clinical or radiographic assessment of suprastructures and implants.[279] A consensus report from 2004 addressed the following criteria for success, survival, and loss of suprastructure and implant.[298] Success is defined as the suprastructure or implant is present at the follow-up examination, and complications are absent. Survival is defined as the suprastructure or implant present at the follow-up examination, but its condition is not specified, while loss is defined as the suprastructure or implant no longer present at the follow-up examination.[298]

Survival of suprastructures was 100% according to the criteria used in this doctoral thesis at 1-year of FIL (XII, XV, XVIII).[229,231,233] However, loosening of the crown and remaking of the crown due to unsatisfactory esthetic occurred (XV, XVIII).[231,233] Thus, according to the definitions of the consensus report,[298] loss of suprastructure was 0%, but the success rate was 95% (XV),[231] 97% (XVIII),[233] and 100% (XII),[229] at 1-year of FIL. Long-term assessment of suprastructures following MSFA, MSME, or OMSFE has never been conducted in RCTs, as described within the systematic reviews of this doctoral thesis (I-III).[210-212]

Survival of implants was 100% according to the criteria used in this doctoral thesis at 1-year of FIL (XII, XV, XVIII).[229,231,233] However, late infections occurred following MSFA (XV, XVIII).[231,233] Thus, according to the definitions presented in the consensus report,[298] the implant loss was 0%, but the success rate was 97.5% (XV),[231] 97.5% (XVIII),[233] and 100% (XII),[229] at 1-year of FIL. Long-term implant assessments following OMSFE with or without the use of a grafting material have been conducted in one RCT revealing low implant loss with high success and survival rate.[141] Long-term RCTs assessing implant treatment outcomes following MSFA and MSME are lacking.

MSFA, MSME, or OMSFE are associated with a high survival rate of suprastructures and implants, regardless of the grafting material. However, long-term RCTs are lacking.

Implant stability

Implant stability is required for achieving implant osseointegration. Primary implant stability is defined as the biomechanical anchoring within the bone at implant placement, while secondary implant stability is defined as the osseointegration achieved due to remodeling at the bone-to-implant interface.[299] The primary implant stability is influenced by various factors including, bone quality, BD, implant design, and preparation of the implant bed. Osseodensification or undersized drilling protocols have proven to enhance primary implant stability in the low-density bone. However, in the pre-clinical (XIV, XVI, XX),[223-225] and clinical studies (IX-XIII, XV, XVII-XIX),[226-234] the implant bed was successively prepared according to the manufactory's recommendations. Implant stability can be measured clinically by percussion, perception, reverse torque, cutting resistance analysis, or by objective non-invasive measurements such as resonance frequency analysis or Periotest.[300-302] Resonance frequency analysis uses magnetic pulses that are sent to a metal sensor, which is mounted on the implant. As the sensor vibrates, the probe automatically converts the resonance frequency into an ISQ value on a scale from 1 (lowest stability) to 99 (highest stability). An adequate ISQ value after osseointegration normally lies between 55 and 85. The Periotest uses an ultrasonically vibrating probe to measure the micro-mobility of the implant. Periotest value ranges from -8 (low mobility) to +50 (high mobility), and values between -8 to -6 are considered as good implant stability. Resonance frequency analysis or Periotest are frequently used for monitoring of implant stability over time to predict the prognosis and time for FIL.

In the clinical studies, resonance frequency analysis was used as an indirect indicator for the assessment of implant stability and BIC (XII, XV, XVIII).[229,231,233] The mean ISQ value at implant placement range between 60.0-62.8, 64.5-66.3, and 73.3-76.0 following MSFA, MSME, and OMSFE, respectively. Corresponding values at healing abutment connection were 77.5-79.4, 73.9-78.8, and 80.0-82.1, respectively. The ISQ value significantly increased from implant placement to healing abutment connection following MSFA, MSME, and OMSFE, indicating an increase in the BIC, regardless of the grafting material (XII, XV, XVIII).[229,231,233] However, the ISQ value is influenced by various clinical and biological parameters including gender, bone quality and quantity, implant location and design, length of healing time, vascularization, size of bone defect, and measuring devices.[300,303,304] The clinical studies within this doctoral thesis (XII, XV, XVIII) demonstrated that high primary and secondary implant stability is achievable following MSFA, MSME or OMSFE, regardless of the grafting material. However, ISQ does not correspond to BIC, but is an arbitrary value that can be used as information to predict implant prognosis. ISQ is, therefore, considered a valuable prognostic and diagnostic device for monitoring of implant stability and progress of osseointegration when applied as a supplementary measurement to histologic and radiographic assessments. The reliability and predictability of ISQ for estimates of BIC or correlation with implant osseointegration, bone quality, and quantity, therefore, remain controversial.[300,305]

