

BONE REGENERATION IN MAXILLARY SINUS FLOOR ELEVATION WITH CALCIUM PHOSPHATE CERAMICS AND AUTOGENOUS BONE GRAFTS

Wilhelmus F. Bouwman

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VRIJE UNIVERSITEIT

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Het maakt niet uit hoe langzaam je gaat, zolang je maar niet stopt.
Confucius (ca. 500 v. Chr.)

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1

General introduction and outline of the thesis

Resorption of the alveolar ridge in the posterior region of the maxilla progressively occurs after loss of teeth. Additionally, pneumatization of the maxillary sinus further reduces the bone volume of the alveolar crest [1, 2]. Prosthetic solutions to replace lost natural teeth range from removable partial dentures made of synthetic materials and/or metal to fixed dentures, using dental implants to restore function and esthetics. However, insufficient bone volume of the alveolar ridge in the posterior region of the maxilla can be a contraindication for dental implant placement. In such cases, pre-implant surgical procedures are required to restore the horizontal and/or vertical dimensions of the alveolar ridge. A commonly used pre-implant procedure to restore the bone height in the posterior maxilla is the maxillary sinus floor elevation (MSFE), as described by Tatum [3].

Surgical techniques

Tatum introduced a lateral window technique for MSFE, which he termed "sinus lifting", to enhance the vertical dimension of the alveolar ridge, allowing dental implant placement. Nonetheless, Boyne and James were the first to document this surgical procedure in the literature. Tatum's MSFE consists of preparing a lateral bony top-hinge trapdoor, which is turned inward and upward into a horizontal position, simultaneously elevating the Schneiderian membrane [3, 4]. The created space underneath the lifted door can be filled with a bone graft, a bone substitute, or even left ungrafted [5, 6].

In 1994, Summers introduced the trans-crestal osteotome technique as a minimally invasive alternative MSFE procedure, utilizing special osteotomes after initial dental implant bed preparation by burr to gradually elevate the sinus floor by means of controlled tapping [7]. In addition to the Summers osteotome technique, several other minimally invasive approaches have been introduced to further reduce surgical trauma and enhance patient comfort. These include the minimally invasive antral membrane balloon elevation, hydraulic pressure-assisted sinus membrane elevation, the transcrestal approach with calcium phosphosilicate putty, the piezoelectric minimally invasive system, and reamer-mediated sinus floor elevation. Collectively, these methods aim to simplify the procedure, shorten treatment time, and minimize postoperative morbidity, while maintaining clinical outcomes comparable to more conventional techniques. Nevertheless, they are associated with limitations, particularly a restricted capacity for vertical bone augmentation and an increased risk of (undetected) Schneiderian

membrane perforation [8].

A unique aspect of MSFE is that it may serve as a research model for bone regeneration. The well-defined and consistent anatomical structure allows for standardized comparisons of different graft materials under similar biomechanical and physiological conditions. The maxillary sinus provides a confined space with minimal mechanical loading, enabling researchers to evaluate the osteoconductive, osteoinductive, and osteogenic potential of various graft materials with a high degree of reproducibility. A major advantage of this research model is that biopsies can be obtained from the grafted area at dental implant positions using trephine drills when dental implant preparations are made, thereby enabling histological and histomorphometric analyses. In this way MSFE offers an excellent in vivo environment for assessing graft integration, bone formation rates, and resorption patterns over time. It serves as a clinically relevant model that bridges the gap between preclinical studies and clinical applications, providing valuable insights into the long-term performance of emerging biomaterials in dental, craniofacial, and orthopedic applications [9-11].

Graft materials

Different graft materials have been reported as suitable for MSFE procedures, including autografts (bone graft material obtained from the same patient), allografts (bone graft material received from a donor of the same species, such as human tissue donors), xenografts (bone graft material obtained from a different species, often of bovine or porcine origin), synthetic grafts (artificial materials engineered to replicate the characteristics of natural bone tissue), composite grafts (combinations of two or more graft materials to improve their properties), and growth factor-enriched grafts (grafts enriched with biological substances to facilitate tissue regeneration) [12-15].

Stem cell-based grafts are gaining attention as an innovative approach for MSFE, utilizing mesenchymal stem cells (MSCs) in combination with a bone substitute carrier to promote osteogenic differentiation, enhance bone regeneration, and accelerate the healing process [10, 16, 17]. Previous studies have demonstrated that the addition of stromal vascular fraction (SVF), a heterogeneous autogenous cell population rich in adipose-derived stromal/stem cells (ASCs), to graft materials increased bone formation and enhanced vascularization compared to ceramic-only controls, especially in the case of β-tricalcium phosphate (β-TCP) [10, 18, 19].

Autogenous bone

Autogenous bone remains the gold standard for bone grafting due to its biocompatibility, osteoinductive and osteoconductive properties, and ability to support bone regeneration through the presence of vital osteoblasts, osteoprogenitor cells, and growth factors like bone morphogenic proteins (BMPs) [20, 21]. Autogenous bone is typically harvested from both extraoral sources, such as the iliac crest and calvarial bone [22], and intraoral areas, including the symphyseal and retromolar regions of the mandible, as well as the maxillary tuberosity. Intraoral grafting is often favored since it usually does not require general anesthesia, is closer to the augmentation location, and leaves no cutaneous scars. Histological research indicates that intraoral donor sites, apart from the chin, produce more total bone volume than the iliac crest [23, 24]. Notably all autogenous and alloplastic grafts frequently show postoperative bone height reduction after an initial gain [25]. Clinically, its use has been associated with high dental implant survival rates and predictable outcomes [21]. However, obtaining sufficient autogenous bone is often challenging as intraoral harvesting is limited and extraoral sources such as the iliac crest are associated with donor site morbidity. Harvesting autogenous bone can, amongst other things, lead to sensory disturbances, unpredictable resorption rates of the grafts, and an extended recovery period [23, 26-31]. Recent randomized controlled trials have shown that mixtures of autogenous bone with xenogenic materials, or even pure xenografts, can achieve comparable bone volume outcomes and dental implant survival rates. These findings suggest that while autogenous bone remains biologically superior, its necessity in all cases of MSFE is being questioned [32]. These clinical and practical limitations, along with emerging evidence questioning the indispensability of autogenous bone in MSFE, underscore the need to critically evaluate its role relative to alternative grafting materials.

Calcium phosphate ceramics

Calcium phosphate ceramics are widely used in biomedical applications due to their chemical similarity to the mineral phase of bone, biocompatibility, ease of processing, and strong cell attachment properties. These ceramics have found applications as bone substitutes, coatings, cements, drug delivery systems, and scaffolds in bone regenerative procedures [33, 34].

The safety, predictability, unlimited availability, reduced patient morbidity, and cost-

effectiveness of these materials offer clear advantages over autografts and allografts. These benefits support their use in reconstructive, orthopedic, dental implant and maxillofacial surgeries. Beyond their established role in dental implant surgery, calcium phosphates have also shown clinical value in neurosurgical procedures by promoting bone regeneration and defect repair through their biocompatibility and osteoconductive properties [11, 35].

Bone substitutes, particularly those composed of calcium phosphate ceramics such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), or biphasic calcium phosphate (BCP), a composite of HA and β-TCP that has been studied in two distinct compositions (60/40 and 20/80 HA/β-TCP), are osteoconductive due to their chemical similarity to natural bone and have been extensively investigated. These porous materials also provide mechanical stability and ease of handling. While these substitutes lack the inherent osteoinductive capabilities of autogenous bone, studies have explored their potential, particularly that of biphasic calcium phosphates, as suitable alternatives for bone regeneration [19, 36, 37].

BCP has gained significant attention for its dual role in bone regeneration. HA provides long-term structural integrity, while β-TCP enhances bioresorbability, facilitating gradual bone replacement [14, 36-42]. This combination offers an optimal balance between mechanical stability and bioresorbability, making BCP a promising bone substitute, particularly in MSFE [34]. Micro-computed tomography (micro-CT) analysis demonstrated that BCP with a 20/80 HA/β-TCP ratio outperformed the commercially available 60/40 ratio as a scaffold for bone augmentation in the MSFE model [19]. Patients treated with BCP 20/80 exhibited more bone formation and more osteoid deposition on the cranial side, indicating enhanced early-stage osteogenic potential [19].

The main limitations of bone substitutes are the absence of blood vessels, vital osteoblasts, and osteoprogenitor cells at the time of implantation. In addition, bone substitutes present challenges, including: (1) delayed integration: substitutes lack osteoinductive properties, potentially prolonging healing and delaying full integration; (2) risk of immune reactions: although rare, xenografts and allografts may trigger immune responses or inflammation, and (3) reduced bone quality: while substitutes provide adequate volume, studies indicate they may not achieve the same bone quality and density as autogenous grafts[43-45].

Clinical implications for dental implant outcome

While autogenous bone provides the highest rate of new bone formation, bone substitutes are increasingly comparable in terms of dental implant survival rates. MSFE using bone substitutes has demonstrated dental implant survival rates exceeding 93.8% after three years, with a 10-year survival rate of up to 96.4%, comparable to the use of autogenous bone [21, 46]. A review of 31 studies with an average follow-up of nearly eight years reported dental implant survival rates of around 95% for non-vascularized iliac grafts and 97% for non-vascularized calvarial grafts. Mean dental implant survival rates were around 83% for iliac grafts and 92% for calvarial grafts [47]. Research also shows that BCP mixtures retain bone volume better than pure β-TCP, as the latter may dissolve too rapidly relative to the rate of new bone formation [48].

Outline of the thesis

The overall aim of this thesis was to evaluate the performance of graft materials used in MSFE procedures, with emphasis on the use of calcium phosphate ceramics, particularly BCP and β-TCP, as well as autogenous bone grafts and mixtures of autogenous bone and calcium phosphate ceramics. The performance of these graft materials was investigated by assessing the quality and quantity of bone formation at various time points following MSFE by means of clinical, radiological, histological, and histomorphometric analyses.

In this thesis, the following topics regarding bone regeneration after MSFE were addressed:

In Chapter 2, a study is presented on the quality and quantity of bone formation following MSFE using BCP (60% HA and 40% β-TCP), with a focus on the clinical, radiological, histological, and histomorphometric aspects after a 6-month healing period. Radiological measurements were performed on panoramic radiographs at multiple time points, up to 1 year postoperatively.

In Chapter 3, a study is presented on the clinical, radiological, histological, and histomorphometric aspects of BCP (60% HA and 40% β-TCP) used in MSFE, with healing times of 9 and 12 months after the procedure. Radiological measurements were performed on panoramic radiographs at multiple time points, up to 5 years postoperatively.

In Chapter 4, the potential for improved bone formation is evaluated by using autogenous bone mixed with BCP (60% HA and 40% β-TCP) in MSFE. Histological and histomorphometric analyses were conducted on bone biopsies obtained 6 months after the procedure. The results were compared with those of the previous study using pure BCP, as described in Chapter 2. Radiological measurements were performed on panoramic radiographs at multiple time points, up to 5 years postoperatively.

Chapter 5 provides an analysis of the radiological changes in tissue height after MSFE using three types of calcium phosphate ceramics. Patients were divided into three groups and treated with the following materials: β-TCP, BCP (20% HA and 80% β-TCP), and BCP (60% HA and 40% β-TCP). Radiological measurements were performed on panoramic radiographs at multiple time points, up to 5 years postoperatively.

Chapter 6 outlines an evaluation of radiological changes in bone height after MSFE using two types of autogenous bone grafts, harvested from either the maxilla or the mandible. Radiological measurements were performed on panoramic radiographs at multiple time points up to 5 years postoperatively. The results were compared with those from the previous study, using three types of calcium phosphate ceramics, as described in Chapter 5.

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2

The use of Straumann® Bone Ceramic in a maxillary sinus floor elevation procedure: A clinical, radiological, histological and histomorphometric evaluation with a 6-month healing period

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ABSTRACT

Introduction: In this study, we evaluated the quality and quantity of bone formation in a maxillary sinus floor elevation procedure using a new fully synthetic biphasic calcium phosphate (BCP) consisting of a mixture of 60% hydroxyapatite and 40% of β-tricalcium phosphate (Straumann® Bone Ceramic).

Methods: A unilateral maxillary sinus floor elevation procedure was performed in six patients using 100% BCP. Biopsy retrieval for histological and histomorphometric analysis was carried out before implant placement after a 6-month healing period.

Results: In this study, the maxillary sinus floor elevation procedure with the use of BCP showed uneventful healing. Radiological evaluation after 6 months showed maintenance of vertical height gained immediately after surgery. Primary stability was achieved with all Straumann® SLA Dental Implants of 4.1 mm diameter and 10 or 12 mm length. The implants appeared to be osseointegrated well after a 3-month healing period. Histological investigation showed no signs of inflammation. Cranial from the native alveolar bone, newly formed mineralized tissue was observed. Also, osteoid islands as well as connective tissue were seen around the BCP particles, cranial from the front of newly formed mineralized tissue. Close bone-to-substitute contact was observed. Histomorphometric analysis showed an average bone volume/total volume (BV/TV) of 27.3% (SD ± 4.9), bone surface/total volume (BS/TV) 4.5 mm^2/mm^3 (SD ± 1.1), trabecula thickness (Tb.Th) 132.1 µm (SD ± 38.4), osteoid volume/bone volume (OV/BV) 7.5% (SD ± 4.3), osteoid surface/bone surface (OS/BS) 41.3% (SD ± 28.5), osteoid thickness (O.Th) 13.3 µm (SD ± 4.7) and number of osteoclasts/total area (N.Oc/Tar) 4.4 1/mm (SD ± 5.7).

Conclusions: Although a small number of patients were treated, this study provides radiological and histological evidence in humans confirming the suitability of this new BCP for vertical augmentation of the atrophied maxilla by means of a maxillary sinus floor elevation procedure allowing subsequent dental implant placement after a 6-month healing period. The newly formed bone had a trabecular structure and was in intimate contact with the substitute material, outlining the osteoconductive properties of the BCP material. Bone maturation was evident by the presence of lamellar bone.

INTRODUCTION

Reconstruction of the severely atrophied posterior maxilla is often performed using a maxillary sinus floor elevation procedure and endosseous dental implants [1, 2]. The use of autogenous bone grafts is still considered as the gold standard because of both osteoinductive and osteoconductive properties [3-6]. However, there are several disadvantages, i.e. donor site morbidity [7, 8], the unpredictable resorption rate [3] and the limited amounts of bone available. For these reasons, bone substitutes have been sought, and several types of bone substitutes have been investigated. Most of these bone substitutes resemble the composition of a natural bone matrix and consist of calcium phosphates, such as hydroxyapatite (HA), tricalcium phosphate (TCP) or mixtures of HA/TCP [9, 10].

HAs are biocompatible and do not induce a sustained foreign body response or a toxic reaction. At physiological pH, it is the least soluble of the naturally occurring calcium phosphates. This contributes to the relative resistance of HA to resorption [11-13]. TCP is another biocompatible osteoconductive calcium phosphate. It can provide a scaffold for potential bony ingrowth [14]. However, unlike HA, TCP resorbs. The latter is true for the β-form. The biomaterial is replaced by newly formed bone [15, 16]. The problem is that this replacement does not necessarily occur in a 1:1 ratio. Often less bone is produced as compared with the volume of TCP resorbed [17-19].

Combining the relatively unresorbable HA and resorbable TCP on a molecular level might solve the above-mentioned problems. Recent research has focused on using the HA as a scaffold and TCP as a degradable component [10, 14-16, 20, 21]. With this combination, the biphasic calcium phosphate (BCP) showed accelerated new bone formation in critical alveolar bone defects in animal and human models [14, 22-24]. Straumann® Bone Ceramic is a new fully synthetic BCP with a mixture of 60% HA and 40% β-TCP. It is 100% crystalline, highly pure, and has a porosity of 90%. The pores are 100–500 μm in diameter.

The purpose of this study was to evaluate the quality and quantity of bone formation in a maxillary sinus floor elevation procedure using a new fully synthetic BCP consisting of a mixture of 60% HA and 40% β-TCP (Straumann® Bone Ceramic) with a 6-month healing period. The clinical, radiological, histological, and histomorphometric results of a multicenter study are presented.

MATERIALS AND METHODS

Patient selection

Six healthy patients who were partially edentulous in the posterior maxilla and required implant placement for dental rehabilitation were included in this study. The vertical dimension of the residual alveolar bone was < 8 mm in the posterior maxilla, but > 4 mm at the implant location. Because of inadequate alveolar bone height for implant placement, they were scheduled for a unilateral, two-stage maxillary sinus floor elevation procedure, as described by Tatum [2].

The average age was 54 years, ranging from 37 to 77 years. Four patients were females and two were males. All patients were non-smokers. All six patients gave written informed consent. In this study, patients with conditions like systemic diseases and drug abuse were excluded. Patients in need of buccal onlay bone grafting to achieve an adequate alveolar ridge were also excluded from this study.

Maxillary sinus floor elevation procedure, dental implant surgery, and biopsy retrieval

All six patients were treated in an outpatient procedure under local anesthesia. Perioperatively, the patient received an antibiotic (amoxicillin 500 mg, four times daily) for 7 days, and an oral rinse with chlorhexidine-digluconate 0.12% (10 cm^3 three times daily for 1 min) for 2 weeks for local antisepsis. A midcrestal incision was made with vertical release incisions at the canine and tuberosity side. A preoperative panoramic radiograph was taken and carefully inspected for contours of the maxillary sinus. A full-thickness mucoperiosteal flap was elevated and the cortical bone, as well as the preoperative panoramic radiograph, were carefully inspected for contours of the maxillary sinus. A preparation was made in the lateral maxillary sinus wall using a diamond burr with copious irrigation with sterile isotonic saline. A bony top-hinge trapdoor was mobilized and turned inward and upward into a horizontal position in the maxillary sinus, together with the carefully elevated Schneiderian membrane (Figure 1). In case this membrane got perforated during the mobilization of the bone piece, the perforation was covered with a resorbable freeze-dried laminar bone sheet (100-300 μm thick; Ultimatics, Springdale, Arkansas; Pacific Coast Tissue Bank, Los Angeles, CA, USA). The space created between the lifted lid and the sinus floor was filled with BCP

(Figure 2). No membrane was used to cover the lateral window. Primary wound closure was performed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). Immediately after the procedure, an orthopantomogram was taken. Postoperative examination and removal of sutures were performed after two weeks. After a 6-month healing period, under local anesthesia, a crestal incision was made with mesial and distal buccal vertical release incisions. Next a full-thickness mucoperiosteal flap was raised. Bone was inspected for suitable implant placement. Then, implant preparations were made, and biopsies were taken using a trephine drill with an external diameter of 3.5 mm (Straumann® Trephine Drill, Institut Straumann AG, Basel, Switzerland) from the grafted area at the planned dental implant positions, with copious irrigation with sterile saline.

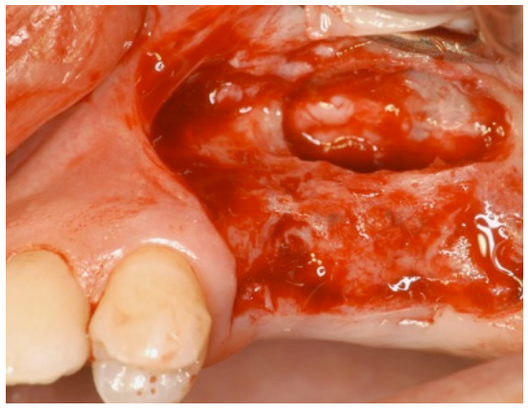


Figure 1.
A bony top-hinge trapdoor, after mobilizing the Schneiderian membrane, is turned inward and upward into a horizontal position in the maxillary sinus.



Figure 2.
The space created between the lifted lid and the maxillary sinus floor is filled with the new biphasic calcium phosphate (Straumann® Bone Ceramic).

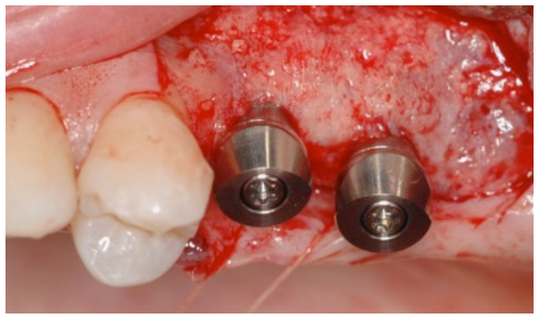


Figure 3.
Two regular neck Straumann® dental implants with 4.1 mm diameter and an SLA surface have been placed.

In each patient one adequate biopsy could be retrieved from the dental implant sites. Finally, in all patients, 13 regular neck (diameter 4.8 mm) Straumann® dental implants with a root diameter of 4.1 mm and an SLA surface and a length of 10 or 12 mm could be placed into the implant bed (Figure 3). The implants were left to heal in a non-submerged fashion. Soft tissue closure was performed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). A postoperative examination was performed at the outpatient clinic. Sutures were removed after 10 days and provisional prosthetics, if necessary, were adapted to the new situation. Attention was paid to prevent premature loading of the dental implants. The patients were instructed to avoid loading of the posterior maxilla until the 3-month integration time of the dental implants had passed and the superstructures were fabricated and placed.

Clinical evaluation

During the dental implant surgery, the width of the alveolar crest was checked for sufficient volume for placement of the intended implants. At implant surgery, the primary implant stability was tested. All examinations were carried out by one trained clinician under adequate conditions, as described previously [25, 26].

Radiological evaluation

Panoramic radiographs were taken before surgery (T0), directly after the maxillary sinus floor elevation procedure (T1) (Figure 4), immediately after dental implant placement (T2) (Figure 5), and 1 year after dental implant placement (T3). On the panoramic radiographs, the increase in the height of the grafted area (mm) was measured on T1-T3. An average magnification of 1.25 was taken into account.



Figure 4.
Panoramic radiograph directly after the maxillary sinus floor elevation procedure (T1).



Figure 5.
Panoramic radiograph directly after dental implant placement (T2).

Qualitative histological and quantitative histomorphometric analysis

The bone biopsies were taken during implant surgery, fixed overnight in 4% phosphate-buffered formaldehyde, and transferred to alcohol 70% [27]. After dehydration, the bone specimens were embedded without prior decalcification in methyl methacrylate supplemented with 20% plastoid-N and 0.13 g/mL perkadox. Longitudinal sections of 5 µm were prepared using a Jung K microtome (Leica microtome type sm2500s, Leica, Wetzlar, Germany). Bone mass indices, osteoid surface, and the eroded surface were measured in Goldner's trichrome-stained [28] sections (Figures 6 and 7).

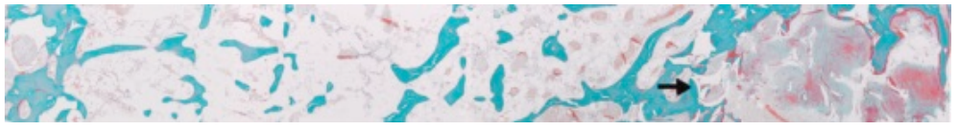


Figure 6.
Histological overview of a bone biopsy stained with Goldner's Trichrome (magnification x 10). Bone formation is observed especially in the area covering the scaffold (black arrow).

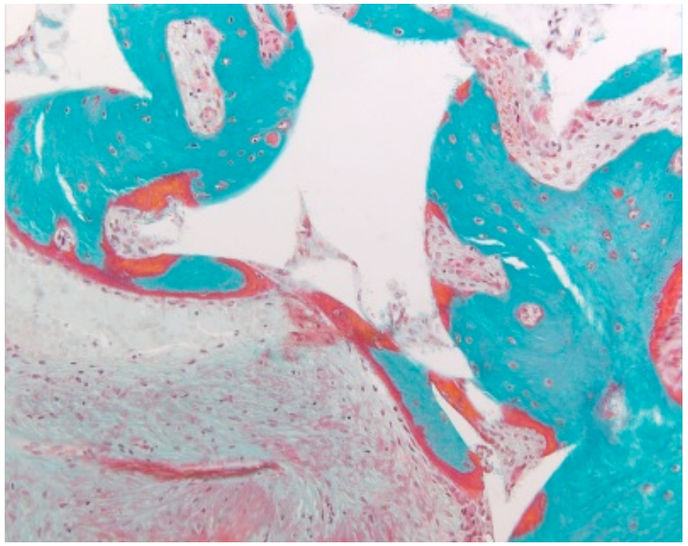


Figure 7.
Detail from Figure 6 (magnification x 100). Increased bone formation following the shape of the scaffold.

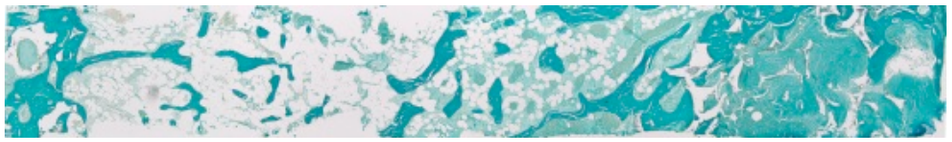


Figure 8.
Overview of a typical example of a bone biopsy stained with tartrate-resistant acid phosphatase (magnification x 10).

Tartrate-resistant acid phosphatase (TRAP) staining was performed to visualize TRAP-positive cells, i.e., osteoclasts and Howship's lacunae (Figures 8 and 9). Von Kossa [29] staining was used to detect calcified matrices that contained HA (Figure 10). In this study, the Von Kossa staining was used to verify remnants of SBC. Measurements were

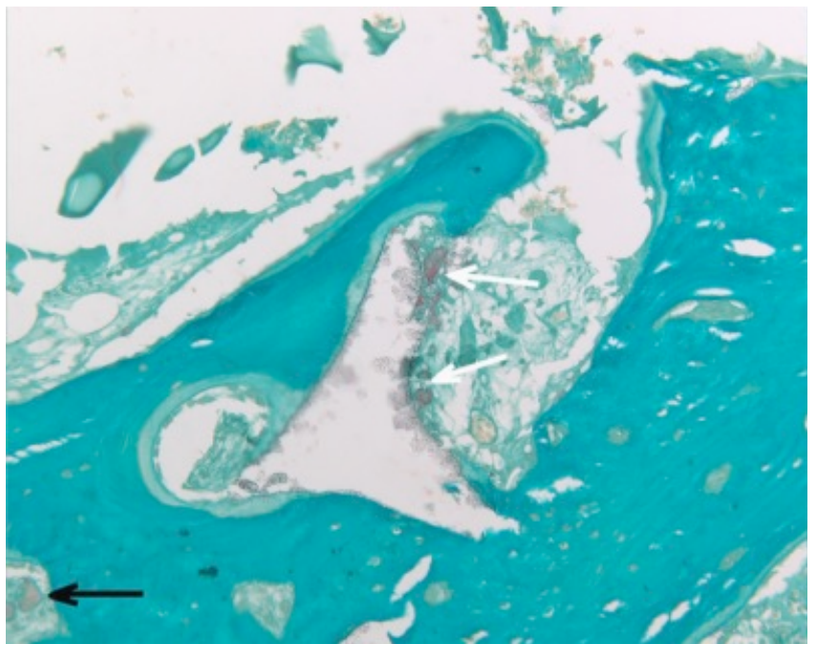


Figure 9.
Detail of Figure 8 (magnification x 100). Osteoclasts are visible at the border of the scaffold location (see white arrows), but also at the border of the bone tissue (black arrow).

performed semi-automatically using a drawing tube, a digitizer, and image analysis software (Osteomeasure, Atlanta, GA, USA). Nomenclature is used according to the American Society for Bone and Mineral Research (ASBMR) nomenclature committee [30].
The histomorphometric measurements were performed over the total section of the biopsy, including residual and newly formed bone. Separately, a partial field of the biopsy was measured from the first visible BCP particle in the cranial direction in order to exclude the native alveolar bone. This area was defined as the new bone area.

The specimens were examined for the following parameters:
Parameters evaluating bone mass/bone structure:

- Bone Volume (BV): Fraction of the grafted section that is vital bone tissue (%).
- Bone Surface (BS): BS expressed as a fraction of the total bone volume (mm^2/mm^3).
- Thickness of Bone Trabeculae (Tb.Th) (µm).

These parameters were measured by consecutive fields of a complete section, in four

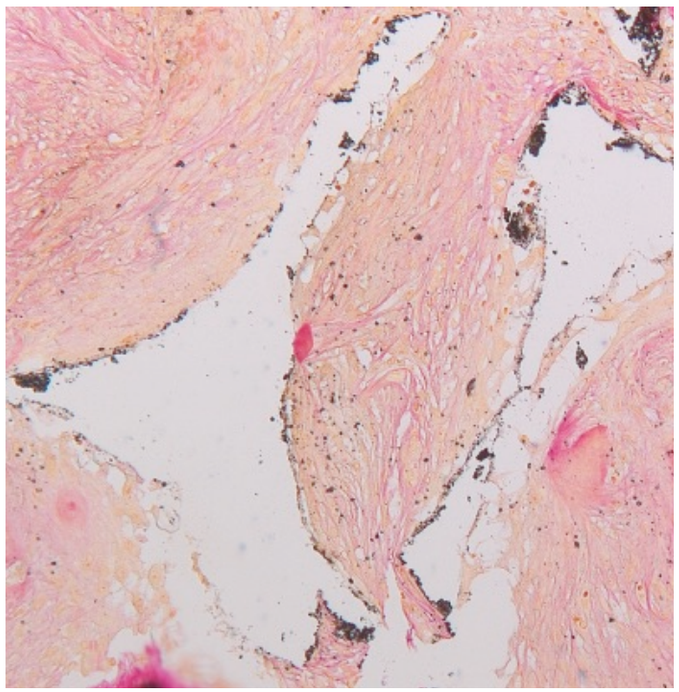


Figure 10.
Bone biopsy with Von Kossa staining (magnification x 100). Only edges of the scaffold remain in the section during the histological procedure. However, shape and positively stained remnants confirm the presence of scaffold.

sections throughout the biopsy, 150 µm separated. The number of fields varied between 30 and 60 fields, depending on the quality of the biopsy specimen.

Parameters evaluating bone turnover:

- Osteoid Volume (OV): Fraction of the bone tissue section that is osteoid (%).
- Osteoid Surface (OS): Osteoid-covered surfaces expressed as the fraction of the total BS (%).
- Osteoid Thickness (O.Th) (µm).
- Number of Osteoclasts (N.Oc).

Statistical analysis

Because of the observational nature of this study, only descriptive statistics were performed. Results were expressed as mean ± standard deviation.

RESULTS

Clinical evaluation

All six patients showed uneventful healing after the maxillary sinus floor elevation procedure as well as after dental implant placement. No postoperative inflammation or infection was observed.

At the time of re-entry for dental implant placement, the grafted area was well vascularized, and the tissue at the site of the former trapdoor location was flexible and had a fibrous aspect. Adhesions were seen between the periosteum and the bone graft area. No cysts or presence of purulent discharge were seen. A demarcation was seen between the grafted area and the original bone of the alveolar process, but there was continuity of the grafted area to native bone. The lateral aspect of the bone at the trapdoor location was flat. Drilling resistance was similar to that of drilling into maxillary bone. No jiggling of the drill was noticed, even though bone substitute particles could still be recognized in the tissue specimen retrieved. All particles were well integrated into newly formed tissue. These findings were consistent in all six patients.

In total, 13 Straumann® SLA solid screw (standard plus) dental implants were placed. Primary stability was achieved with dental implants with a root diameter of 4.1 mm and a length of 10 or 12 mm at all treatment sites. All dental implants osseointegrated well and could be loaded at the foreseen time point (3-4 months after implant surgery). No implants were lost after a 1-year follow-up.

Radiological evaluation

The increase in the height of the grafted area achieved by the maxillary sinus floor elevation procedure was on average 8.7 mm (range: 3.1-11.9 mm). At T2 and T3, in most patients, there was a slight reduction of graft height. In Table 1, the radiological findings are described in detail.

Qualitative histological evaluation

New bone formation was observed in all six specimens and followed the scaffold offered by the bone substitute material. The bone trabeculae that arose from the residual bone had started to invade the grafted area in the cranial direction (Figures 6 and 7).

The vital bone was composed of both lamellar and woven bone. In five out of six

samples, the primary trabecular structure was already reinforced by lamellar bone in some areas. The amount of woven bone varied between 10% and 60%.

Also, some osteoid islands were observed among the connective tissue formed around the bone substitute particles more cranial from the front of newly formed mineralized tissue.

The histological observations failed to demonstrate any pronounced infiltration of inflammatory cells in the tissue adjacent to the bone substitute material. The particles of the bone substitute were integrated into the network of newly formed bone trabeculae. Close bone-to-substitute contact was observed. The presence of Howship's lacunae could not be detected on the characteristic outlines of the substitute particles (Figures 8 and 9). The Von Kossa staining confirmed that remnants of the substitute material were present in the histology sections (Figure 10). Most of the very dense and brittle substitute materials were lost during histological procedures.

Quantitative histomorphometric evaluation

Quantitative evaluation was performed on the total area of the biopsy specimens, but also on the newly formed bone area. This area was defined as the area with bone trabeculae with visible remnants of BCP present excluding the native alveolar bone. In the total area, the average bone volume was 27.3% (range: 21.9-34.7%), of which 7.5% (range: 3.8-13.9%) was osteoid. The osteoid surface covered 41.3% (range: 22-94%) of the bone surface. The BS covered 4.5 mm^2/mm^3 (range: 2.8-5.6). The average thickness of the bone trabeculae measured was 132.1 µm (range: 81.5-200.5 µm). In the newly formed bone area, bone volume was 27.4% ± 6.7%. Trabeculae were thinner: 108.9 µm ± 64.7. Bone formation was extremely high in this area: OV/BV 11.9% ± 3.1 and OS/BS 69.6% ± 21.2. An overview of the findings from the histomorphometric analysis is listed in Tables 2 and 3.

Table 1. Radiological results (alveolar bone height measurements in mm)

Patients (no.)	Gender/Age	Location	T0	T1	Increase	T2	T3
1	F/56	26	5.5	15.5	10.0	15.2	15.0
2	M/67	16	5.5	15.9	10.4	14.3	11.7
3	F/37	26	7.1	10.2	3.1	10.2	9.7
4	M/45	16	6.5	18.4	11.9	17.1	13.7
5	F/77	26	6.4	15.9	9.5	15.8	15.3
6	F/46	25	8.0	15.1	7.1	14.9	14.7
Mean			6.5	15.2	8.7	14.6	13.4

M: male; F: female; age in years; corrected for magnification (x1.25) on panoramic radiograph.
T0: preoperative alveolar bone height; T1: after maxillary sinus elevation procedure; T2: immediately after dental implant placement; T3: 1 year after dental implant placement.

Table 2. Histomorphometric findings of the total section

Patients (no.)	Gender/Age (years)	Location	BV/TV (%)	BS/TV (mm^2/mm^3)	Tb.Th (µm)	OV/BV (%)	OS/BS (%)	O.Th (µm)	N.Oc/Tar ($1/mm^2$)
1	F/56	26	34.7	5.6	124.0	5.8	54.4	12.5	2.9
2	M/67	16	27.3	4.2	129.0	4.5	22.8	12.7	0.4
3	F/37	26	24.9	4.1	123.6	12.1	28.9	11.5	1.2
4	M/45	16	31.2	4.7	133.9	3.8	25.5	10.3	5.8
5	F/77	26	21.9	5.6	81.5	13.9	94.0	10.3	15.4
6	F/46	25	23.6	2.8	200.5	5.1	22.0	22.7	0.9
Mean			27.3	4.5	132.1	7.5	41.3	13.3	4.4
SD			4.9	1.1	38.4	4.3	28.5	4.7	5.7

M: male; F: female; BV/TV: bone volume/total volume; BS/TV: bone surface/total volume; Tb.Th: trabeculae thickness; OV/BV: osteoid volume/bone volume; OS/BS: osteoid surface/bone surface; O.Th: osteoid thickness; N.Oc/Tar: number of osteoclasts in total area.

Table 3. Histomorphometric findings of the 'newly formed bone area'

Patients (no.)	Gender/Age (years)	Location	BV/TV (%)	BS/TV (mm^2/mm^3)	Tb.Th (µm)	OV/BV (%)	OS/BS (%)	O.Th (µm)	N.Oc/Tar ($1/mm^2$)
1	F/56	26	35.6	6.9	106.1	9.3	69.6	12.7	3.8
2	M/67	16	27.5	5.9	92.1	10.2	86.6	10.3	8.5
3	F/37	26	25.3	6.4	78.0	11.7	69.2	11.5	4.5
4	M/45	16	19.4	5.9	66.2	16.6	47.4	11.8	3.2
5	F/77	26	21.7	5.9	73.7	14.9	99.3	10.3	16.7
6	F/46	25	34.9	3.4	237.8	9.2	45.3	24.3	2.2
Mean			27.4	5.7	108.9	11.9	69.6	13.5	6.5
SD			6.7	1.1	64.7	3.1	21.2	5.4	5.5

M: male; F: female; BV/TV: bone volume/total volume; BS/TV: bone surface/total volume; Tb.Th: trabeculae thickness; OV/BV: osteoid volume/bone volume; OS/BS: osteoid surface/bone surface; O.Th: osteoid thickness; N.Oc/Tar: number of osteoclasts in total area.

DISCUSSION

In this article, the first clinical, radiological, histological and histomorphometric results of an ongoing multicenter study on BCP are presented. During the clinical evaluation, it was apparent that after a 6-month healing period, the grafted BCP had integrated with the original maxillary bone (maxillary sinus floor) and was stable enough to ensure successful dental implant placement. An adequate bone height in the grafted area was found clinically and radiologically at the time of implant placement in all patients, although the sample size could be considered small.