Health status of the peri-implant tissue

The soft and hard tissue surrounding an osseointegrated implant defines the peri-implant tissues. A healthy clinical and radiographical peri-implant tissue is required for long-term implant survival.[306] Inflammation or infection in the peri-implant tissue leads to peri-implant mucositis or peri-implantitis, which is a pathological condition characterized by inflammation in the peri-implant mucosa and

progressive loss of supporting bone.[307] The clinical health status of the peri-implant tissue has been assessed by various methods, including the absence of clinical inflammatory signs, no bleeding and suppuration on mild probing, and stable probing depth compared to previous visits.[306,308] The peri-implant tissue health status is considered as an essential outcome following implant treatment, as evaluated by the presence of peri-implant mucositis and peri-implantitis.[280] A healthy peri-implant tissue is characterized by the absence of erythema, bleeding on probing, swelling, and suppuration.[309] The assessment of the peri-implant tissue health status should, therefore, include bleeding on probing, suppuration on probing, probing pocket depth, and radiographic assessment of marginal bone level.[280]

Papilla morphology, plaque index, gingival index, and probing pocket were used for assessment of the clinical peri-implant tissue health status following MSFA (XVIII),[233] and MSME (XV).[231] A satisfying health status of the peri-implant tissue was observed following MSFA and MSME, regardless of the grafting material at 1-year of FIL.

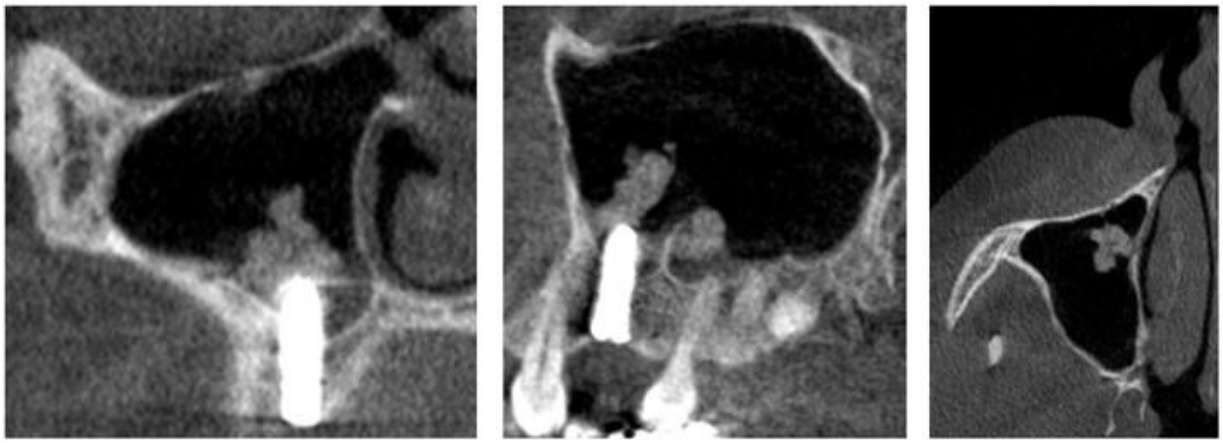
MSFA and MSME reveal satisfying clinical health status of the peri-implant tissue, regardless of the grafting material. The papilla morphology, plaque index, gingival index, and probing pocket are valuable prognostic and diagnostic indexes for monitoring the clinical health status of the peri-implant tissue when applied as a supplementary measurement to radiographic assessments.

Complications

ARA and simultaneous implant placement in the APM are associated with the risk of surgical, biological, and technical complications, which increases the risk of suprastructure or implant failure. Surgical complications involve SM perforation, intra- and postoperative bleeding, epistaxis, bruising, facial swelling, dehiscence, infection, benign paroxysmal positional vertigo, migration of the graft, and sinusitis, while PIMBL, implant loss, oroantral communications are define as biological

complications. Chipping of ceramic, loss of the mounted crown, or loosening of the abutment screw are considered technical complications.[310]