As in previously evaluated bone substitute products [18, 19, 31], in BCP bone formation also occurred along the scaffold offered by the bone substitute [14-16, 20, 21]. Histological analysis showed that the mineralized bone tissue was in intimate contact with the BCP particles. The borders between residual bone, new bone and BCP were difficult to define. Osteoid islands were observed among the connective tissue formed around the bone substitute particles, even further cranially from the front of newly formed bone trabeculae. These observations confirm the principle of the pattern for early bone development presented earlier [32], where the elaboration of highly organized bone tissue requires a mechanically stable surface and, in fact, bone is only deposited on a solid base. In direct or intramembranous ossification, connective tissue serves as a template for bone deposition.

The present study provides histological evidence in humans confirming the bone ingrowth of similar BCPs reported earlier [14, 15]. Mineralized bone tissue was observed to be in intimate contact with the bone substitute particles, indicating that the material possesses osteoconductive properties [14]. This positive effect of the bone substitute material on new bone formation might be explained by the chemical composition.

BCP materials have shown bone formation simultaneously with material degradation [14, 15]. However, the BCP evaluated showed limited signs of substitute degradation within the observation period of 6 months in humans, even though osteoclasts were detected next to the characteristic outlines of the substitute particles. In this study, it seems that BCP is resorbed by osteoclasts and is replaced by new bone. This process of substitution is not finished after 6 months of follow-up [33]. The high variance in the number of osteoclasts is commonly observed, because osteoclasts typically exist in small but concentrated masses. It is assumed that the very dense and brittle substitute

material was lost during histological procedures. However, the area formerly occupied by bone substitute material could still be detected as empty (Von Kossa staining), colorless spaces with characteristic outlines on the histological section.

The observed osteoid islands cranial from the newly formed mineralized tissue could be explained by oblique cutting of fields of osteoconductive activities or from osteoconductive processes arising from the palatal or the buccal walls of the maxillary sinus floor.

The high bone formation especially in the newly formed bone area indicates that after 6 months bone cells are still actively replacing BCP in vital bone tissue. Although clinically the tissue seems stable enough for dental implant placement, at the cellular level, this process is still continuing. More time is necessary to achieve a new bone balance, but the histological observation at this time promises continuing replacement of the BCP by vital bone, possibly resulting in complete replacement. Future data could corroborate this hypothesis.

CONCLUSIONS

Despite a limited number of patients, this study provides clinical, radiological, histological and histomorphometric results in humans confirming the suitability of the new BCP Straumann® Bone Ceramic for vertical augmentation of the atrophied maxilla by means of a maxillary sinus floor elevation procedure allowing subsequent dental implant placement.

After a healing period of 6 months, histological and histomorphometric evaluation showed newly formed bone possessing a trabecular structure. The newly formed bone was in intimate contact with substitute material, outlining the osteoconductive properties of the BCP material. Bone maturation was evident by the presence of lamellar bone.

Substitute degradation could not be thoroughly addressed. However, osteoclasts were detected histomorphometrically next to the characteristic outlines of the substitute particles. Additional investigations are necessary to fully understand the degradation properties of the BCP material applied.

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3

The use of a biphasic calcium phosphate in a maxillary sinus floor elevation procedure: a clinical, radiological, histological and histomorphometric evaluation with 9- and 12-month healing time

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ABSTRACT

Introduction: This study evaluates the clinical, radiological, histological, and histomorphometric aspects of a fully synthetic biphasic calcium phosphate (BCP) (60% hydroxyapatite and 40% β-tricalcium phosphate), used in a human maxillary sinus floor elevation (MSFE) procedure with 9- and 12-month healing time.

Methods: A unilateral MSFE procedure, using 100% BCP, was performed in two series of five patients with healing times of 9 and 12 months respectively. Clinical and radiological parameters were measured up to 5 years postoperatively. Biopsy retrieval was carried out during dental implants placement. Histology and histomorphometry were performed on 5-μm sections of undecalcified bone biopsies.

Results: The MSFE procedure with BCP showed uneventful healing in all cases. All dental implants appeared to be well osseointegrated after 3 months. Radiological evaluation showed less than 1 mm tissue height loss from MSFE to the 5-year follow-up examination. No signs of inflammation were detected on histological examination. Newly formed mineralized tissue was found cranially from the native bone. The BCP particles were surrounded by connective tissue, osteoid islands, and newly formed bone. Mineralized bone tissue was in intimate contact with the BCP particles. After 12 months, remnants of BCP were still present. The newly formed bone had a trabecular structure. Bone maturation was demonstrated by the presence of lamellar bone. Histomorphometric analysis showed at 9 and 12 months respectively an average vital bone volume/total volume of 35.2 and 28.2%, bone surface/total volume of 4.2 mm^2/mm^3 and 8.3 mm^2/mm^3, trabecular thickness of 224.7 and 66.7-μm, osteoid volume/bone volume of 8.8 and 3.4%, osteoid surface/bone surface (OS/BS) of 42.4 and 8.2%, and osteoid thickness of 93.9 and 13.6-μm.

Conclusions: MSFE with BCP resulted in new bone formation within the augmented sinus floor and allowed the osseointegration of dental implants in both groups. From a histological and histomorphometric perspective, a 9-month healing time for this type of BCP may be the optimal time for placement of dental implants.

INTRODUCTION

Maxillary sinus floor elevation (MSFE) is a surgical procedure to enhance the bone height in the posterior maxilla with graft material, allowing dental implant placement (later or at the same time) [1, 2]. This pre-implant procedure is predictable and results in a dental implant survival of more than 93.8% 3 years after dental implant placement [3]. According to Pjetursson [4] in his systematic review on success of implants inserted in combination with sinus floor elevation, the implant survival increases to 98.3% after 3 years when compared to non-augmented jawbone.

Autogenous bone is still the gold standard, because of its osteoconductive and osteoinductive properties, due to the possible osteogenic capacity [5-10]. Moreover, the bone morphogenic proteins, present in autogenous bone grafts, can attract osteogenic cells from the surrounding tissues, in their turn containing other growth factors essential for the process of bone graft incorporation [4].

As the maxillary tuberosity, mandibular retromolar or chin region do not always supply enough bone graft volume, bone grafts can also be harvested from the anterior iliac crest, the tibia, the rib, and the calvarial bone. However, these harvesting procedures have disadvantages, such as prolonged operating time, donor site morbidity, hospitalization [9, 11-13], sensory disturbances [14], and unpredictable resorption rate of the bone grafts [5, 15]. Donor site morbidity may be a major reason to question the use of autogenous bone [16]. Therefore, several types and properties of bone substitutes (alloplast, xenograft, allograft, and mixtures of various materials) have been developed [16, 17] to overcome the disadvantages mentioned above.

Calcium phosphates, such as hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), or biphasic calcium phosphate (BCP), a mixture of HA and β-TCP, are osteoconductive as they resemble the chemical composition of natural bone [18, 19]. Calcium phosphates are biocompatible and do not induce a sustained foreign body response or toxic reaction [20]. At a physiological pH, calcium phosphates are the least soluble of the naturally occurring calcium phosphates, which makes them relatively resistant to resorption [21-23].

β-TCP is a biocompatible osteoconductive calcium phosphate that may provide a scaffold for potential bony ingrowth [24]. β-TCP resorbs rather quickly but not necessarily at the same rate as new bone formation [25-27]. Most research focused on either using the

relative unresorbable HA as a scaffold or β-TCP as a degradable component [19, 24-26, 28, 29]. Zerbo et al. [30] concluded that due to the absence of osteoinductive properties of TCP, the rate of bone formation was delayed in comparison with autogenous bone grafts. It would be beneficial for the patient to reduce the interval between the MSFE procedure and dental implant placement to accelerate the process of integration of the grafted material. BCP, in a combination of 60% HA and 40% β-TCP, demonstrated new bone formation in both animals and humans [24, 31-33]. This biphasic calcium phosphate (BCP) appeared to be a suitable graft material for vertical augmentation of the posterior maxilla by means of an MSFE procedure and dental implants placement in a study with a healing time of 6 months [16, 27, 34]. The process of bone substitution may not be completed after 6 months of follow-up [27, 35]. Even though clinically, the tissue seems stable enough for dental implant placement, the high bone formation, especially in the newly formed bone areas, indicates that after 6 months, bone cells are still actively replacing BCP in vital bone tissue. To date, no long-term follow-up has been reported on the use of a synthetic BCP, consisting of 60% HA and 40% β-TCP, which may elucidate the degradation properties of BCP material. One may have to consider that more time is necessary to achieve a new bone balance. The aim of this study is to evaluate the clinical, radiological, histological, and histomorphometric aspects of a synthetic BCP (Straumann® Bone Ceramic, Institut Straumann AG, Basel, Switzerland) that was used in MSFE procedure with 9- and 12-month healing times.

METHODS

Study population

In this study, 10 consecutive healthy patients were selected for a unilateral MSFE procedure. Five patients received dental implants 9 months after MSFE and five patients underwent dental implant surgery 12 months after MSFE. In the 9-month group (three men and two women), the average age was 56.6 years (range 40 to 64 years); in the 12-month group (one man and four women), the average age was 58.2 years (range 51 to 67 years). All patients were partially edentulous in the posterior maxilla without the need for onlay bone grafting of the alveolar crest to achieve an adequate alveolar ridge. A minimal native bone height of 4 mm (calculated from measurements on a preoperative panoramic radiograph) was preferred in both study groups. All selected patients were non-smokers, showed no systemic disease, and were not drug users.

The study was performed in accordance with the principles of the Declaration of Helsinki. Since the study involved CE-marked devices (calcium phosphates) being used for their intended purpose (use as carrier material for bone augmentation in sinus floor elevation procedures) and the harvested material can be regarded as surgical waste, no specific regulatory approval from a medical ethical committee was required. Patients provided written consent before the study-related procedures were undertaken. The biopsies were retrieved during dental implant surgery by means of trephine drills, implicating the tissue in the hollow drill is considered surgical waste. For the patient, this is not an additional invasive procedure. The different healing times did not have a negative impact on the patients.

Maxillary sinus floor elevation procedure

Ten patients were scheduled for a unilateral two-stage MSFE top-hinge door lateral window technique procedure, as described by Tatum [2]. All 10 patients were treated in an outpatient procedure under local anesthesia. Perioperatively, all patients received an antibiotic prophylaxis, consisting of amoxicillin 500 mg four times daily for 7 days, starting 1 day before the MSFE procedure. An oral rinse with chlorhexidine-digluconate 0.12%, three times, 10 cm^3 daily for 1 min for 2 weeks was prescribed, as part of the standard protocol for an MSFE procedure.

A midcrestal incision was made with vertical release incisions at the canine and tuberosity

region. A full-thickness mucoperiosteal flap was elevated. The lateral maxillary sinus wall was prepared using a diamond burr with copious irrigation with sterile isotonic saline, regarding the contour of the maxillary sinus as observed on the preoperative panoramic radiograph. A bony top-hinge trapdoor was mobilized and turned inward and upward into a horizontal position in the maxillary sinus, together with the carefully elevated Schneiderian membrane. The area created between the lifted lid and the sinus floor was filled only with BCP (Straumann® Bone Ceramic). The BCP was 100% crystalline, highly pure, and had a porosity of 90%. The pores were 100 to 500 µm in diameter. No membrane was used to cover the lateral window [36]. Primary wound closure was performed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). Immediately after the procedure, a panoramic radiograph was taken. Postoperative examination and removal of the sutures were performed 10 to 14 days after the MSFE procedure.

Dental implant surgery and biopsy retrieval

After 9-month (five patients) and 12-month (five patients) healing times, a crestal incision was made with small mesial and distal buccal vertical release incisions. Subsequently, a full-thickness mucoperiostal flap was raised. The alveolar ridge was inspected for suitable implant placement, and the former lateral window area was inspected for tissue condition. Implant preparations were made, and biopsies were obtained from the grafted area at planned dental implant positions using trephine drills with an external diameter of 3.5 mm and internal diameter of 2.5 mm (Straumann® Trephine Drill) with copious irrigation of sterile saline. In the 10 patients, 22 standard plus, regular neck, soft tissue level Straumann® SLA dental implants with a diameter of 4.1 mm and a length of 10 or 12 mm were placed (Figure 1). The implants were left to integrate in a non-submerged unloaded fashion. Soft tissue closure was performed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). A postoperative radiological examination (panoramic radiograph) was taken directly after dental implantation. Sutures were removed after 10 to 14 days and, if needed, provisional prosthetics were adapted to the new situation. Attention was paid to prevent premature loading of the dental implants. The patients were instructed to avoid loading of the posterior maxilla upon which the operation had been conducted until the 3-month integration time of the dental implants had passed and the fixed superstructures were fabricated and placed.

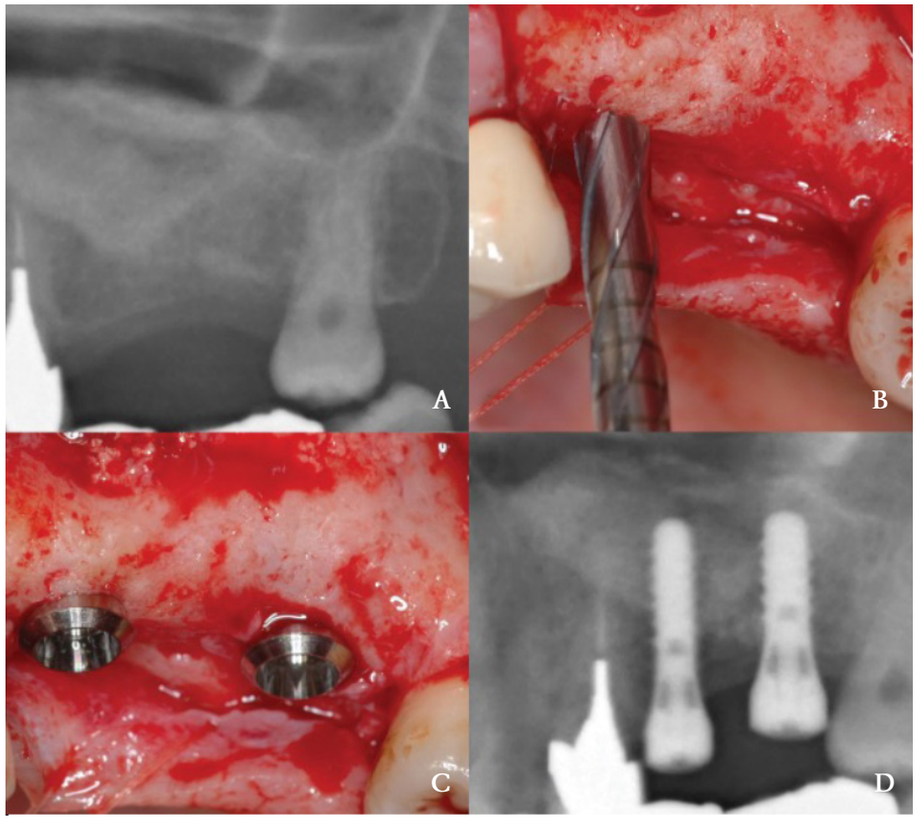


Figure 1.
Images of patient # 5 (9-month healing time). A: radiograph of the left maxillary sinus: situation 9 months after the maxillary sinus floor elevation procedure; B: with a trephine drill, the implant osteotomy is made and the biopsy is obtained; C: clinical situation after placing two Straumann® SLA implants in the left posterior maxilla; D: radiograph of two Straumann® SLA implants in the left posterior maxilla.

Clinical evaluation

All 22 inserted dental implants were clinically tested for good primary stability. Osseointegration at abutment connection was tested with a 35-Ncm torque. One experienced oral and maxillofacial surgeon (CB) carried out all follow-up examinations.

Radiological evaluation

Panoramic radiographs were taken at patient's intake (T0); immediately after the MSFE procedure (T1); immediately after dental implant placement (T2); 1 year after dental implant placement (T3); and 5 years after dental implant placement (T4).

On the panoramic radiographs, changes in tissue height (mm) of the grafted area were measured at the implant site on the following time points: T0, T1, T2, T3, and T4. An average magnification of ×1.25 was taken into account to calculate true tissue heights.

Qualitative histological and quantitative histomorphometric analysis

Bone biopsies were obtained during implant surgery as previously described [37]. Trephine drills were split and opened in order to secure the orientation of the biopsies. The biopsies were fixed overnight in 4% phosphate-buffered formaldehyde and transferred to alcohol 70% [38]. After dehydration, the bone specimens were embedded without prior decalcification in methyl methacrylate supplemented with 20% dibutyl phthalate and 0.008 g/mL Lucidol. The biopsies were cut into 5-µm longitudinal sections (Polycut S., Leica microtome type sm2500s, Leica, Wetzlar, Germany). Bone mass indices and osteoid surface were measured in Goldner's trichrome stained sections [39]. Tartrate-resistant acid phosphate (TRAP) staining was performed to visualize osteoclasts. Measurements were performed semi-automatically using a digitizer and image analysis software (Osteomeasure, Atlanta, GA, USA). In this study, the Von Kossa staining was used to verify remnant particles of BCP (Straumann® Bone Ceramic). BCP particles were detected semi-quantitatively by three independent observers and classified into quartiles (< 25% of BCP, > 25% and < 50% of BCP, > 50 < 75% of BCP, > 75% of BCP). Nomenclature was used according to the American Society for Bone and Mineral Research (ASBMR) nomenclature committee [40].

Since it was impossible to discriminate between resident and augmented bone, histomorphometric measurements were performed over the total section of the biopsy, including native and newly formed bone. The parameters were measured in consecutive fields of a complete section, in four 150-µm separated sections throughout the biopsy, covering a total measured area of 60 mm^2. The specimens were examined for the following parameters:

Parameters evaluating vital bone mass/bone structure:

1. Vital bone volume (BV): percentage of the grafted section that is vital bone tissue (%).
2. Bone surface (BS): BS expressed as a fraction of the total vital bone volume (mm^2/mm^3).
3. Thickness of bone trabeculae (Tb.Th) (µm).

Parameters evaluating bone turnover:

1. Osteoid volume (OV): fraction of the vital bone tissue section that is osteoid (%).
2. Osteoid surface (OS): osteoid-covered surfaces expressed as the fraction of the total BS (%) to measure new vital bone formation.
3. Osteoid thickness (O.Th) (µm).
4. Number of osteoclasts (N.Oc) per mm^2 total area.

Statistical analysis

Because of the observational nature of this study and the limited number of biopsies, only descriptive statistics are presented. Results are expressed as mean ± standard deviation.

RESULTS

Clinical evaluation

None of the 10 patients showed postoperative inflammation or infection after the MSFE procedure nor during surgical re-entry for dental implant placement. When opening the area for dental implant insertion, the grafted area proved to be well vascularized and the tissue at the site of the former trapdoor location was slightly flexible and had a fibrous aspect. Between the periosteum and the bone graft area, adhesions were seen. Macroscopically, no voids or presence of purulent discharge were observed. Although a demarcation was observed between the grafted area and the original bone of the alveolar process, there was continuity between the grafted area and the native bone. There was no jiggling of the drill, even though bone substitute particles could still be recognized in the tissue specimen retrieved. All particles appeared well integrated in newly formed tissue. These findings were consistent in all 10 patients. In total, 22 Straumann® SLA solid screw (standard plus regular neck, soft tissue level) dental implants with a diameter of 4.1 mm and a length of 10 or 12 mm were placed. Primary stability was achieved with all dental implants. All dental implants osseointegrated well and could be loaded with fixed prostheses 3 months after implant surgery. No dental implants were lost during 5-year follow-up.

Radiological evaluation

The increase in height of the grafted area achieved by the MSFE procedure was on an average of 7.5 mm (SD ± 2.8) in the 9-month group (Table 1) and 9.3 mm (SD ± 3.1) in 12-month group (Table 2). The measured tissue height appeared to be stable between 1 and 5 years in the 9-month group (Figure 2) and the 12-month group (Figure 3).

Qualitative histological evaluation

The histological evaluation was performed on the complete section, comprising native bone, newly formed bone, and residual graft material. The BCP particles were surrounded by connective tissue, osteoid islands, and newly formed bone. From the residual bone in all specimens, new bone formation was detected following the scaffold of the bone substitute, starting in cranial direction. This newly formed bone consisted of woven bone as well as lamellar bone and appeared as vital bone tissue containing

Table 1. Alveolar tissue height measurements on panoramic radiographs (in true mm) in the 9-month group

Patient	Gender/Age	Location	T0	T1	Increase	T2	T3	T4
1	F/54	15	5.4	15.2	9.8	14.0	13.6	13.2
1	F/54	16	5.7	14.3	8.6	14.6	13.0	13.5
2	M/62	16	5.5	15.1	9.6	13.2	12.4	12.4
3	F/64	15	7.0	15.2	8.2	13.4	12.8	12.2
4	M/63	26	6.0	11.7	5.7	14.7	14.8	14.6
4	M/63	27	10.0	11.3	1.3	14.8	13.5	13.4
5	M/40	26	4.1	12.3	8.2	12.4	12.0	12.5
5	M/40	27	7.3	16.3	9.0	15.5	14.3	13.8
Mean	56.6		6.4	13.9	7.5	14.1	13.3	13.2
SD			1.7	1.9	2.8	1.0	0.9	0.8

Age in years at biopsy retrieval; hard tissue height corrected for magnification (x1.25) on panoramic radiograph. M: male; F: female; T0: (native bone height) preoperative alveolar bone height; T1: directly after MSFE procedure; T2: immediately after dental implant placement; T3: 1 year after dental implant placement; T4: 5 years after dental implant placement.

Table 2. Radiological results (alveolar tissue height measurements in true mm) in the 12-month group

Patient (no.)	Gender/Age	Location	T0	T1	Increase	T2	T3	T4
1	F/53	15	6.3	17.6	11.3	18.7	17.4	17.4
1	F/53	16	2.5	17.6	15.1	17.9	16.4	15.9
1	F/53	17	1.3	15.5	14.2	13.7	12.8	12.6
2	F/53	26	8.8	17.2	8.4	16.7	16.1	17.0
2	F/53	27	7.9	13.1	5.2	11.3	12.0	11.9
3	F/67	14	4.2	13.4	9.2	14.1	14.0	14.0
3	F/67	15	4.1	11.0	6.9	9.9	12.7	12.8
3	F/67	16	5.6	9.9	4.3	9.0	11.4	11.0
4	M/67	14	2.5	13.9	11.4	13.8	13.3	14.1
4	M/67	15	3.0	12.2	9.2	12.5	11.2	11.8
4	M/67	17	4.3	10.7	6.4	10.5	10.1	10.3
5	F/51	24	5.5	13.7	8.2	14.0	13.8	14.4
5	F/51	25	2.5	13.0	10.5	14.6	13.6	13.2
5	F/51	26	3.6	14.1	10.5	14.0	13.2	13.4
Mean	58.2		4.4	13.8	9.3	13.6	13.4	13.5
SD			2.0	2.3	3.1	3.8	2.0	2.1

Age in years at biopsy retrieval; hard tissue height corrected for magnification (x1.25) on panoramic radiograph. M: male; F: female; T0: (native bone height) preoperative alveolar bone height; T1: directly after MSFE procedure; T2: immediately after dental implant placement; T3: 1 year after dental implant placement; T4: 5 years after dental implant placement.

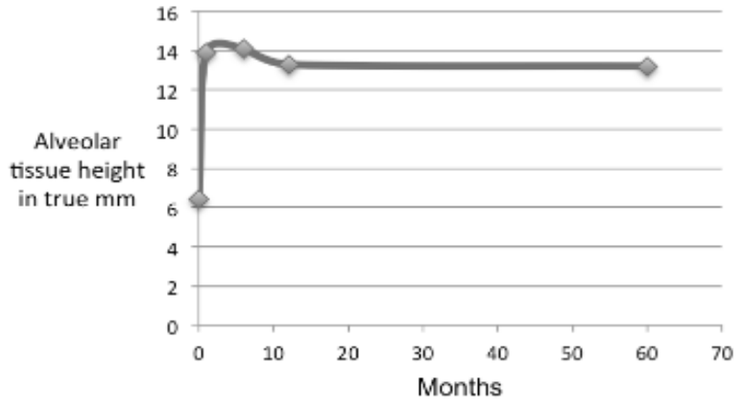


Figure 2.
Alveolar tissue height (in true mm) over a 5-year period in the 9-month group.

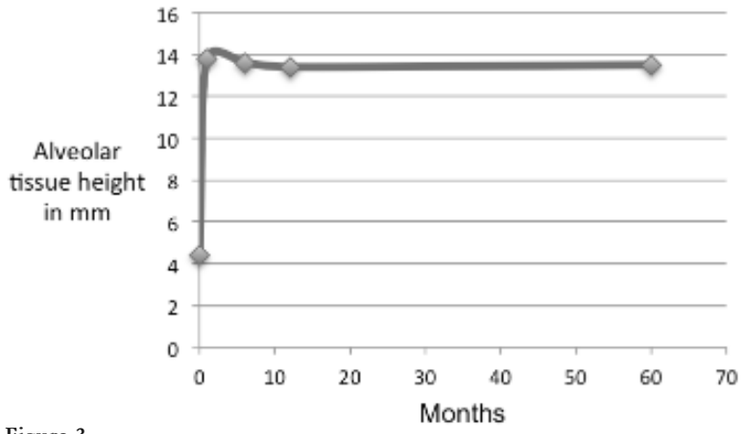


Figure 3.
Alveolar tissue height (in true mm) over a 5-year period in the 12-month group.

osteoblasts, osteoid covering the border, and osteocytes inside bone lacunae.

Cranially, near the lifted trapdoor, some osteoid islands with osteogenic activity were detected.

Histological observations did not show inflammatory cells in the tissue adjacent to the bone substitute particles. Bone marrow-like tissue, which included blood vessels, was observed in between the bone trabeculae (Figure 4). Reinforcement by lamellar bone was shown in some areas after 9 and 12 months (Figures 5 and 6). No Howship's lacunae could be detected on the characteristic outlines of the substitute particles. Fragments of the substitute particles were present in the sections of the 9-month group and the

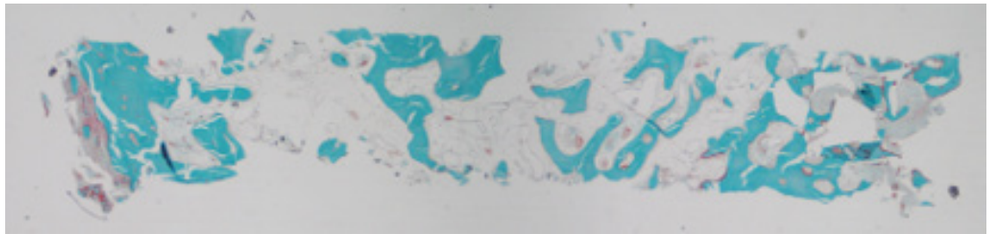


Figure 4.
Patient # 1 (12 month healing time): overview of a typical example of a bone biopsy stained with Goldner trichrome staining (magnification x 10).

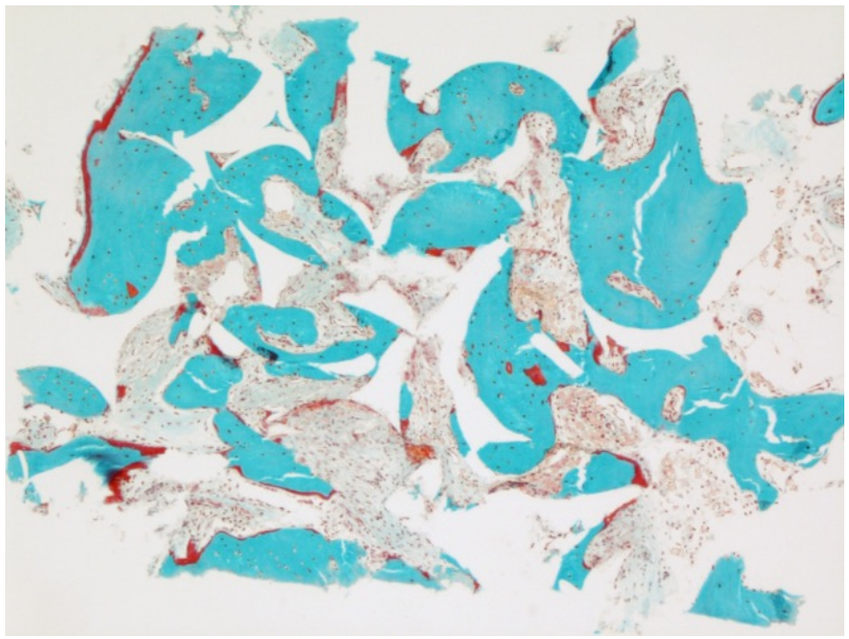


Figure 5.
Patient # 4 (9 month healing time): increased bone formation following the shape of the grafted particles stained with Goldner trichrome staining (magnification x 100).

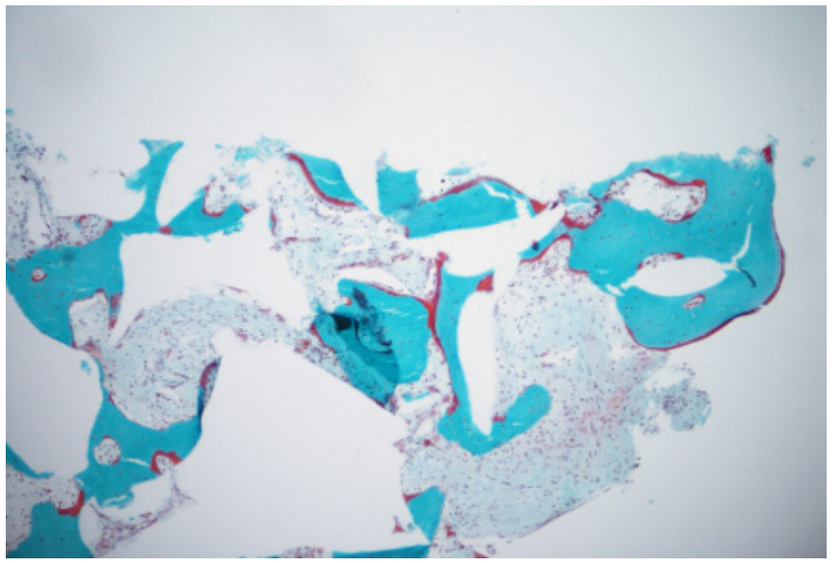


Figure 6.
Patient # 1 (12 month healing time): increased bone formation following the shape of the grafted particles that are still present (magnification x 100).

12-month group, as confirmed by Von Kossa staining. Regardless of the histological process, the contours of the bone substitute remnants were clearly detectable which enabled analyses.

Quantitative histomorphometric evaluation

In the 9-month group, the average vital bone volume was 35.2% of the total biopsy volume (SD ± 9.5) of which 8.8% (SD ± 3.8) was osteoid. The osteoid surface covered 42.4% (SD ± 12.1) of the bone surface. The BS covered 4.2 mm^2/mm^3 (SD ± 1.9). In the total area for the 12-month group, the average vital bone volume was 28.2% of the total biopsy volume (SD ± 3.2) of which 3.4% (SD ± 2.5) was osteoid. The osteoid surface covered 8.2% (SD ± 5.3) of the bone surface. The BS covered 8.3 mm^2/mm^3 (SD ± 1.3). In conclusion, vital bone volume and bone turnover decreased in the 12-month group compared to the 9-month group. An overview of the individual histomorphometric findings is listed in Tables 3 and 4.

Table 3. Histomorphometric evaluation of the biopsies after 9-month healing time

Patients (no.)	Gender/Age (years)	Location	BV/TV (%)	BS/TV (mm^2/mm^3)	Tb.Th (µm)	OV/BV (%)	OS/BS (%)	O.Th (µm)	N.Oc/Tar ($1/mm^2$)
1	F/54	15	51.3	2.3	461.3	5.4	43.4	28.3	0.8
2	M/62	16	30.4	2.2	278.6	13.3	53.3	331.8	2.0
3	F/64	15	29.3	4.6	121.7	8.5	50.0	10.2	2.5
4	M/63	27	36.3	5.8	168.8	4.7	22.3	18.8	2.3
5	M/40	26	28.5	6.2	93.0	12.0	43.0	80.2	5.0
mean			35.2	4.2	224.7	8.8	42.4	93.9	2.5
SD			9.5	1.9	150.0	3.8	12.1	135.8	1.5

Not-intact biopsies were excluded from histomorphometric examination. Age (years) at biopsy retrieval.
M: male; F: female; BV/TV: vital bone volume/total volume; BS/TV: bone surface/total volume; Tb.Th: trabeculae thickness;
OV/BV: osteoid volume/vital bone volume; OS/BS: osteoid surface/bone surface; O.Th: osteoid thickness;
N.Oc/Tar: number of osteoclasts in total area.

Table 4. Histomorphometric evaluation of the biopsies after 12-month healing time

Patients (no.)	Gender/Age (years)	Location	BV/TV (%)	BS/TV (mm^2/mm^3)	Tb.Th (µm)	OV/BV (%)	OS/BS (%)	O.Th (µm)
1	F/53	16	25.5	6.9	74.1	1.7	5.2	12.8
2	F/53	25	30.8	9.2	66.8	1.1	3.1	12.7
2	F/53	26	29.3	9.5	61.5	4.2	9.2	14.7
3	M/67	17	24.0	7.5	64.4	6.6	15.2	14.0
Mean			28.2	8.3	66.7	3.4	8.2	13.6
SD			3.2	1.3	5.4	2.5	5.3	1

Not intact biopsies were excluded from histomorphometric examination. Age in years at biopsy retrieval.
M: male; F: female; BV/TV: vital bone volume/total volume; BS/TV: bone surface/total volume; Tb.Th: trabeculae thickness;
OV/BV: osteoid volume/vital bone volume; OS/BS: osteoid surface/bone surface; O.Th: osteoid thickness;
N.Oc/Tar: not measured as an insignificant number of osteoclasts were available.

DISCUSSION

This study presents the clinical, radiological, histological and histomorphometric results on the use of a biphasic calcium phosphate (Straumann® Bone Ceramic) in an MSFE procedure with healing times of 9 and 12 months. During the clinical evaluation, it appeared that both 9-month and 12-month healing times resulted in integration of the grafted BCP with the original maxillary bone (sinus floor), which was stable enough to ensure successful dental implant placement. It should be mentioned that in this study, a minimal native alveolar bone height of 4 mm was preferred, ensuring a certain primary stability of the dental implants placed. An adequate and stable tissue height in the grafted area was observed radiologically in a 5-year follow-up in all patients in both 9-month and 12-month healing time groups.

Radiological observations show very stable results in different healing times, in a previous 6-month study [27] and after 9- and 12-month healing times in the present study. However, this does not reveal the actual vital bone height available for attachment to the dental implant surface. This can only be measured by histological investigations. Reviews show that the loss of dental implants with an intra-osseous length of 8 mm or more, placed in native bone, is minimal [4]. Previously, the histomorphometrical and histological evaluation, 6 months after an MSFE procedure, using Straumann® Bone Ceramic was reported with a 1-year follow-up. At that time, no loss of dental implants was reported. In the present study, none of the implants in the 9- and 12-month groups were lost. Histological investigation showed that mineralized bone tissue was observed to be in intimate contact with the bone substitute particles, indicating that the graft material possesses osteoconductive properties [27] (which is in agreement with other observations) [16, 24, 34]. This positive effect might be explained by its chemical composition. BCP materials have shown bone formation simultaneously with material degradation [24, 25]. BCP exhibited moderate signs of substitute degradation in humans not only after 6 months, as previously reported by Frenken et al. [27]. The present study still observed remnants of BCP after 9 and 12 months which suggests that the ossification rate is not the same as the resorption rate of the BCP. Because osteoclasts were detected next to the characteristic outlines of the substitute particles, it is suggested that BCP is resorbed by osteoclasts. The high bone formation in the newly formed bone area indicates that after 12 months, bone cells are still actively forming

new bone matrix, thereby absorbing and replacing BCP in vital bone tissue.

In the cranial part of the biopsy, some osteoid islands with osteogenic activity were detected, possibly caused by osteoinductive properties from the lifted bony trapdoor.

In the present study, histomorphometric analyses revealed that the vital bone volume was higher in the 9-month healing time group than in the 12-month healing time group, while one would expect to find more newly formed bone in time as more of the bone substitute resorbs. As the mean original native alveolar bone height is 6.4 mm in the 9-month group and 4.4 mm in the 12-month group and augmented portion of the 12-month group (9.3 mm) is higher than the 9-month group (7.5 mm), this may have a negative impact on the relatively smaller portion of the bone volume of the total biopsy in the 12-month group. This is a limitation of the present study.

However, the average 2 mm of difference in the native bone height between the 9- and 12-month groups does not fully explain the difference in BT/TV that was found between the two groups. Furthermore, the thickness of the bone trabeculae decreased suggesting that at 12 months, bone turnover returns to a relatively normal bone remodeling status, indicative of a new balance in bone tissue. However, woven bone (data not shown) and the remnants of the BCP were still present at 12 months, contradicting this hypothesis. Nevertheless, from a histological and histomorphometric perspective in the present study, a 9-month healing time may be the optimal time for the placement of dental implants. Although the sample size of the two groups is small, multiple dental implant placement deliver sufficient data for evaluation. The 12-month period from MSFE to implant placement(s) is considered to be a long time. Most patients are not willing to wait that long, which makes these bone samples very scarce and therefore valuable for long-term observations. The implication of the small sample size is that this study has an observational nature and, therefore, only descriptive statistics are presented.

CONCLUSION

Based on clinical, radiological, histological, and histomorphometric analysis, this study confirms the suitability of BCP for vertical augmentation of the posterior maxilla by means of an MSFE procedure, allowing dental implant placement after 9 and 12 months healing times. Yet, complete degradation of the BCP particles does not occur within a 12-month healing time. From a histological and histomorphometric perspective, a 9-month healing time for this type of BCP may be the optimal time for the placement of dental implants.

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4

The use of autogenous bone mixed with a biphasic calcium phosphate in a maxillary sinus floor elevation procedure with a 6-month healing time:
A clinical, radiological, histological and histomorphometric evaluation

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ABSTRACT

Introduction: In this study it is evaluated whether autogenous bone mixed with biphasic calcium phosphate (BCP) used in a maxillary sinus floor elevation (MSFE) leads to improved bone formation.