SM perforation is the most frequent surgical complication, with a prevalence of up to 21.4% following OMSFE,[252] and 58.3% following MSFA and MSME.[206,251] A narrow MS, sinus septa, RARH <3.5 mm, and a thin SM predispose for a higher perforation rate.[206,207] SM perforation is associated with a higher risk of sinusitis, infection, graft or implant failure, and less bone regeneration.[207-209,311,312] In the clinical studies, SM perforation occurred in 2.5%,[226] 15.0%,[227] and 17.5%,[228] following OMSF (IX), MSFA (X), and MSME (XI), respectively. The frequency of SM perforation seems to be lower following OMSME compared with MSFA and MSME. However, OMSME is performed through a transcrestal approach with limited visibility to detect a SM perforation. SM perforation following OMSME is, therefore, probably underestimated, which has been reported in cadaver studies.[313] In the clinical study (IX), the integrity of the SM was tested by Valsalva maneuver, and patients were asked, whether they had the sensation of water in the nose or throat during OMSFE.[226] Furthermore, the presence of an intact SM was checked with an implant depth gage. SM perforation occurred in 2.5% based on intraoperative assessment. However, some of the postoperative CBCT images revealed indicators of SM perforation with displacement of the grafting material, implying that the frequency of SM perforation was larger than estimated. Moreover, minor epistaxis during the first postoperative days was reported by 12.5%.[226,229] Application of grafting material in conjunction with OMSFE may, therefore, increase the risk of surgical complications involving graft displacement, sinusitis, infection, and implant failure due to an undiagnosed SM perforation. Despite the suspicion of SM perforation and graft displacement, none of the patients develop postoperative sinusitis or infection (IX).[226,229]



A-C. Coronal, sagittal, and axial CBCT-scan raises suspicion of SM perforation and graft displacement.

The incidence of chronic rhinosinusitis, benign paroxysmal positional vertigo, displacement of graft or implant, severe bleeding, or infection following MSFA, MSME, and OMSFE are uncommon.[314] In the clinical studies, no serious surgical complications occurred (IX, X, XI).[226-228]

Biological complications following MSFA, MSME, and OMSFE occur rarely.[249-269] High long-term implant survival and minimal PIMBL have been reported in systematic reviews,[249-269] which are in accordance with the conclusions of the systematic reviews within this doctoral thesis (I-IV).[210-213] In the clinical studies (XII, XV, XVIII), high implant survival, limited PIMBL, and good health status of the peri-implant tissue were observed at 1-year of FIL.[229,231,233] A late infection occurred following OMSFE with Bio-Oss Collagen, which was treated with an antibiotic and the removal of presumable Bio-Oss Collagen remnants underneath the buccal mucosa (XII).[229]

Technical complications following MSFA, MSME, and OMSFE occur rarely.[249-269] High survival of suprastructures have been reported in a systematic review,[265] which are in accordance with the conclusions of the systematic reviews within this doctoral thesis (I-IV).[210-213] In the clinical studies (XII, XV, XVIII), high survival of suprastructures were observed at 1-year of FIL.[229,231,233] Loosening of the implant crown (XV, XVIII), and dissatisfaction with the aesthetics and function of the implant

crown (XV) were observed 1-year after MSFA and MSME.[231,233] Thus, MSFA, MSME, or OMSFE are associated with a low frequency of surgical, biologic, and technical complications. However, the incidence of SM perforation following OMSFE is probably underestimated.

Radiographic changes of the grafting material

The requisite implant-supporting bone volume following MSFA, MSME, and OMSFE is unknown. A gradual resorption of the grafting material always occurs.[291,292] However, the progress and amount of resorption are related to the applied grafting material, length of the observation period, and radiographic assessment method. Moreover, a wide MS, large lateromedial angle, and loss of multiple teeth are considered predictors of extensive resorption.[188] ABG reveal the highest resorption, while slow or non-resorbable xenograft represents the least resorption,[291,292] which are in accordance with the systematic review within this doctoral thesis (VIII).[216] The resorption of ABG occurs primarily within the first year and seems to stabilize over time.[88]

Different techniques and methods have been applied for two- and three-dimensional assessment of radiographic changes of the grafting material over time following MSFA, MSME, and OMSFE.[216] The grafting material within the MS is a heterogenous and three-dimensional anisotropic structure.[68] Thus, repeating three-dimensional radiographic measurements are required for precise assessment of radiographic volume changes over time, while two-dimensional measurements can be used for assessment of height changes. Moreover, the demarcation of the original border between the grafting material and the adjacent MS walls becomes indistinct as the grafting material is integrated. Hence, assessment of volumetric changes without superimposing the original border of the MS may, therefore, not create a reliable estimate of the actual volumetric changes of the grafting material.