Methods: In five patients a unilateral MSFE was performed. Histological and histomorphometric analyses were performed on bone biopsies that were obtained 6 months after MSFE during dental implant surgery.

Results: The average vital bone volume was 29.9% of the total biopsy (BV/TV, SD ± 10.1) of which 7.1% was osteoid (OV/BV, SD ± 4.8). The osteoid surface (OS/BS) covered 26.0% (SD ± 13.4) of the bone surface. The BS/TV covered 4.7 mm^2/mm^3 (SD ± 2.3). Compared with previous studies the analyses showed a difference for trabecular thickness (Tb.Th.) and osteoid surface (OS/BS), but not for BV/TV, OV/BV and the number of osteoclasts.

Conclusion: MSFE with autogenous bone mixed with BCP shows an amount of newly formed bone that is comparable with the findings from the previously published 6-month study with pure BCP. However, a better distribution of the new bone over the entire biopsy was observed.

INTRODUCTION

Lack of vertical bone height in the posterior maxilla limits standard dental implant placement. In order to increase the vertical dimension in the posterior maxilla, a maxillary sinus floor elevation (MSFE) with graft material can be performed [1, 2]. MSFE is a predictable pre-implant surgical procedure with a high survival rate of the dental implants, exceeding 93.8% [3]. Pjetursson systematically reviewed the success of dental implants placed in combination with MSFE, and reported an implant survival rate after 3 years up to 98.3%, using rough surface dental implants, related to non-augmented jawbone [4].

Due to its osteoinductive, osteoconductive and osteogenic properties autogenous bone is still considered the gold standard as graft material [5-12]. This osteogenic capacity of autogenous bone grafts may be attributed to the presence of bone morphogenic proteins, attracting osteogenic cells from the adjacent tissues, thus mobilizing other growth factors essential for bone regeneration [4].

Bone grafts can be obtained either intraorally or extraorally. Harvesting these bone grafts has drawbacks, such as an extended operating time, donor site morbidity, hospitalization, unpredictable resorption rate of the bone grafts [9, 13-15] and sensory disturbances [5, 16, 17]. Different types of bone substitutes have been developed to overcome these drawbacks (e.g., allograft, xenograft, alloplast and mixtures of different materials) [18, 19]. The comparison of bone grafts from different origins has been the subject of study extensively. Meta-analyses have confirmed the superiority of autogenous bone grafts over allografts, xenografts and synthetic bone grafts with respect to new bone formation [20-22]. Ideally, such a bone substitute should be biomechanically stable, capable of degradation within an appropriate time frame, exhibiting osteoconductive, osteogenic and osteoinductive properties, biologically safe, low patient morbidity, volume stable, easy available on the market with low production costs and providing a favorable environment for the entry of blood vessels and bone-forming cells [23-26]. For cranio-maxillofacial purposes, autografts (due to the drawbacks) play a minor role today. In terms of costs and benefits, allografts were the most commonly used bone graft in the United States and xenografts were the most commonly used grafts in Europe [27]. Allografts are tissue grafts from a donor of the same species as the recipient, but not genetically identical, with a risk of immune responses, infection transmission and are

known to have high failure rates with long-term use. Additionally, many osteoinductive properties are lost during the manufacturing of allografts [21, 28-30]. In Europe, the use of allografts is often abandoned in clinical practice, advised by the Medical Device Regulation [31].

Xenografts are usually of porcine or bovine origin. The use of xenografts involves a number of risks and complications, e.g., disease transmission (Creutzfeldt-Jakob disease), immune responses, foreign body response and chronic inflammation. The production process can lead to a lack of viable cells and reduced osteoinductive properties [32]. For cranio-maxillofacial applications, bovine xenografts are allowed for safe use without reports of transmissible spongiform encephalopathies (TSE) and bovine spongiform encephalopathy (BSE) risk [27, 33, 34].

Alloplastic (synthetic) grafts are currently most commonly used for their osteoconduction, hardness and acceptability by bone. Most alloplasts consist of hydroxyapatite, a naturally occurring ceramic that is also the primary mineral of bone, or other calcium phosphate compounds, such as β–tricalcium phosphate (β–TCP). Calcium phosphates, like hydroxyapatite (HA), β–tricalcium phosphate (β–TCP) or biphasic calcium phosphate (BCP), a mixture of HA and β-TCP, are osteoconductive, biocompatible and simulate the chemical composition of natural bone. Calcium phosphates do not induce a sustained foreign body response or toxic reaction [35-37]. Hydroxyapatite is, at a physiological pH, the least dissolvable of the naturally occurring calcium phosphates, making it relatively resistant to resorption and suitable for clinical use [9, 38-40]. β-TCP does not have osteoinductive properties and resorbs rather quickly, but not necessarily at the same rate as the formation of new bone [11, 12, 41-44].

In previous studies a mixture of 60% HA and 40% β-TCP (BCP) as graft material in an MSFE procedure demonstrated sufficient bone (re)generation after 6 months for placement of dental implants, although remnants of BCP could still be observed, indicating that the process of bone substitution was not yet completed [12, 45]. After 9- and 12-months healing time, a high bone formation was still observed and remnants of BCP particles could still be detected [46]. A significant lower total bone volume is found for each biomaterial or combination of different graft materials compared to autogenous bone [11, 47].

This study was based on the use of an autogenous bone graft, harvested from the

maxillary tuberosity, in an MSFE procedure, as the gold standard [10]. Though, if autogenous bone graft volume is insufficient, a bone substitute can be supplemented to achieve sufficient graft volume for completion of the MSFE procedure, thereby avoiding a second surgical intervention and minimizing donor site morbidity. Referring to previous studies on the use of BCPs only [12, 46], it would be interesting to further study the use of a mixture of autogenous bone and Straumann® Bone Ceramic (SBC), a BCP (Straumann Holding AG, Basel, Switzerland).

Therefore, the purpose of this study was to determine whether a mixture of autogenous bone and BCP in an MSFE procedure leads to an improved bone formation compared to MSFE with pure BCP and ideally a total remission of BCP remnants in the entire augmented MSFE area, eventually leading to a sufficient bone structure, qualitatively and quantitatively, for dental implant placement. Five subsequent patients were evaluated clinically, radiologically, histologically and histomorphometrically after a 6-month healing period. The results were compared with the results of the previously reported studies with pure BCP (no autogenous bone added), after 6-, 9- and 12-month healing time, which were conducted according to the same study protocol [12, 46].

MATERIALS AND METHODS

Study population

Five subsequent, healthy patients (3 males and 2 females), with a partially edentulous posterior maxilla with vertical dimensions of less than 8 mm but preferably more than 4 mm, requiring dental implants for dental rehabilitation, were included in this study and underwent a unilateral MSFE procedure 6 months before the dental implants were placed. The average age was 61 years (range: 51-70).

The study was performed in accordance with the principles of the Declaration of Helsinki. Since the study involved a Conformité Européenne (CE)-marked device (biphasic calcium phosphate) being used for its intended purpose (use as carrier material for bone augmentation in sinus floor elevation procedures) and the harvested material is regarded as surgical waste, no specific regulatory approval from a medical ethical committee was required. Patients provided written consent before the study-related MSFE and dental implant procedures were undertaken. Biopsies were retrieved during dental implant surgery, with trephine drills, implicating the tissue in the hollow drill is considered surgical waste and no extra inconvenience to the patient.

Maxillary sinus floor elevation procedure

A unilateral two-stage MSFE was performed as described by Tatum [2] and similar to the previously reported 6-month and 9-12-month studies with pure BCP [12, 46]. MSFE surgery was performed under local anesthesia. All patients took amoxicillin 500 mg orally, 4 times daily during 7 days, starting one day preoperatively. Oral hygiene was performed with 0.12% chlorhexidine-digluconate 3 times daily for two weeks. The autogenous bone graft was harvested from the maxillary tuberosity at the implant site using a mallet, chisel and ground into small pieces. Before filling the created area at the sinus bottom, the bone graft was mixed in equal proportions with BCP granules (60% HA and 40% β–TCP, Straumann® Bone Ceramic, Straumann Holding AG, Basel, Switzerland). No collagen membrane was placed to cover the lateral window [48] (Figure 1A-E).

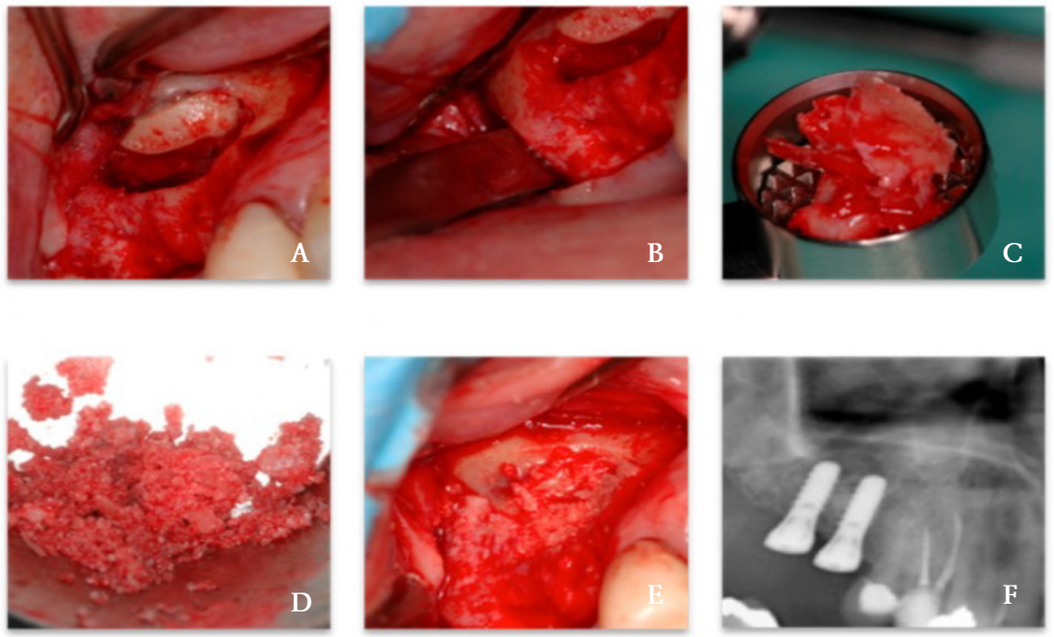


Figure 1.
Maxillary sinus floor elevation (MSFE) procedure using a mixture of autogenous bone from the maxillary tuberosity and a biphasic calcium phosphate (BCP).

A: The preparation of the top-hinge trapdoor in the lateral window of the right maxillary sinus.

B: Harvesting of an autogenous bone graft from the maxillary tuberosity using a chisel at the same surgical side and during the same procedure.

C: The harvested bone graft is groud in smaller pieces by means of a bone mill.

D: The milled bone graft is mixed with a biphasic calcium phosphate (Straumann® Bone Ceramic 60/40).

E: Area between the lifted lid and the maxillary sinus floor is filled with the mixed bone graft.

F: Radiograph taken directly after the insertion of two Straumann® SLA dental implants in the augmented right posterior maxilla (6 months after MSFE).

Dental implant surgery and biopsy retrieval

The dental implants were placed six months after the MSFE procedure. Implant osteotomies were made and biopsies were obtained from the previously grafted area at the planned dental implant positions, using trephine drills with an external diameter of 3.5 mm and internal diameter of 2.5 mm (Straumann® Trephine Drill) with copious irrigation of sterile saline. In the five patients 11 standard plus, regular neck, soft tissue level Straumann® SLA dental implants with a diameter of 4.1 mm and a length of 10 or 12 mm were placed (Figure 1F). The dental implants were left to integrate in a non-submerged unloaded fashion. A panoramic radiograph was taken immediately after dental implantation to allow postoperative radiological evaluation. After 10-14 days the Gore-Tex® (W.L. Gore and Associates, Newark, DE, USA) sutures were removed and, if needed, provisional prosthetics were adapted to the new situation. Loading of the dental implants was prohibited for three months. After osseointegration of the implants, a restorative dentist fabricated and placed the superstructures.

Clinical evaluation

One experienced oral and maxillofacial surgeon (CB) assessed clinically all 11 inserted dental implants for good primary stability. At abutment connection the osseointegration was tested with a 35-Ncm torque. All placed Straumann® SLA dental implants resisted the applied 35-Ncm torque.

Radiological evaluation

According to the same study protocol as previously reported [12, 46], panoramic radiographs were taken at patient's intake (T0); immediately after the MSFE procedure (T1); immediately after dental implant placement (T2); 1 year after dental implant placement (T3) and, 5 years after dental implant placement (T4). On the panoramic radiographs changes in tissue height (mm) of the grafted area were measured at the implant sites on all time points. An average magnification of 1.25 was taken into account to calculate the actual tissue heights.

Biopsy processing and analyses

Bone biopsies were prepared for histology according to previously described procedures [49]. In short, the biopsies were fixed overnight in 4% phosphate-buffered formaldehyde

and transferred to alcohol 70% [50]. After dehydration, the bone specimens were embedded without prior decalcification in methyl methacrylate supplemented with 20% dibutyl phthalate and 0.008 g/mL Lucidol. The biopsies were cut into 5-µm longitudinal sections (Polycut S., Leica microtome type sm2500s, Leica, Wetzlar, Germany). Goldner's trichrome staining was used to evaluate bone mass indices and osteoid surface [51]. Tartrate resistant acid phosphate (TRAP) staining was performed to visualize osteoclasts. Von Kossa staining was performed to visualize mineralized tissue.

Qualitative histological analysis

Qualitative assessment included screening the presence of BCP (Straumann® Bone Ceramic) remnants, clearly visible in the Von Kossa staining and a judgment of the vitality of the bone tissue. Moreover, the tissue was screened for inflammatory infiltrate. Three independent observers detected semi-quantitatively BCP particles and classified the particles into quartiles (< 25% of BCP, 25%-50% of BCP, 50%-75% of BCP and > 75% of BCP).

Quantitative histomorphometric analysis

Quantitative measurements were performed semiautomatically using a digitizer and image analysis software (Osteomeasure, Atlanta, GA, USA). Since it was difficult to distinguish the exact border between augmented and native bone, histomorphometric measurements were executed over the total section of the biopsy, including newly formed and native bone. The parameters were measured in consecutive fields of a complete section, in four 150-µm separated sections throughout the biopsy, covering a total measured area of 60 mm^2. Nomenclature was used according to the American Society for Bone and Mineral Research (ASBMR) nomenclature committee [52].

The biopsy was examined for the following parameters:

Parameters evaluating vital bone mass/bone structure:

- Vital bone volume (BV/TV): percentage of the total section that is vital bone tissue (%).
- Bone surface (BS/TV): BS expressed as a fraction of the total vital bone volume (mm^2/mm^3).
- Thickness of bone trabeculae (Tb.Th; µm).

Parameters evaluating bone turnover:

- Osteoid volume (OV/BV): percentage of the vital bone tissue section that is osteoid (%).
- Osteoid surface (OS/BS): osteoid-covered surfaces expressed as the percentage of the total BS (%), to measure new vital bone formation.
- Osteoid thickness (O.Th; µm).
- Number of osteoclasts (N.Oc) per mm^2 total area.

Statistical analysis

Results are expressed as mean ± standard deviation. The results of this study were compared to the results of previously reported experiments, which were conducted in our institution in a similar manner by use of a non-parametric Kruskal-Wallis test.

RESULTS

Clinical evaluation

All five patients responded identically. None of them displayed postoperative infections, neither after the MSFE procedure nor after the placement of dental implants. During the insertion of the dental implants, it was observed that the graft material was well vascularized. Although there was a clear demarcation between the grafted area and the original bone of the alveolar process, there was continuity between the graft and the original bone. Although bone substitute particles could still be recognized in the retrieved tissue specimen, the drill remained stable during implant bed preparation. Clinically, all particles appeared to be well integrated in newly formed tissue. All dental implants osseointegrated well and could be loaded with fixed prostheses three months after implant surgery. There was no loss of dental implants during the 5-year follow-up.

Radiological evaluation

The results of the alveolar tissue height measurements on panoramic radiographs in time are shown in Table 1. On average an 8.7 mm (SD ± 1.6) increase in height of the grafted area was accomplished using the mentioned MSFE.

Table 1. Alveolar tissue height measurements on panoramic radiographs (in true mm) in five patients in whom a maxillary sinus floor elevation (MSFE) procedure was performed with a mixture of autogenous bone from the maxillary tuberosity and Straumann Bone Ceramic (60/40) and 6 months healing time.

Patient	Gender/Age	Location	T0	T1	Increase	T2	T3	T4
1	M/53	15	8.0	16.2	8.2	16.1	16.2	16.0
1	M/53	16	6.1	14.1	8.0	15.0	15.0	15.0
2	M/70	16	6.8	14.8	8.0	16.0	13.7	15.6
2	M/70	17	3.6	12.4	8.8	14.0	13.3	12.1
3	M/68	14	5.6	11.5	5.9	12.1	11.3	10.4
3	M/68	15	4.6	14.1	9.5	14.1	13.0	12.9
3	M/68	16	4.3	14.1	9.8	14.2	12.7	12.6
4	F/64	15	9.3	17.1	7.8	16.8	14.1	14.0
4	F/64	16	6.0	14.9	8.9	16.9	15.8	15.7
5	M/51	16	9.0	18.1	9.1	17.6	16.2	NA
5	M/51	17	5.8	18.0	12.2	16.0	16.7	NA
Mean	61.2	-	6.3	15.0	8.7	15.3	14.4	13.8
SD	-	-	1.9	2.1	1.6	1.6	1.7	1.9

M: male; F: female; age in years at biopsy retrieval; tissue height corrected for magnification (×1.25) on panoramic radiograph;
T0: (native bone height) preoperative alveolar bone height; T1: directly after MSFE procedure; T2: immediately after dental implant placement (6 months after MSFE); T3: 1 year after dental implant placement; T4: 5 years after dental implant placement; NA: not available.

The measured tissue height appeared to be stable between 1- and 5-years follow-up (Figure 2). The results of the present study (6-month mixed graft) when compared with the results of our former MSFE procedures with pure BCP, also show a stable gain in tissue height (a total of four studies). An overview of the results of the present study (6-month mixed graft) and the results of previously reported studies with pure BCP after 6-, 9- and 12 months healing time [12, 44] is shown in Table 2. Comparing the results, the gained tissue height appears to be stable in all four studies.

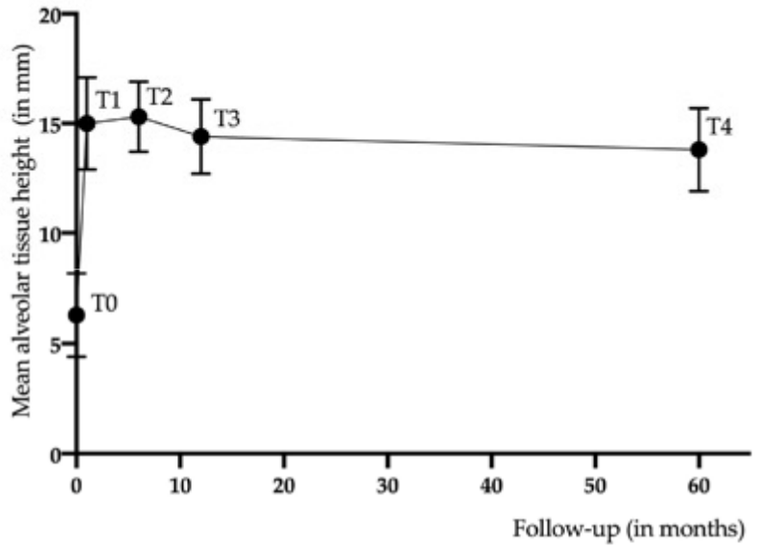


Figure 2.
Mean alveolar tissue height (in true mm) over a 5-year period in five patients in whom a maxillary sinus floor elevation procedure was performed with autogenous bone from the maxillary tuberosity and Straumann® Bone Ceramic (60/40) with 6 months healing period. T0: (native bone height) preoperative alveolar bone height (SD ± 1.9); T1: directly after a maxillary sinus floor elevation (MSFE) procedure (SD ± 2.1); T2: immediately after dental implant placement (6 months after MSFE; SD ± 1.6); T3: 1 year after dental implant placement (SD ± 1.7); T4: 5 years after dental implant placement (SD ± 1.9).

Table 2. Alveolar tissue height measurements on panoramic radiographs (in true mm), overview of the mean values of the 6-month mixed graft group, autogenous bone mixed with Straumann® bone ceramic (60/40), compared to the 6-, 9- and 12-month results with pure Straumann® bone ceramic (60/40), as previously published, in a maxillary sinus floor elevation (MSFE) procedure. Tissue height corrected for magnification (×1.25) on panoramic radiographs.

Patient Group	T0	T1	Increase	T2	T3	T4
6-month mixed	6.3	14.8	8.7	15.3	14.4	13.8
6-month (*)	6.5	15.2	8.7	14.6	13.4	NA
9-month (**)	6.4	13.9	7.5	14.1	13.3	13.2
12-month (**)	4.4	13.8	9.3	13.6	13.4	13.8

Note: T0: (native bone height) preoperative alveolar bone height; T1: directly after MSFE procedure; T2: immediately after dental implant placement; T3: 1 year after dental implant placement; T4: 5 years after dental implant placement; NA: not available.
* Study by Frenken et al. (2010) [12]; ** Study by Bouwman et al. (2017) [46].

Qualitative histological evaluation

The histological evaluation in six biopsy specimens was executed on the complete section, comprising native bone, newly formed bone and residual graft material. BCP particles were scattered and detected throughout the entire biopsy from caudal to cranial (Figures 3 and 4a). The BCP particles were surrounded by connective tissue, osteoid islands and newly formed bone. The newly formed bone comprised of both woven and lamellar bone; it appeared as vital bone tissue containing osteoblasts, osteoid covering the border of BCP and osteocytes inside bone lacunae (Figure 4b). No inflammatory cells in the tissue adjacent to the bone substitute particles were found during histological analysis. Bone marrow-like tissue, including blood vessels, was observed in between the bone trabeculae. Fragments of the BCP particles as shown by Von Kossa staining showed in four biopsies < 25% of BCP, in one biopsy 25%-50% of BCP and in one biopsy 50%-75% of BCP. The presence of > 75% of BCP fragments was not detected.

Quantitative histomorphometric evaluation

Table 3 shows the individual histomorphometric indices. An average vital bone volume of 29.9% (BV/TV) was measured in the complete biopsies (SD ± 10.1) of which 7.1% (OV/BV, SD ± 4.8) was osteoid. The osteoid surface (OS/BS) covered 26.0% (SD ± 13.4) of the bone surface. The BS/TV covered 4.7 mm^2/mm^3 (SD ± 2.3). As can be read from Table 3, Patient #4 had extremely high values for trabecular bone volume

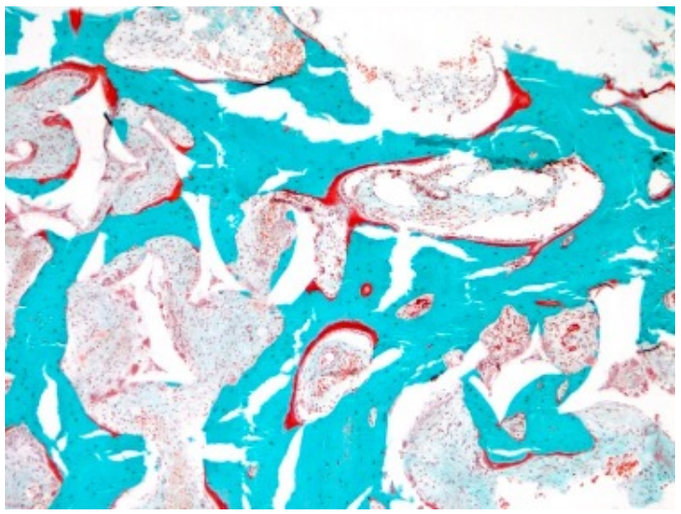


Figure 3.
Increased bone formation following the shape of the grafted particles in a maxillary bone biopsy after a maxillary sinus floor elevation procedure from a patient with autogenous bone mixed with Straumann® Bone Ceramic (60/40) after 6 months healing time, stained with Goldner trichrome staining. No Howship's lacunae could be detected on the characteristic outlines of the calcium phosphate particles. (original magnification x 100).

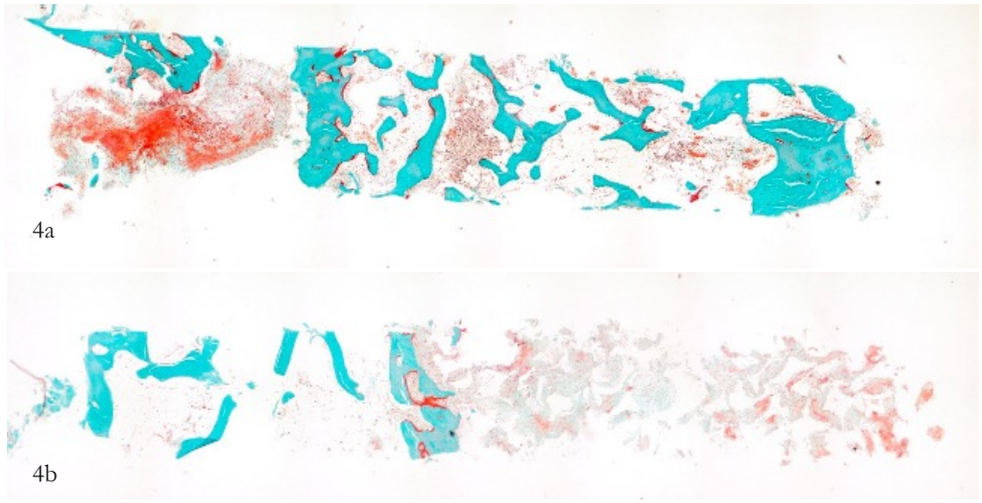


Figure 4.
(a) Overview of an example of a bone biopsy from the maxilla of a patient, 6 months after a maxillary sinus floor elevation procedure using a mixture of autogenous bone and Straumann® Bone Ceramic (60/40), stained with Goldner trichrome staining. Bone is scattered throughout the entire biopsy (original magnification × 10).
(b) Overview of a not previously shown bone biopsy from the maxilla of a patient, 6 months after a maxillary sinus floor elevation procedure using pure Straumann® Bone Ceramic (60/40) as studied by Frenken et al. [12], stained with Goldner trichrome staining. Bone formation at the first 3 mm immediately cranially from the former floor of the maxillary sinus (original x 100 magnification).

(BV/TV and Tb.Th.). This high BV/TV is in accordance with the high T0 value, most likely caused by an oblique section of the cortical maxillary sinus wall (Table 1). A low bone surface (BS/TV: 2.2 mm^2/mm^3) and a high osteoid thickness (O.Th: 481.9 μm) were observed in the bone biopsy of patient #5 (Table 3).

An overview of the histomorphometric findings from the present study (6-month mixed graft) and previously reported studies with pure BCP after 6-, 9- and 12 months healing time is shown in Table 4. A non-parametric Kruskal-Wallis test showed significant differences between OS/BS ($p = 0.0233$) and Tb.Th. ($p = 0.0244$). Other tested histomorphometric indices (BV/TV, OV/BV, and N.Oc) were not different.

Table 3. Histomorphometric evaluation of the six biopsies from five patients in whom a maxillary sinus floor elevation (MSFE) procedure was performed with a mixture of autogenous bone from the maxillary tuberosity and Straumann® Bone Ceramic (60/40) after 6 months healing time.

Patients (no.)	Gender/Age (years)	Location	BV/TV (%)	BS/TV (mm^2/mm^3)	Tb.Th (µm)	OV/BV (%)	OS/BS (%)	O.Th (µm)	N.Oc/Tar ($1/mm^2$)
1	F/53	16	40.5	2.4	335.8	6.9	38.8	342.2	0.62
2	M/70	16	29.2	6.8	85.5	3.2	11.1	10.7	1.52
3	M/68	14	19.7	6.9	57.5	7.6	17.9	11.6	-
3	M/68	15	29.3	6.5	91.2	3.5	12.9	11.7	2.54
4	F/64	15	42.4	3.5	290.0	5.1	35.3	97.5	1.91
5	M/51	16	18.3	2.2	163.4	16.3	39.8	481.9	1.58
Mean	-	-	29.9	4.7	170.6	7.1	26.0	159.3	1.79
SD	-	-	10.1	2.3	116.6	4.8	13.4	203.5	0.5

M: male; F: female: age in years at biopsy retrieval; BV/TV: vital bone volume/total volume; BS/TV: bone surface/total volume; Tb.Th: trabeculae thickness; OV/BV: osteoid volume/vital bone volume; OS/BS: osteoid surface/bone surface; O.Th: osteoid thickness; N.Oc/BPM: number of osteoclasts per bone perimeter.

Table 4. Histomorphometric evaluation of the total section: overview of the mean values of the 6-month mixed graft group (autogenous bone mixed with Straumann® Bone Ceramic (60/40)) compared to the 6-, 9- and 12-month results with pure Straumann® Bone Ceramic (60/40), as previously published, in a maxillary sinus floor elevation procedure.

Patients Group	BV/TV (%)	SD ±	BS/TV (mm^2/mm^3)	SD ±	Tb.Th (µm)	SD ±	OV/BV (%)	SD ±	OS/BS (%)	SD ±	O.Th (µm)	SD ±	N.Oc/Tar ($1/mm^2$)/	SD ±
6-month mixed	29.9	10.1	4.7	2.3	170.6	116.6	7.1	4.8	26.0	13.4	159.3	203.5	1.79	0.5
6-month (*)	27.3	4.9	4.5	1.1	132.1	38.4	7.5	4.3	41.3	28.5	13.3	4.7	1.1	1.3
9-month (**)	35.2	9.5	4.2	1.9	224.7	150.0	8.8	3.8	42.4	12.1	93.9	135.8	1.8	1.1
12-month (**)	28.2	3.2	8.3	1.3	66.7	5.4	3.4	2.5	8.2	5.3	13.6	1.0	***	-

BV/TV: vital bone volume/total volume; BS/TV: bone surface/total volume; Tb.Th: trabeculae thickness; OV/BV: osteoid volume/vital bone volume; OS/BS: osteoid surface/bone surface; O.Th: osteoid thickness; N.Oc/BPM: number of osteoclasts per bone perimeter. * Study by Frenken et al. (2010) [12]; ** Study by Bouwman et al. (2017) [46]; *** N.Oc/BPM not measured as an insignificant number of osteoclasts were available.

DISCUSSION

Addition of Straumann® Bone Ceramic (60/40 BCP) to autogenous bone did not seem to improve the outcome after 6 months healing time compared to the use of pure BCP in a maxillary sinus floor elevation (MSFE), as demonstrated by histomorphometric analyses in the five patients included in the present study. Histomorphometric indices show a high variability, which in most cases can be explained individually. For instance, an oblique section of the cortical maxillary sinus wall could explain, to some extent, the variability mentioned. Compared to autogenous bone, for each biomaterial or combination of graft materials in an MSFE procedure a significant lower BV/TV was found (reference value 41% for autogenous bone) [53]. The autogenous bone graft, in the present study was harvested from the maxillary tuberosity, at the same side as the MSFE procedure was performed, implicating no extra or at least far less morbidity for the patient. However, the disadvantages of a second surgical procedure of harvesting a bone graft should also be taken into account. This disadvantage remains in the situation of a mixed graft, consisting of autogenous bone and a bone substitute.

Since the procedures in this study were similar to the procedures in the previously reported studies using pure BCP as a bone substitute in an MSFE procedure [12, 32], it was possible to compare the histomorphometric findings. This analysis showed a difference for trabecular thickness (Tb.Th.) and osteoid surface (OS/BS) but not for the other parameters (BV/TV, OV/BV, and N.Oc). The osteoid surface suggested a gradual decrease over healing time for pure BCP while the 6-month mixed graft group did not fit in this pattern, which suggests a different healing pattern. Surprisingly, the presence of autogenous bone in the graft does not seem to result in a higher bone volume at 6-month healing time. According to Klijn et al. [9], a healing time of 6 months may not show the ultimate favorable effect in bone regeneration procedures.

In this study, no dental implants were lost during the 5-year follow-up. A minimum native bone height of 4 mm was chosen as a prerequisite to ensure primary stability and high survival rates of the dental implants [12, 46] after an MSFE procedure with a bone substitute, regardless of the type of graft used. Klijn et al. indicated that the measured bone volumes are higher in the first stage of healing (first 4.5 months) and in the later stages of healing after 9 months, which indicates that our study design of 6 months healing time does not entirely demonstrate the advantage of adding a bone substitute to

autogenous bone. It should, however, be stressed that an MSFE procedure using pure autogenous bone provides a higher vital bone volume after 6 months if a block graft is used compared to a particulate graft or a mixed graft of autogenous bone with a bone substitute [9]. This is also confirmed by meta-analyses on histomorphometric outcome of bone substitutes and autogenous bone grafts in various combinations. Altogether, autogenous bone (and if needed a mixture of autogenous bone with BCP) is superior in terms of the amount of the newly formed bone.

The low number of patients (n = 5) in this study was considered a limitation since quantitative histomorphometric data may be less reliable. Indeed, the histomorphometric indices do not always show a clear difference between pure BCP and autogenous bone mixed with BCP. However, qualitative assessment, in contrast, demonstrated consistently a different distribution of bone throughout all biopsies. In the 6-month mixed graft group bone matrix was scattered throughout the entire biopsy with a slightly less dense trabecular pattern in the centers of the grafted area, while in the 6-month pure BCP group a concentration of bone formation at the first 3 mm immediately cranially from the former floor of the maxillary sinus and less bone in the center of the graft was seen. This might be beneficial for bone-to-implant contact (BIC).

Dental implants are endosseous implants, which implicates that the implant should be anchored in and surrounded by vital bone for a stable result with a high (and long lasting) survival rate. In that respect the presence of vital bone over a larger area in grafted sites is important for the longevity of the dental implants to be inserted later. In this study, a minimal native bone height of 4 mm was required to achieve a good primary stability after the MSFE procedure. Using 100% autogenous bone in the MSFE procedure could shorten the healing time to 4 months and would result in a better BIC. If no or not enough autogenous bone is available, alternatively a bone substitute could be added in the MSFE procedure to achieve a good BIC. However, longer healing times (6-, 9- or 12 months studies) should be respected. In our previous studies with pure BCP the optimal healing time seemed to be 9 months, based on the BV/TV, Tb.Th. and, O.Th. observed [45]. In cases with less than 4 mm native bone height, an autogenous bone graft is preferably used in an MSFE procedure. If the availability of autogenous bone is limited, it may be considered to use a mixture of autogenous bone and bone substitute to achieve on the one hand a larger graft volume and on the other hand a larger bone

volume, that approximates the bone volume in case a full autogenous bone graft is used. The newly formed bone in the present mixed graft study was observed throughout the entire biopsy, suggesting a large BIC after 6 months. However, the consequences of these findings for dental implant survival still have to be unraveled.

CONCLUSIONS

Based on clinical, radiological, histological and histomorphometric analyses in this study with five patients, the use of an autogenous bone graft mixed with a biphasic calcium phosphate (BCP) in a maxillary sinus floor elevation procedure does not result in a higher bone formation, compared with the results of previously reported studies with pure BCP. However, a better distribution of new bone was seen throughout the entire augmented area, which might eventually improve the bone-to-implant contact.

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5

Tissue level changes after maxillary sinus floor elevation with three types of calcium phosphate ceramics: A radiological study with a 5-year follow-up

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ABSTRACT

This study evaluates the radiological changes in tissue height after maxillary sinus floor elevation (MSFE) using three types of calcium phosphate ceramics over a period of up to 5 years after dental implant placement. In 163 patients, MSFE was performed. Three groups of patients were distinguished and treated based on the type of calcium phosphate ceramic used and radiologically evaluated: 40 patients with β-tricalcium phosphate (β-TCP), 76 patients with biphasic calcium phosphate (BCP) 20% hydroxyapatite (HA)-80% β-TCP, and 47 patients with BCP 60% HA-40% β-TCP. Radiological measurements were performed on panoramic radiographs at several time points up to 5 years after dental implant placement. After MSFE, a slow decrease in tissue height measured over time was seen in all three study groups. Resorption of the grafted bone substitutes was more prominent in β-TCP than in BCP ceramics with an HA component (60/40 and 20/80). Loss of tissue height after 5 years was lowest in BCP 60/40 and highest in β-TCP. This radiological study shows a predictable and comparable behavior of the slow decrease in tissue height over time for all three types of calcium phosphate ceramics used in MSFE. The fraction of HA in calcium phosphate ceramics and dental implant loading seems to be beneficial for tissue height maintenance after MSFE.

INTRODUCTION

Maxillary sinus floor elevation (MSFE) is a common pre-implant surgical procedure to increase the vertical dimension in the posterior edentulous maxilla in order to place dental implants for oral rehabilitation [1-4]. For this internal augmentation, the surgeon has the choice between autogenous bone grafts and bone substitutes [5-7]. Although autogenous bone grafting, considered to be the gold standard, is a well-known and reliable grafting procedure [8, 9], it has the disadvantage of the necessity of a second surgical procedure and, therefore, a higher risk of surgical morbidity and complications [10-14]. For this reason, in some cases a bone substitute is chosen as graft material [12, 15]. Different available bone substitutes, such as calcium phosphate ceramics, seem to behave similarly [16-20]. They will be partially replaced in time by vital bone when used in MSFE [5, 21]. On the cranial site, the grafted calcium phosphate ceramics should be stable in height as a space maintaining structure to allow new bone to grow into the bone substitute at a later stage and keep the "new" maxillary sinus floor away from the "apical" parts of the dental implants.