Three-dimensional radiographic changes of the grafting material following MSFA have previously been assessed by stereology or computer software systems.[68] Stereology utilizes random, systematic sampling to provide unbiased and quantitative data for obtaining information about three-dimensional structures, based mainly on observations of two-dimensional images.[315,316] The Cavalieri volume estimation principle is an unbiased stereological method for estimating the volume of three-dimensional structures based on observations on two-dimensional images,[315,316] which has proven to be a reliable method for assessment of three-dimensional radiographic changes of the grafting material.[68] In the pre-clinical study (XIV),[223] and clinical studies (XIII, XVII, XIX)[230,232,234] a modified version of the Cavalieri volume estimation principle was used as systematic random sampling at all levels was not performed. OnDemand computer software was used to manually orient the CT and CBCT scan images along the longitudinal implant axis, and manual drawing were used to outline the original border of the MS and the grafting material on 1 mm images. The intraobserver reliability was estimated and demonstrated almost perfect reliability in the pre-clinical (XIV),[223] and clinical studies (XIII, XVII, XIX),[230,232,234] which are in accordance with similar studies assessing three-dimensional changes of the grafting material following MSFA with the use of other computer software systems.[217,218] The pre-clinical (XIV),[223] and clinical studies (XIII, XVII, XIX),[230,232,234] revealed that ABG and coagulum were associated with the highest volumetric reduction, while xenogenic bone substitutes revealed the least reduction. The volumetric stability of ABG was improved by combining ABG and xenogenic bone substitutes. A 1:1 ratio of ABG and alloplastic bone substitutes revealed improved volumetric stability than ABG, but less than 1:1 ABG and xenogenic bone substitutes.

Two-dimensional measurements on orthopantomography are the most frequently used method for the assessment of radiographic changes of the grafting material. However, two-dimensional

radiographic assessment on orthopantomography is associated with distortion and magnification errors compared with CT or CBCT, and the inhomogeneous and anisotropic structure of the grafting material compromises two-dimensional assessment. In the clinical studies (XIII, XVII, XIX),[230,232,234] two-dimensional measurements on coronal CBCT-scans were performed in addition to three-dimensional measurements for estimates of graft height changes. Correspondingly to the three-dimensional radiographic assessment, ABG and coagulum revealed the highest graft height reduction, while 1:1 ABG and DBBM revealed the least.

Bone density

BD measurements indicate the amount of inorganic bone mineral, which is an important parameter for determining the bone quality as bone mineral provide compressive strength and mineral storage for calcium and phosphorous. The implant prognosis and the probability of achieving primary and secondary implant stability are improved by higher BD values.[319] Moreover, a positive correlation has been documented between radiographic BD and primary implant stability as well as bone volumetric fraction.[320,321] Various radiographic methods have been used to predict the BD value at the implant site, including CT-scan (HU) and CBCT-scan (Grayscale density). HU is a quantitative scale measuring pixel values, which is proportional to radiodensity. HU values between 300-400 and 500-1900 represent cancellous and cortical bone, respectively. Grayscale density scale measures voxel values, which are proportional to radiodensity. Grayscale density values of 830 and 1068 in the posterior maxilla represent cancellous and cortical bone, respectively.[322] Although the quantitative scales are different, a strong correlation between HU and grayscale density has been demonstrated.[323,324] In the pre-clinical study (XIV),[223] and clinical studies (XVII, XIX)[232,234] BD was assessed using HU or grayscale density. The mean BD (HU) immediately after MSFA with AAMCSs

seeded on DBBM or DBBM was 777.34 and 761.97, respectively (XIV).[223] The BD significantly increased over time with both treatment modalities, but a significantly higher BD was observed with DBBM after four months, indicating that AAMSCs seeded on DBBM did not improve BD. In the clinical studies (XVII, XIX),[232,234] the mean BD (grayscale density) immediately after MSME with coagulum, or MSFA with 1:1 ABG and DPBM was 203.5 and 481.3, respectively. The BD significantly increased over time with both treatment modalities, but the BD was always significantly higher with 1:1 ABG and DPBM compared with coagulum (XVII).[232] Likewise, the mean BD (grayscale density) immediately after MSFA with ABG, 1:1 ABG and DPBM, and 1:1 ABG and BBGM were 419.9, 506.0, and 528.6, respectively. The BD significantly increased over time with all treatment modalities, but the BD was always significantly higher with 1:1 ABG and DPBM compared with ABG, or 1:1 ABG and BBGM, while no significant difference was observed between ABG and 1:1 ABG and BBGM.

HU and grayscale density are often used for BD estimates. However, the radiographic BD of the augmented area within the MS is affected by the density and macrostructure of the applied grafting material.[325] DPBM is a slow or non-resorbable grafting material that is radiographically denser than pristine bone and not completely replaced by bone, while ABG or BBGM undergoes remodeling and biodegradation. Thus, a higher BD doesn't necessarily have a direct clinical implication since BD is not automatically associated with the amount of de novo bone formation or higher BIC.[326] It should, therefore, be emphasized that BD, as assessed from CT and CBCT, must be critically evaluated in connection with other parameters. Moreover, it has been advocated that the quantitative use of HU should actually be avoided.[327]