Several types of calcium phosphate ceramics have become available with different ratios regarding the crystalline components. Examples of calcium phosphate ceramics are 100% β-tricalcium phosphate (β-TCP), which is osteoconductive and provides a scaffold for the ingrowth of newly formed bone, a biphasic calcium phosphate (BCP) consisting of 20% hydroxyapatite (HA) and 80% β-TCP (BCP 20/80), a BCP consisting of 60% HA and 40% β-TCP (BCP 60/40), or 100% HA (all percentages are weight-based). β-TCP is thought to dissolve much quicker than HA. HA is brittle, rigid and resorbs hardly when used in MSFE, which might hinder replacement of the bone substitute by vital bone [5, 22-25]. The purpose of using a combination of β-TCP and HA is to balance the rate of vital bone ingrowth with the resorption rate of the bone substitute. The choice for β-TCP is in line with the theory that this ceramic would dissolve rather quickly in favor of bone replacement of the dissolved calcium phosphate [6-8, 19, 20, 26-28]. Nevertheless, it takes substantial time for new bone to invade into the graft material [1, 5].

In the literature, several studies evaluated one type of calcium phosphate ceramic β-TCP or β-TCP and HA, in different ratios, mixed with autogenous bone, platelet-rich plasma, or stem cells in MSFE with a study duration ranging from 1 to 9 years [4, 29-33]. These

studies generally compared the calcium phosphate ceramic with autogenous bone, since this is considered the gold standard. However, as yet, volume changes in different ceramics containing different proportions of HA were never compared amongst one another. Comparison of the clinical behavior of different calcium phosphate ceramics without any modifications is important to help the surgeon to choose a suitable bone substitute in maxillary sinus augmentation procedures. To optimize the results of MSFE, it is important to gain insight into the tissue maintenance, resorption patterns, final gain and absolute loss of tissue height, and the specific properties of the available calcium phosphate ceramics with different ratios of HA.

Newly formed bone, especially non-loaded vital bone, is at risk for resorption, resulting in height loss [34]. Therefore, placement of dental implants 6 months after MSFE is important, as dental implants are considered as "loaded pillars" preventing the resorption of bone. A certain degree of vital bone and substitute level dips between the "apices" of dental implants is reported in the literature [35]. This scalloping of the bone (in fact, this is the elevated maxillary sinus floor) would indicate that vital bone resorbs faster in non-loaded areas than in loaded areas [36-38].

The aim of this study was to investigate the radiological changes in tissue height after MSFE using three types of calcium phosphate ceramics (β-TCP, BCP 20/80, and BCP 60/40) with a follow-up time of 5 years after dental implant placement. In particular, the following issues were addressed: (1) the initial gain and subsequent loss in tissue height after MSFE, (2) the influence of dental implants on the maintenance of tissue height after MSFE, (3) the difference in tissue height maintenance between the three types of calcium phosphate ceramics used, and (4) the influence of the type of calcium phosphate on the maintenance of tissue height between the measurements at implant site (loaded bone) and distal position (unloaded bone).

MATERIALS AND METHODS

Patients

This retrospective study is based on chart reviews (data collection from the medical records of patients) and measurements on panoramic radiographs taken during yearly follow-up visits of patients. In total, 169 patients underwent MSFE as a pre-implant surgical procedure with a calcium phosphate ceramic. Of these 169 patients, 163 were available for follow-up evaluation. In these 163 patients, 256 dental implants were placed. At 4 years follow-up, 81 implant sites were available for investigation, and at 5 years, 43 implant sites were available for radiological measurements. The criteria for treatment selection was a minimal native alveolar bone height of minimal 4 mm in the posterior maxilla and the patients' wish for prosthetic rehabilitation with dental implants. Patients with a history of radiation of the jaws, patients with heart valve prostheses and a history of endocarditis and patients who had MSFE with simultaneous lateral augmentation of the posterior maxilla were not included in this study. Smokers (21%) were not excluded. All patients received standard care and signed a written consent prior to both surgical procedures (MSFE and dental implant surgery) for the use of their data.

One hundred and sixty-three patients (75 males, 88 females, age ranging from 18 to 78 years) were divided in three groups based on the type of bone substitute used: β-TCP (Ceros®, Thommen Medical, Grenchen, Switzerland), BCP 20/80 (Institut Straumann AG, Basel, Switzerland), BCP 60/40 (Straumann® Bone Ceramic (SBC), Institut Straumann AG, Basel, Switzerland). Ceros® TCP granules had a total porosity of 60% with interconnecting macropores of 100-500 μm and a particle size of 700-1400 μm. The two BCPs had similar particle size (500-1000 μm), microporosity (2%), interconnected pores (100-500 μm), and porosity (90%). BCP 20/80 had a crystal size of 1.0-6.0 μm and a specific surface area of 9.5×10^{-3} m^2/g, while BCP 60/40 had a crystal size of 0.6-6.0 μm and a specific surface area of 6.9×10^{-3} m^2/g. Table 1 shows an overview of the physical properties of three types of calcium phosphate ceramics. All calcium phosphate ceramics were used as received without any modifications.

Table 1. Physical properties of three types of calcium phosphate ceramics, as specified by the manufacturers.

	β-TCP	BCP 20/80	BCP 60/40
Porosity	60%	90%	90%
Interconnecting macropores	100–500 µm	100–500 µm	100–500 µm
Particle size	700-1400 µm	500–1000 µm	500–1000 µm
Microporosity (vol%)	1–2%	2%	2%
Crystal size	Not specified.	1.0–6.0 µm	0.6–6.0 µm
Specific surface area	Not specified.	9.5×10^{-3} m²/g	6.9×10^{-3} m²/g

β-TCP: β-tricalcium phosphate; BCP: biphasic calcium phosphate; HA: hydroxyapatite.

Table 2. Patient data of the three types of calcium phosphate ceramic.

	β-TCP	BCP 20/80	BCP 60/40
Number of patients included	40	76	47
Number of implant sites included	69	120	67
M/F	21 M, 19 F	32 M, 44 F	22 M, 25 F
Mean age in years	57	59	55
Age range in years	27–78	18–79	18–77
MSFE performed between	2/2009–6/2012	3/2010–9/2012	1/2009–11/2013

β-TCP: β-tricalcium phosphate; BCP: biphasic calcium phosphate; HA: hydroxyapatite; M: male; F: female; MSFE: maxillary sinus floor elevation.

The group treated with β-TCP consisted of 40 patients (21 males, 19 females; mean age: 57 years; range: 27 to 78 years), the group treated with BCP 20/80 consisted of 76 patients (32 males, 44 females; mean age: 59 years; range: 18 to 79 years), and the group treated with BCP 60/40 consisted of 47 patients (22 males, 25 females; mean age: 55 years; range 18 to 77 years). Patient data are shown in Table 2.

Maxillary sinus floor elevation procedure

The MSFE was performed according to Tatum's "top-hinge trapdoor technique" under local anesthesia [3]. Patients received an antibiotic prophylaxis, amoxicillin 500 mg, 4 times daily (or in case of allergy, clindamycin 300 mg 4 times daily) for 7 days, starting the day before MSFE. For oral hygiene, chlorhexidine digluconate 0.12% (w/w) 2 times daily (10 mL) for 2 weeks was prescribed, according to the manufacturers' instructions.

A midcrestal incision was made as surgical flap design with mesial and distal buccal and vertical release incisions. In the three groups, the created area at the maxillary sinus bottom was filled with the selected graft material for that group of patients. No membrane was used to cover the lateral window [39]. The wounds were closed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). After 10 to 14 days the sutures were removed.

Dental implant placement

The 256 Straumann® SLA Soft Tissue Level dental implants with a diameter of 3.3, 4.1, or 4.8 mm and implant length of 10 or 12 mm were placed under local anesthesia 6 months after MSFE, according to the manufacturers' instructions (Institut Straumann AG, Basel, Switzerland). The wounds were closed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). All patients received a prophylactic dose of 3 g amoxicillin 1 h prior to dental implant surgery (or in case of an allergy, clindamycin 600 mg). The dental implants were left to integrate in a non-submerged unloaded fashion. For oral hygiene chlorhexidine-digluconate 0.12% (w/w), 2 times daily 10 mL for 2 weeks was prescribed, according to the manufacturers' instructions, as part of the standard procedure for dental implant surgery. To allow postoperative radiological evaluation, a panoramic radiograph (Orthophos XG, Sirona Dental Systems GmbH, Bensheim, Germany) was taken immediately after dental implant placement. Removal of the sutures was performed 10 to 14 days after dental implant surgery. Three months after dental implant placement, prosthetic treatment was started by a restorative dentist.

Radiological evaluation

Panoramic radiographs were taken at patient's intake, approximately 2 months prior to MSFE (T0), immediately after MSFE (T1), and 4 weeks prior to dental implant surgery ridge mapping is performed, which is a measurement procedure to ensure that the diameter of a dental implant does not exceed the dimensions of available bone (T2), immediately after dental implant placement (T3), at the end of the integration period, after prosthetic loading (T4), and later during the yearly recall visits (T5-T9). On these panoramic radiographs, changes in tissue height of the grafted area were measured at the implant site (black line) and 2-3 mm distally of the dental implant site (red line) (Figure 1). All panoramic radiographs were taken with an average magnification of 1.25.

The measured tissue height on the panoramic radiographs was multiplied with 0.8 to obtain the true height in mm.

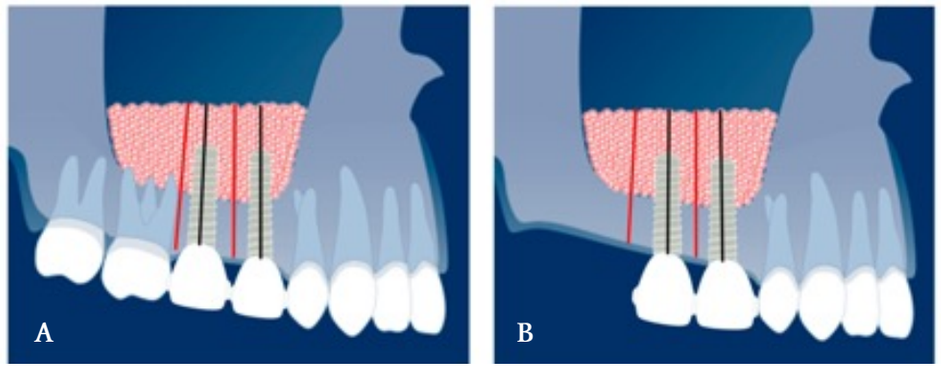


Figure 1.
A: This graphic shows the tissue height measurements at inter-implant positions. The black lines indicate the measurement positions at implant sites; the red lines (2-3 mm distally) the "distal" or intermediate positions.
B: This graphic shows the tissue height measurements at distal positions (free-end situation). The black lines indicate the measurement positions at implant sites; the red lines (2-3 mm distally) the "distal" positions. Source: graphic used with courtesy of the ITI Foundation, Basel, Switzerland.

Statistical analysis

Data are expressed as mean plus or minus standard deviation. Since the heights were measured several times (T0-T9) in the same individual and 256 implants were measured in 163 patients, a mixed model analysis (T0-T9) was applied to adjust for the non-independence in the data. Correction/adjustment was performed by estimating the variance of the intercepts (random intercepts). The effect modification was checked by estimating the variance of the slope (random slope). Maximum height loss was calculated at T8 and tested using an ANOVA. $p < 0.05$ was considered significant. IBM SPSS version 26 was used for all statistical analyses.

RESULTS

Patient data

Patient data of all 512 sites (256 implant sites and 256 distal positions) in 163 patients after MSFE with calcium phosphate ceramics were gathered and combined. In Table 2, the demographic data of the study patients and the numbers and types of calcium phosphate ceramics used as a graft material in MSFE are shown.
In Table 3, the number of measurements that could be performed based on the availability of radiological data are shown.

Table 3. Number of measurements available at several time points up to 5-year follow-up.

	Months of Observation	β-TCP	BCP 20/80	BCP 60/40	Total
T0	−8	40	76	47	163
T1	−6	40	76	47	163
T2	−1	40	76	47	163
T3	0	40	76	47	163
T4	3	40	38	47	125
T5	12	35	21	26	82
T6	24	17	34	27	78
T7	36	23	28	15	66
T8	48	29	30	22	81
T9	60	25	8	10	43

β-TCP: β-tricalcium phosphate; BCP: biphasic calcium phosphate; HA: hydroxyapatite; T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 1 year; T6: follow-up visit after 2 years; T7: follow-up visit after 3 years; T8: follow-up visit after 4 years; T9: follow-up visit after 5 years.

Maxillary sinus floor elevation with calcium phosphate ceramics

Tissue levels (163 patients at 256 implant sites and 256 distal positions) were measured on panoramic radiographs and calculated in millimeters (Figure 1). Table 4 shows the data from the "combined measurements" and "the individual measurements" of the three calcium phosphate ceramic groups.

Comparison of three individual types of calcium phosphate ceramics

The mean tissue heights of the three individual different types of calcium phosphates are shown in Table 4 and Figure 2.

Table 4. Individual and combined tissue height measurements (in mm) of 512 sites (256 implant site and 256 distal positions) of three types of calcium phosphate bone substitutes in maxillary sinus floor elevation (MSFE), after 5-year follow-up.

Time points	Months of observation	β-TCP			BCP 20/80			BCP 60/40			Combined calcium phosphates		
		Implant site height mm (mean ± SD)	Distal position height mm (mean ± SD)	Mean tissue height mm	Implant site height mm (mean ± SD)	Distal position height mm (mean ± SD)	Mean tissue height mm	Implant site height mm (mean ± SD)	Distal position height mm (mean ± SD)	Mean tissue height mm	Mean tissue height implant site mm	Mean tissue height distal site mm	Mean tissue height mm
T0	-8	7.4 ± 2.8	6.5 ± 2.3	7.0 ± 2.6	6.5 ± 2.4	5.8 ± 1.8	6.2 ± 2.1	6.5 ± 2.6	5.8 ± 1.9	6.2 ± 2.3	6.7 ± 2.6	6.2 ± 2.0	6.5 ± 2.3
T1	-6	14.2 ± 2.2	12.8 ± 2.8	13.5 ± 2.6	14.0 ± 2.2	12.8 ± 2.5	13.4 ± 2.4	14.2 ± 2.1	13.0 ± 2.2	13.6 ± 2.2	14.1 ± 2.2	12.8 ± 2.5	13.5 ± 2.4
T2	-1	13.2 ± 2.4	11.8 ± 2.8	12.5 ± 2.7	13.6 ± 2.3	12.5 ± 2.5	13.1 ± 2.4	14.0 ± 1.9	12.7 ± 2.1	13.4 ± 2.1	13.5 ± 2.2	12.4 ± 2.5	13.0 ± 2.4
T3	0	13.5 ± 2.2	11.8 ± 2.8	12.7 ± 2.6	13.6 ± 2.2	12.0 ± 2.7	12.8 ± 2.6	13.9 ± 1.8	12.5 ± 2.2	13.2 ± 2.1	13.6 ± 2.1	12.1 ± 2.6	12.9 ± 2.5
T4	3	13.1 ± 2.2	11.5 ± 2.6	12.3 ± 2.5	13.3 ± 2.4	11.7 ± 2.7	12.5 ± 2.7	13.6 ± 1.9	12.2 ± 2.2	12.9 ± 2.2	13.3 ± 2.2	11.8 ± 2.6	12.6 ± 2.5
T5	12	12.6 ± 2.1	10.7 ± 2.5	11.7 ± 2.5	13.3 ± 2.4	11.8 ± 2.8	12.6 ± 2.7	13.6 ± 2.0	11.8 ± 2.3	12.7 ± 2.3	13.2 ± 2.2	11.4 ± 2.7	12.3 ± 2.6
T6	24	12.1 ± 1.7	10.9 ± 2.7	11.5 ± 2.3	13.0 ± 2.3	11.0 ± 3.1	12.0 ± 2.9	13.8 ± 2.2	12.3 ± 2.2	13.1 ± 2.3	13.0 ± 2.2	11.4 ± 2.7	12.2 ± 2.6
T7	36	12.4 ± 2.3	10.5 ± 2.6	11.5 ± 2.6	11.8 ± 1.9	10.1 ± 2.6	11.0 ± 2.4	13.2 ± 2.0	11.5 ± 2.5	12.4 ± 2.3	12.6 ± 2.0	10.8 ± 2.6	11.8 ± 2.5
T8	48	12.7 ± 2.1	10.6 ± 2.8	11.7 ± 2.6	12.8 ± 2.5	10.9 ± 2.8	11.9 ± 2.8	13.0 ± 1.8	11.6 ± 2.2	12.3 ± 2.1	12.8 ± 2.1	11.0 ± 2.6	11.9 ± 2.6
T9	60	12.4 ± 1.6	10.4 ± 2.2	11.4 ± 2.2	12.4 ± 2.8	10.3 ± 3.4	11.4 ± 3.1	12.4 ± 1.7	11.1 ± 1.8	11.8 ± 1.8	12.4 ± 1.8	10.5 ± 2.3	11.5 ± 2.3

β-TCP: β-tricalcium phosphate; BCP: biphasic calcium phosphate; HA: hydroxyapatite; T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 1 year; T6: follow-up visit after 2 years; T7: follow-up visit after 3 years; T8: follow-up visit after 4 years; T9: follow-up visit after 5 years.

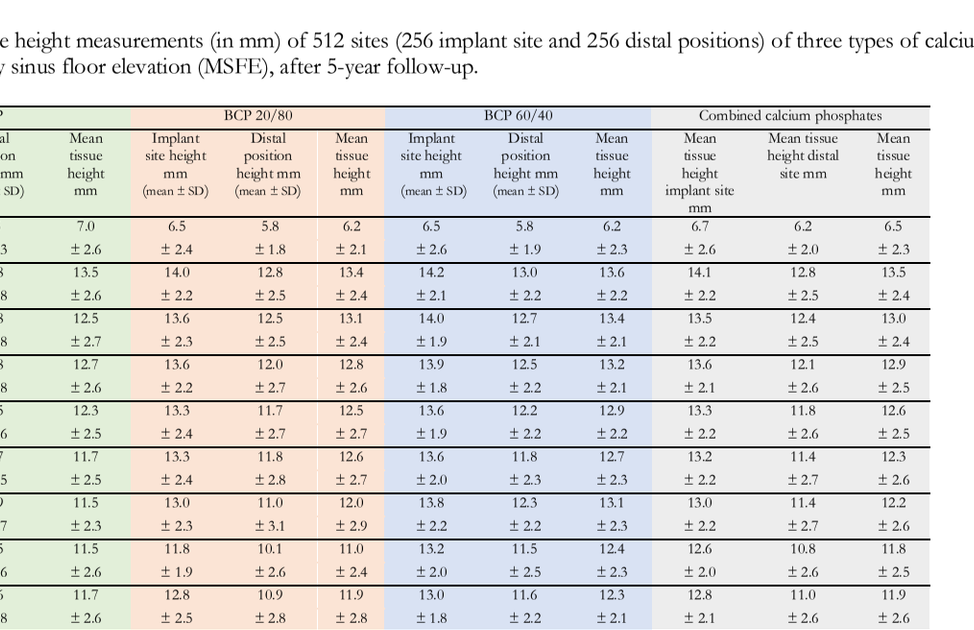


Figure 2.
Mean tissue height changes at implant site (A) and distal position (B) measured (in mm) over a period of 5 years. T0 (-8): patient intake, T1 (-6): maxillary sinus floor elevation, T2 (-1): ridge mapping, T3 (0): dental implant placement, T4 (3): prosthetic loading, T5 (12): follow-up visit after 1 year, T6 (24): follow-up visit after 2 years, T7 (36): follow-up visit after 3 years, T8 (48): follow-up visit after 4 years, T9 (60): follow-up visit after 5 years. β-TCP: β-tricalcium phosphate; BCP: biphasic calcium phosphate; HA: hydroxyapatite.