Bone regeneration and implant protrusion length or alveolar ridge height

MSME and OMSFE necessitate simultaneous implant placement to preserve the raised SM and original MS floor in its elevated position. A correlation between ESBG and IPL, surgical approach, and RARH following MSME and OMSFE has been reported.[185,261,295,328-332] Moreover, a long-term study concluded that the amount of radiographic ESBG is proportional to the IPL within the MS following MSME.[295] In the clinical studies (XIII, XVII, XIX),[230,232,234] two- and three-dimensional radiographic ESBG was positively correlated with IPL and negatively correlated with decreased RARH following OMSFE and MSME (XIII, XVII).[230,232] However, no significant correlation between two- and three-dimensional radiographic ESBG and IPL or RARH was observed following MSFA with ABG, 1:1 ABG and DBBM, or 1:1 ABG and BBGM (XIX).[234] Moreover, a systematic review reported that MSFA is associated with increased ESBG compared with OMSFE, which are in accordance with the clinical studies within this doctoral thesis (XIII, XVII, XIX).[230,232,234]

Radiographic ESBG seems, therefore, to be influenced by the IPL, surgical approach, and RARH. However, the IPL seems not to be automatically proportional to the amount of ESBG,[185,332] since the ESBG decreases when the IPL exceed 4 mm in conjunction with OMSFE without a grafting material.[185] Moreover, an increased IPL following OMSFE without a grafting material creates a larger cavity underneath the raised SM, which causes a greater pressure on the SM during the early healing period, with a risk of coagulum dissolving and compromised bone regeneration.[332]

Histomorphometric analysis

Bone histomorphometry is frequently used for quantitative analysis of bone biopsies to obtain detailed information about the percentage of bone, non-mineralized tissue, and grafting materials remnants. Different techniques, including histomorphometric analysis or non-invasive imaging techniques like

µCT have been used to quantitate the percentage of newly formed bone, non-mineralized tissue, and residual grafting material. Manual or semi-automatically computerized histomorphometric analyses are used for two-dimensional assessment of structural parameters on histologic sections, including bone area, whereas stereological techniques are used for assessment of three-dimensional structures, including bone volume on two-dimensional histologic sections.[333] Systematic uniform random sampling at all levels of the stereological procedure is mandatory for obtaining unbiased and efficient estimates.[334] Unbiased estimates of surface area can be obtained by using the vertical section technique and a systematic test system of cycloids.[335] In the pre-clinical studies (XVI, XX),[224,225] the vertical section technique was applied, but estimates of the proportions of bone, non-mineralized tissue, and DBBM particles in a randomly selected ROI were conducted and not on estimates of the total surface area or the total bone volume. Thus, systematic uniform random sampling at all levels was not performed in the pre-clinical studies (XVI, XX).[224,225] However, the specimens were randomly rotated around the vertical implant axis and divided into four tissue blocks longitudinally to the vertical implant axis. A standardized grid was randomly positioned on the sections, and the ROI was selected. The percentage of bone, non-mineralized tissue, and DBBM were estimated within the ROI, revealing that the percentage of bone was significantly increased with larger proportions of ABG within the grafting material following MSFA with different ratios of ABG and DBBM (XVI),[224] while AAMSCs seeded on DBBM revealed comparable bone regeneration to DBBM (XX).[225] Quantitative evaluation of bone biopsies using histomorphometric analysis is a frequently used method for assessment of bone regeneration.[285] Systematic reviews focusing on histomorphometric outcomes following MSFA concluded that ABG generated the highest amount of newly formed bone compared with other grafting materials,[284,285] which are in accordance with the results of the systematic review within this doctoral thesis (VII).[215] However, histologic similarities between newly formed bone and residual ABG compromise assessment of newly formed bone if ABG is used as

grafting material.[285] In the pre-clinical study (XVI),[224] the percentage of bone was estimated without distinguishing between newly formed bone and residual ABG particles, which could potentially have contributed to a higher percentage of bone when the grafting material contained higher ABG ratio.[224]

Ground sections of undecalcified bone tissue with a thickness of 5-10 µm were originally suggested for histological evaluation.[336] Various modifications to the original sawing-grinding protocols have subsequently been proposed.[337] In the pre-clinical studies (XVI, XX),[224,225] sections with a thickness of 30 µm were obtained according to a previously described cutting and grinding procedure.[338] However, the cutting and grinding procedure for obtaining undecalcified bone samples with a thickness of 30 µm involves a risk of damage to the tissue specimen, compromising histomorphometric assessment.[339] In the pre-clinical studies (XVI, XX),[224,225] a large proportion of the sections were not applicable for histomorphometric assessment. The conclusions drawn from the results of the pre-clinical studies should, therefore, be cautiously interpreted.

Bone-to-implant contact

BIC is defined as the proportion of the implant surface in direct contact with the surrounding bone on a microscopic level. BIC is a prerequisite for osseointegration and maintenance of the implant's ability to withstand load during masticating. The least BIC to obtain osseointegration is unknown, but BIC values between 50-80% are associated with a successful long-term implant outcome.[340] Quantification of osseointegration is performed in histological sections by measuring the proportion of BIC within the external implant surface. However, the percentage of BIC is influenced by various parameters including bone quality and quantity, macroscopic implant design and surface properties, loading conditions, and smoking habits.[341-343] A meta-analysis concluded that the posterior maxilla disclosed the least BIC compared with the mandible and the anterior regions.[344] Proportion of BIC is

estimated by histomorphometric analysis using histological sections or µCT involving point counting of intersections between test lines and the implant surface or as a ratio between the length of bone in contact with the external implant surface within a well-defined ROI.[181,345] A pre-clinical study (minipigs) revealed significantly increased BIC following MSFA with different ratios of ABG and DBBM compared with DBBM using point counting of intersections.[181] In the pre-clinical study within this doctoral thesis (XVI),[225] the proportion of BIC was estimated by dividing the total length of each implant thread´s by the length of the bone in contact with the surface within the implant threads. The percentage of BIC was 19.5, 23.2, and 30.4 following MSFA, with AAMSCs seeded on DBBM at one month, two months, and four months, respectively. Corresponding values for DBBM were 13.9, 23.3, and 36.6. There was no significant difference between the two treatment modalities at any time point, indicating that AAMSCs seeded on DBBM did not improve BIC compared with DBBM. Although an increase in BIC was observed with longer healing periods, the percentage of BIC was below the considered values of successful osseointegration, indicating that a longer healing period is required to generate a higher BIC when an osteoconductive grafting material is used alone, which are in accordance with the conclusions of previous studies.[181,253,346] The macroscopic implant design and properties of the implant surface influence the probability of BIC.[342] In the pre-clinical study (XVI),[225] an implant with a TiUnite surface was inserted, which has an optimal effect on implant osseointegration, as reported in a meta-analysis.[347] BIC has previously been assessed in clinical studies following MSFA with ABG or MSME with coagulum using experimental implants and µCT.[348] The BIC was 93.5% and 92.0% with ABG or coagulum, respectively.[348]

ABG, coagulum, or different ratios of ABG and xenogenic bone substitutes generate a higher BIC compared with xenogenic bone substitutes. A prolonged healing period is therefore recommended if xenogenic bone substitutes are used alone in conjunction with ARA of the APM.

Patient-reported outcomes measures

Clinical and radiographic parameters are frequently selected as primary outcomes following implant-supported prosthetic rehabilitation of the APM, and assessed by quantitative research methods.[279] However, clinical and radiographic outcomes do not necessarily reflect the patient´s anticipations or satisfaction with the surgical intervention or the final implant-supported prosthetic rehabilitation. It has, therefore, been advocated that objective assessment of implant outcomes should be supplemented by subjective opinions.[349,350] PROMs are valuable instruments for subjective assessment of relevant impressions from a patient´s perspective, including anticipation of the implant outcome, oral health status, impact on their daily life, OHQoL, esthetic, and the patient's previous health care experience.[351] However, PROMs are difficult to quantify, and standardized methods for subjective assessment of PROMs following implant-supported prosthetic rehabilitation are lacking.[351] PROMs reflect psychosocial parameters related to the patient's anticipation of the surgical intervention and postoperative recovery, including pain, swelling, bruising, inability to eat and sleep, physical appearance, working, and social interaction, as well as their self-esteem and satisfaction with their OHQoL.[352] PROMs are affected by patient-related factors like age, gender, smoking habits, alcohol consumption, past dental experiences, pain as well as anxiety during surgery.[352] Moreover, a patient´s perception of recovery is negatively influenced by patient-related predictors such as anticipations, vulnerability, socioeconomic factors, intra- and postoperative pain, and psychologic well-being involving anxiety and levels of distress.[353,354] Quantitative and qualitative research methods have previously been applied for subjective assessment of PROMs following implant-supported prosthetic rehabilitation, including VAS, rating scales, interviews, and questionnaires with the intention of obtaining subjective opinions on their OHQoL and experience from the treatment.[355,356]

There are advantages and disadvantages of the various assessment methods. VAS is a reliable and validated interval-scaled method to obtain data on an ordinal scale. The VAS scale is a straight horizontal line with a fixed length of 100 mm (0 = minimal to 100 = maximum). The VAS scale is commonly used in combination with questionnaires, but the validity of VAS is debatable due to interindividual and intraindividual variability, non-compliant responders, and solely ordinal data.[357] Patients may also be reluctant to use the highest and lowest end points of the VAS scale, potentially limiting the range of responses.[357] Rating scales like Likert scale and OHIP-14 use fixed rating options or numerical scales to obtain validated quantitative data. However, rating scales contain various limitations due to lack of specificity, inflexibility, dissimilar interpreting of the categories by the responders, and heterogenous intervals between the fixed categories compromising quantitative evaluation. Numerous methods have previously been used for the assessment of PROMs following implant-supported prosthetic rehabilitation, which makes study comparison difficult.[352,358,359] However, consensus reports, clinical guidelines, and implant journals have recommended that PROMs become an integrated part of outcome assessment following implant treatment.[280,349,350]

PROMs are rarely reported following ARA of the APM,[265,349,350,360] which are in accordance with the systematic reviews within this doctoral thesis (I-IV).[210-213] In the clinical studies (IX-XII, XV, XVIII),[226-229,231,233] patient´s perception of recovery, OHQoL, and patient´s satisfaction with the peri-implant soft tissue, prosthetic solution, implant function, and implant outcome were assessed by VAS, rating scales, and self-administrated questionnaires. High treatment satisfaction and willingness to undergo similar surgery were reported following MSFA, MSME, and OMSFE, regardless of the surgical procedure or grafting material (IX-XII, XV, XVIII),[226-229,231,233] MSFA was associated with approximate 3-4 days of pain and one day of sick leave, while numbers of days with pain and sick leave was less with MSFE and OMSFE. Moreover, no significant difference was observed in eating

and speaking ability, physical appearance, work performance, and sleep impairment between the different treatment modalities. However, MSFA with 1:1 ABG and DPBM, as well as OMSFE with Bio-Oss collagen revealed significantly higher numbers of days with pain compared with coagulum indicating that harvesting of ABG or application of a grafting material influences patient´s perception of recovery (IX, XI).[226,228] High patient´s satisfaction with the peri-implant soft tissue, prosthetic solution, implant function, and implant outcome was reported at delivery of the prosthetic solution and after 1-year of FIL following MSFA, MSME, and OMSFE, regardless of the grafting material (XII, XV, XVIII).[229,231,233] OHIP-14 questionnaire revealed significant improvement in OHQoL following MSFA, MSME, and OMSFE, regardless of the grafting material (XII, XV, XVIII).[229,231,233] Impaired pre-operative OHQoL, gender, or younger age seems not to generally predispose for delayed recovery following MSFA, MSME, and OMSFE (IX-XI),[226-228] which is in contrast to a previous study concluding that that younger females were predictors for delayed recovery following MSFA.[361]

The clinical studies within this doctoral thesis systematically assessed patient´s perception of recovery, OHQoL, and patient´s satisfaction with the peri-implant soft tissue, prosthetic solution, implant function, and implant outcome following MSFA, OMSFE, and OMSFE by using validated and standardized methods. High patient satisfaction and diminutive patient discomfort were observed following MSFA, MSME, and OMSFE. However, harvesting of ABG or application of a grafting material seems to increase the risk of postoperative discomfort.

Patient-related parameters

Various patient-related parameters like age, gender, alcohol consumption, smoking habits, systemic diseases, polypharmacy, ASA status, and radiotherapy affect the long-term implant outcome.[362-367] Decreased BD is common in older individuals, and higher osteogenic potential is observed in younger

individuals.[47] Systemic diseases like diabetes mellitus, immune suppression, parkinson's disease, and osteoporosis negatively influence bone healing and implant survival.[362,363] Smoking, nicotine, and other chemicals in tobacco products impede vascularization, which may lead to compromised healing, mucosal dehiscence, risk of SM perforation, and implant failure.[368-370] Moreover, alcohol consumption negatively influences bone regeneration following MSFA.[371] However, RCTs assessing MSFA, MSME, and OMSFE in compromised patients are lacking.

In the clinical studies (IX-XIII, XV, XVII-XIX),[226-234] healthy adult patients (ASA score I, II) without systemic diseases, heavy smoking habits, alcohol consumption, infectious diseases, polypharmacy, radiotherapy, or metabolic bone disease were included. The results of the clinical studies may, therefore, not automatically be translated to medically compromised patients.[226-234]

Conclusion

This doctoral thesis intended to address the appropriate surgical approach and grafting material for ARA of the APM in conjunction with implant placement. Based on the findings of the systematic reviews, pre-clinical, and clinical studies, the following main conclusions, and guidelines are suggested for choosing the appropriate surgical approach and grafting material for ARA of the APM.

- Placement of standard-length implants in conjunction with ARA of the APM is associated with successful implant treatment outcomes and high patient satisfaction.
- Harvesting of ABG is associated with increased patient discomfort and prolonged sick leave.
- Volumetric reduction of the augmented area is inevitable, regardless of the grafting material. Varying degrees of overcompensation are necessary, depending on the grafting material.

- Barrier membrane coverage of the lateral window improves bone regeneration and diminishes the proliferation of non-mineralized tissue.
- Primary implant stability is achievable when the RARH of the APM is ≥3 mm, enabling simultaneous implant placement.
- Implant-supported prosthetic rehabilitation of the APM is associated with improved OHQoL, regardless of the surgical approach and applied grafting material.
- MSFA with AAMSCs on DBBM did not improve the histomorphometric or radiographic outcome compared with excipients on DBBM.
- The planned implant length and the RARH determine the surgical approach and appropriate grafting material.
- Recommended surgical approach and grafting material when the RARH at the implant site is ≥3 mm and ≤6 mm:
  - ✓ Maxillary sinus floor augmentation with a mixture of ABG and xenogenic bone substitute if an increase of the alveolar ridge height of ≥6 mm is intended.
  - ✓ Maxillary sinus floor augmentation with ABG and alloplastic bone substitute if an increase of the alveolar ridge height of approximately 5 mm is intended.
  - ✓ Maxillary sinus membrane elevation with coagulum if an increase of the alveolar ridge height of ≤5 mm is intended.
- Recommended surgical approach and grafting material when the RARH at the implant site is ≥6 mm:
  - ✓ Osteotome-mediated maxillary sinus floor elevation with a xenogenic bone substitute if an increase of the alveolar ridge height of ≥5 mm is intended.
  - ✓ Osteotome-mediated maxillary sinus floor elevation without a grafting material if an increase of the alveolar ridge height of ≤4 mm is intended.

Clinical implications and future perspectives

The included studies within this doctoral thesis demonstrate that MSFA, MSME, and OMSFE are associated with high survival of suprastructures and implants, high implant stability, limited PIMBL, bone regeneration, few surgical, biologic, and technical complications, as well as high patient satisfaction, regardless of the grafting material. ABG generates the highest bone regeneration and least volumetric stability than other grafting materials, while xenogenic bone substitutes combined with diminutive quantities of ABG reveal satisfying BIC and volumetric stability. Coagulum reveals the least volumetric stability and radiographic ESBG. The different grafting materials thus contain dissimilar characteristics and potentials. The surgical approach and applied grafting material should, therefore, be individualized to simplify the surgical approach and diminish patient discomfort as the planned implant length and RARA determines the appropriate implant treatment strategy. However, these recommendations need to be verified in long-term RCTs.

The required implant length and surgical approach for an implant-supported prosthetic rehabilitation of the APM is controversial. An implant length of 8-12 mm has been recommended, and an implant length of ≥10 mm should be chosen in conjunction with MSME and coagulum.[28,130] OMSFE has been recommended when the RARH is 5-8 mm, while MSFA should be used if the RARH is <5 mm or when multiple teeth need to be replaced.[28] Several systematic reviews and meta-analyses as well as long-term RCTs with an observation period of 10-years have documented high survival of suprastructures and implants, high implant stability, limited PIMBL, few surgical, biologic, and technical complications as well as high patient satisfaction following placement of short implants (6 mm) in the APM, when the RARH is ≥6 mm.[372-378] Based on the promising results of short implants in the APM, the indication for performing OMSFE, therefore, seem to be limited. This

is supported by the increased risk of complications associated with OMSFE like undetected SM perforation, bleeding, benign paroxysmal positional vertigo, graft displacement, and sinusitis.[144,379]

The required RARH of the APM for simultaneous implant placement in conjunction with MSFA to obtain adequate primary implant stability is debatable. A RARH of >5 mm has been recommended for simultaneous implant placement in conjunction with MSFA.[380,381] The clinical studies within this doctoral thesis demonstrated that primary implant stability is achievable when the RARH of the APM is ≥3 mm, enabling simultaneous implant placement.

PROMs are rarely reported following ARA of the APM. The clinical studies within this doctoral thesis systematically assessed PROMs following MSFA, MSME, and OMSFE using validated and standardized methods. The results demonstrate that MSFA, MSME, and OMSFE are associated with high patient satisfaction with the implant treatment outcome and final prosthetic solution combined with diminutive postoperative discomfort and morbidity. Minimal invasive ARA of the APM has been introduced to diminish postoperative discomfort and morbidity.[382] RCTs assessing PROMs following minimal invasive sinus augmentation procedures compared with conventional treatment strategies are, therefore, needed to verify this assumption.

The results of the clinical studies within this doctoral thesis were obtained in healthy adult patients. However, there is limited knowledge about implant-supported prosthetic rehabilitation of the APM in medically compromised patients. Future research should, therefore, focus on ARA of the APM in medically compromised patients.

Bone tissue engineering using autologous bioactive substances, MSCs, blood-derived growth factors, or recombinant human bone morphogenetic proteins for ARA of the APM seem redundant due to the satisfying implant outcome achieved with the various grafting materials. However, the MS and the surgical approaches used within this doctoral thesis have proven to be a reproducible research

model, which can be applied in pre-clinical or clinical studies to investigate the osteogenic, osteoinductive, and osteoconductive potential of new materials intended for other clinical indications.

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