The initial tissue height gain by means of MSFE, calculated at T1, is comparable in all three groups (β-TCP: 6.5 mm, BCP 20/80: 7.2 mm, BCP 60/40: 7.4 mm). The mixed model analysis revealed no significant difference in the height distribution over time between β-TCP, BCP 20/80, and BCP 60/40 at the implant site. At the distal position, however, a significant difference was observed between β-TCP and BCP 20/80 (p = 0.002), but not between β-TCP and BCP 60/40 (ns). The final tissue height loss at the implant site, calculated at T8 and T9, was the highest in the β-TCP group and the lowest in the 60/40 group (β-TCP: 1.5 mm and 1.8 mm, BCP 20/80: 1.2 mm and 1.6 mm and BCP 60/40: 1.2 mm and 1.8 mm, respectively), although this trend was not significant for both time points. The final tissue height loss at the distal positions, however, was significantly different at T8 (ANOVA: p = 0.012). A post-hoc analysis showed final tissue height loss was lower in the BCP 60/40 compared to β-TCP group (p = 0.017) and compared to the BCP 20/80 group (p = 0.029). Final tissue height loss was also lower in the BCP 20/80 group compared to the β-TCP group (p = 0.018).

Comparison of the combined calcium phosphate ceramics at implant position and inter-implant (distal) position

The pattern of the mean tissue height changes of the combined calcium phosphate ceramics at two positions: at dental implant site and distally of the implant site (Figure 1). These "distal" positions can be regarded as inter-implant or inter-implant-tooth positions or, in case of a free-ending situation, as distal positions. Table 4 shows the pattern of mean tissue height changes in the posterior (partially) edentulous atrophic maxilla after MSFE surgery with a calcium phosphate bone substitute. The maxillary sinus with limited alveolar crest height (initial height 6.5 mm = T0) is internally augmented with a bone substitute 6 months prior to dental implant placement (13.5 mm = T1). Therefore, a mean increase in tissue height is 7.0 mm immediately after MSFE. The tissue height change showed a decrease of 0.6 mm (after MSFE) at the time of dental implant placement (12.9 mm = T3). Over time, the tissue height diminishes further to 2.0 mm 5 years after MSFE (T9). The total tissue height gain after 5 years is 5.0 mm, from 6.5 mm (T0) resulting in a final tissue height of 11.5 mm (T9). The final tissue height loss is 1.6 mm at 4 years and 2.0 mm at 5 years after dental implant

placement. The pattern of tissue height loss at the two positions appears to be the same but the mean tissue height loss at dental implant position is 1.3 mm at 4 years and 1.7 mm at 5 years. At distal position the tissue height loss is 1.8 mm and 2.3 mm at 4 and 5 years after dental implant placement, respectively.

On several panoramic radiographs a particular phenomenon was found, indicating that apically of the inserted dental implant some of the graft material appeared to have been lifted in the cranial direction ("Summers" effect/method) [40]. The tissue height at implant site increased after MSFE. Figure 3 A-C show radiographs with clear signs of this tissue height increase. This postoperative increase in height can also be recognized in Table 4 at timepoint T3.

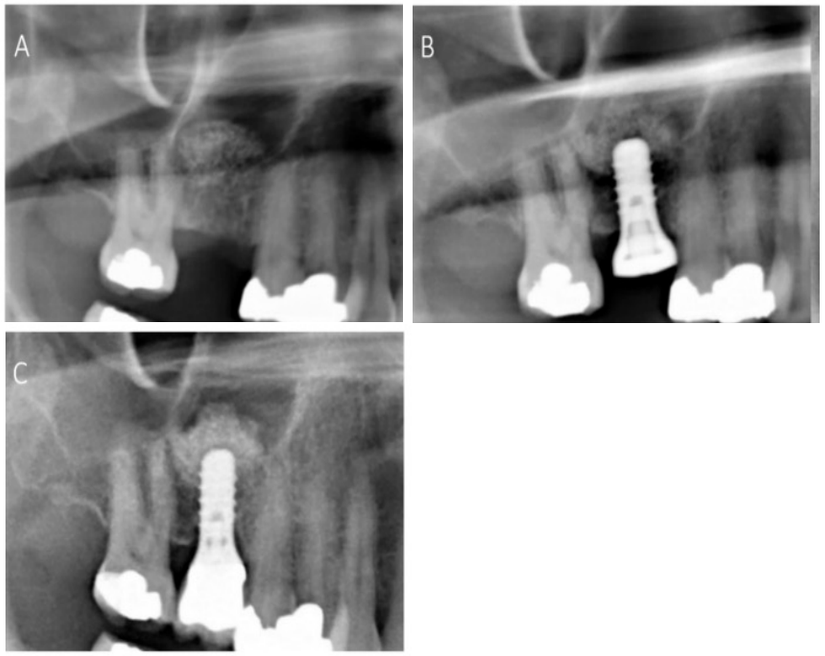


Figure 3.
Radiographs of the right partial edentulous maxilla after maxillary sinus floor elevation (**A**), after dental implant placement (**B**) and at 2-year follow-up (**C**). Apical to the dental implant the graft material has been lifted upwards, resulting in a higher local tissue height at the implant position.

DISCUSSION

In this study, the radiologically derived tissue height distribution following MSFE with three types of calcium phosphate ceramics were compared over a period of 5 years after dental implant placement. In all cases, the use of calcium phosphate ceramics in MSFE resulted in an initial tissue height gain followed by an initial decrease in tissue height which subsides after dental implant placement. This pattern is consistent with previously reported MSFE procedures using bone substitutes [5, 28, 30, 41, 42], also reported in the meta-analyses by Haugen et al. [17].

Apart from the three fully synthetic calcium phosphate bone substitutes used in the present study, xenografts, such as demineralized bovine bone mineral (DBBM), have been also widely used in MSFE procedures [43-47]. Clinical, radiological, and histomorphometrical studies on DBBM confirmed predictable outcomes after MSFE, meaning good quality and volume of regenerated tissue [17]. DBBM has a chemical composition similar to human bone, being osteoconductive and showing a slow resorption rate comparable to 100% HA, resulting in stabilization of the grafted material and a high dental implant survival rate [48-52]. Several studies compared DBBM to 100% β-TCP and/or synthetic BCPs composed of different ratios of HA and β-TCP [29, 51, 53-57]. Overall, MSFE procedures with synthetic BCPs (HA/TCP) and DBBM seem to exhibit similar results, regarding new bone formation and the survival of dental implants. However, studies on volume stability after MSFE, comparing various calcium phosphate ceramics containing different proportions of HA and β-TCP, are scarce in the literature [29, 55, 58]. In this respect, no studies have been reported comparing DBBM to 100% β-TCP or 60/40 or 20/80 mixtures of HA and β-TCP.

Height loss after (MSFE) may be due to settling (or clinging) of the calcium phosphate granules in the maxillary sinus and at a later stage resorption of the grafted material. At the same time, height loss of grafted material due to air pressure from respiration in the maxillary sinus is also unavoidable [59, 60].

In all three groups, the loss of tissue height at the distal positions was more prominent than at the dental implant site. This could have a mechanical explanation [61, 62], since dental implants can be considered as stable pillars, which eventually may lead to some degree of scalloping. Another explanation for the height differences between implant sites and distal positions could be that the calcium phosphate granules are pushed up

at implant sites during the osteotomy and placement of the dental implants at dental implant surgery or by an ossifying hematoma [63]. This can be regularly observed at postoperative radiographs after implant placement [34, 38, 41].

The height of vital bone within the total tissue volume is the relevant structure for dental implant stability [21, 64]. This vital bone consists of the original alveolar bone and the newly formed bone between the bone substitute granules as a result from osteoconduction in cranial direction. As resorption of β-TCP seems to occur at a higher rate than HA, the question is whether the resorption results in replacement by vital bone that is supposed to connect with the titanium implant root surface, eventually resulting in osseo-integration of the dental implant. From the literature, there is little or no support for this. This is the reason why for augmentation purposes BCPs have been developed [6, 29, 52, 65].

A recent micro-CT study by Helder et al. [66] shows BCP 20/80 might perform better, at least in the short term, as a scaffold for bone augmentation in the MSFE model than BCP 60/40 as more bone is formed, and more osteoid is deposited at the cranial side in BCP 20/80 treated patients compared to BCP 60/40 treated patients.

The term "tissue height" is used instead of "bone height" in this study, since we know that, in spite what some commercial companies tend to promote, the transition from a bone substitute to vital bone is a very slow and incomplete process [5, 62].

Many publications refer to radiological bone height after sinus floor elevation, actually meaning tissue height, consisting of three layers of tissues: native bone from the original alveolar crest, a transition layer consisting of a mixture of bone substitute and new vital bone, and a cranial layer of remaining bone substitute [4, 5, 7]. As the process of bone generation in the grafted area is slow, time plays an important role. Six months healing time after MSFE generates approximately 3 mm of bone gain [41]. This means that a substantial native bone height is required for primary stability of the placed dental implants, even after a 6-month healing period. In fact, from our former study, it can be concluded that a 9-month healing period after MSFE using BCP 60/40 would be favorable [5].

Less than 4 mm native bone height does not seem to be the suitable indication for the use of bone substitutes [7]. A further complication could be if the cranially situated bone substitute resorbs, without turning into vital bone in time. If this bone substitute dissolves, the apical parts of the dental implants would become dehiscent. In the present

study, this was not observed over a period of 5 years after dental implant placement. Although the "insolvable" hydroxyapatite component in the calcium phosphate bone substitutes appears to maintain the graft on the cranial side best, it can be regarded as a covering or protective layer of tissue to cover the apical parts of the dental implant from exposing into the elevated maxillary sinus, without giving support to the dental implant. One could regard this layer of mainly calcium phosphate and fibrous tissue as merely a shielding structure for the "new" maxillary sinus.

This study also has some limitations. One limitation is the missing values in the 5-year follow-up. As a result, the consistent trend in final tissue height loss did not show a significant difference at T9. For this reason, final tissue height loss was also calculated at T8, 4 years after the dental implantation. At this time point significant differences were found at the distal position. Nevertheless, studies with a 4- to 5-year follow-up are rare but our study provided valuable insights in MSFE, dental implant placement, and final height loss of different calcium phosphate ceramics.

At the time of surgery, 25.7% of the Dutch population was smoking. As the negative influence of smoking for dental implants was known, our patients were advised to stop smoking if they did. This resulted in a percentage of smokers of 21% in our patient population. However, the aim of this study was to evaluate the changes in tissue height in a certain patient population, not the dental implant survival rate or the influence of risk factors.

CONCLUSIONS

This radiological study shows a predictable and comparable behavior of slow decrease in tissue height over time for all three types of calcium phosphate bone substitutes used in MSFE. Mean tissue height was better maintained at implant sites than at inter-implant or inter-implant-tooth positions or free-end-positions. The use of β-TCP results in a greater tissue height loss, compared to the use of HA-containing calcium phosphate ceramics. The fraction of HA in calcium phosphate ceramics in combination with dental implant loading seems to be beneficial for tissue height maintenance after MSFE.

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6

Long-term bone height changes after sinus floor elevation with maxillary or mandibular bone grafts: A radiological study

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ABSTRACT

Introduction: This retrospective study aimed to assess the impact of maxillary and mandibular autogenous bone grafts on maxillary bone height in patients who underwent maxillary sinus floor elevation (MSFE).

Methods: The study involved 92 patients, divided into two groups: 37 patients receiving maxillary bone grafts for MSFE and 55 patients receiving mandibular bone grafts for MSFE. Bone height after MSFE was measured on panoramic radiographs up to 60 months postoperatively, comparing different positions and situations.

Results: In general, both maxillary and mandibular bone grafts resulted in an increase in bone height directly after the MSFE procedure, followed by a bone height loss over time, with no significant differences between the two groups for gap and free-end positions. However, at distal to implant positions, mandibular bone grafts showed less bone loss. Despite gradual bone height loss, all dental implants remained covered with bone without exposure or subsequent loss, indicating a successful MSFE procedure.

Conclusion: This radiologic study showed that over a long-term period there is a similar bone height pattern at dental implant sites and sites distal to implants when maxillary or mandibular bone grafts are used in MSFE.

INTRODUCTION

Maxillary sinus floor elevation (MSFE) is a frequently performed pre-implant surgical procedure and is regarded as a safe technique for restoring insufficient alveolar bone height in the posterior maxilla to allow dental implant placement for dental rehabilitation. Extraction of one or more teeth frequently results in atrophy of the alveolar ridge and pneumatization of the maxillary sinus [1, 2]. Augmentation of the maxillary sinus floor can be performed with autogenous bone grafts, xenogenic bone substitutes (or a mixture of autogenous bone grafts and xenogenic bone substitutes), allograft bone, or alloplastic materials [3]. Currently, the ideal grafting material for MSFE has not yet been found; ideally, a bone substitute is totally replaced by bone [4-7]. Therefore, and for surgical convenience, bone substitutes are frequently used as graft material [8, 9]. However, bone substitutes only provide an osteoconductive scaffold [10]. The replacement of a bone substitute graft to bone takes time [8, 11]. Even with longer healing times (9-12 months), not all bone substitute will be resorbed and replaced by vital bone [11]. Velich et al. investigated the behavior of several bone substitutes in MSFE: autogenous bone, a calcium carbonate-coated polymer, hydroxyapatite (HA) of algal origin, calcium carbonate gel produced from coral or beta-tricalcium phosphate alone, autogenous bone mixed with these bone substitutes, or a combination of beta-tricalcium phosphate and platelet-rich plasma. Total resorption (disappearance) of the bone substitute material was observed in only 2.7% of the cases. This lack of resorption was similar for most bone substitutes [12]. Autogenous bone is frequently used in MSFE due to its superior osteogenic, osteoinductive, and osteoconductive properties. It is often considered the gold standard for bone grafting because it contains live cells and growth factors that enhance bone regeneration. Specific indications for using autogenous bone in MSFE include: 1. severely atrophic maxillary sinus (< 4 mm), autogenous bone may be required to ensure proper regeneration and stability for dental implant placement; 2. need for rapid bone regeneration due to faster healing and integration compared to some synthetic or allogenic grafts; 3. compromised bone quality (type IV bone); autogenous bone can improve the regenerative environment; 4. large defects or extensive augmentation; 5. previous graft failure; autogenous bone may be used to enhance outcomes; 6. high risk of infection or poor healing, growth factors, and living cells, which can enhance the healing response and reduce the risk of infection, such as

diabetes mellitus; 7. requirement for a graft with osteogenic properties, as autogenous bone contains live osteoblasts and osteoprogenitor cells [3].

The utilization of autogenous bone grafts requires an additional surgical intervention, which carries the potential for complications and adverse effects at the donor site [13-17]. Autogenous bone grafts can be harvested from various extraoral or intraoral donor sites, for instance the iliac crest, the symphyseal or retromolar regions of the mandible, or the maxillary tuberosity. Grafting from different intraoral sites has the advantages of local rather than general anesthesia, a short distance between the donor and augmentation sites, and the avoidance of cutaneous scars. It has been demonstrated that bone grafts collected from intraoral sites other than the chin result in a much higher total bone volume (TBV) than iliac crest bone [18]. There is no comparative evidence on the impact of different donor sites for autogenous bone grafts on bone regeneration, despite the possibility of changes in bone loss and bone induction [19]. Loss of bone height after an initial increase in height is a common phenomenon that occurs with both autogenous bone grafts and alloplastic materials [20]. Both the fraction of HA within the calcium phosphate ceramics and loading of the dental implant appear to be advantageous for tissue height maintenance after MSFE [21]. According to several authors, it is inevitable for grafted material to experience a decrease in height due to the air pressure caused by respiration in the maxillary sinus [22, 23]. Radiographic results indicate that bone substitutes used in MSFE procedures are superior to autogenous bone grafts in similar types of surgery [20].

Non-loaded bone seems to be particularly susceptible to resorption [24]. As resorption-preventing elements, dental implants are crucial as loaded pillars within the bone structure. As such, dental implants provide support for three-dimensional (vertically, longitudinally, and labial/lingual) reconstruction [25]. Several publications mention bone scalloping around the "apices" of dental implants, implying that bone resorbs more rapidly in non-loaded areas than in loaded parts or as a result of pneumatization of the maxillary sinus [26]. There have been no studies, as far as the authors know, on the use of exclusively autogenous bone grafts from the maxilla or the mandible in MSFE, with follow-up lasting up to five years.

The aim of this study was to investigate the radiological changes in bone height after MSFE using two types of autogenous bone grafts with a follow-up time of 60 months after dental implant placement. In particular, the authors focused on the bone height

reduction in implant- and distal to implant positions as well as gap- and free-end situations after MSFE.

MATERIALS AND METHODS

Patients

This retrospective study is based on data collected from medical records (chart reviews) and panoramic radiographs that were obtained during patients' annual follow-up visits. Between 9/1999 and 12/2013 a total of 313 consecutive patients (146 males and 167 females) with a mean age of 55 years (range: 29-81) who underwent MSFE using intraoral bone grafts in a (partially) posterior edentulous maxilla were included. When a substantial quantity of autogenous bone graft was necessary for space expansion in MSFE, it was imperative to extract this larger amount of bone from the mandible rather than the maxilla. Based on patients' specific anatomical conditions, 96 of the 313 patients had received maxillary bone grafts, and 217 patients had received mandibular bone grafts. The 313 patients had received a total of 482 dental implants.

A native alveolar bone height of less than 8 mm in the posterior edentulous maxilla along with the patient's preference for oral rehabilitation with dental implants served as criteria for treatment selection. Patients with a history of radiation of the jaws, heart valve prostheses, or endocarditis were excluded from dental implant surgery. Smokers (14.1%) were not excluded from dental implant surgery. Prior to both surgical procedures (MSFE and dental implant surgery), all patients signed a written consent for the use of their data and received standard care. The MSFE procedure, dental implant placement, and the panoramic radiograph measurements were conducted at the Department of Oral and Maxillofacial Surgery/Oral Pathology, Amsterdam UMC (location VUmc), Amsterdam, The Netherlands. For the purpose of this study, the following patients were excluded: patients with analogue radiographs, poor-quality radiographs, patients with simultaneous buccal bone augmentation, patients with MSFE and simultaneous dental implant placement, fully edentulous patients, and patients with extra-orally harvested bone grafts.

Due to the incomplete participation of the 313 patients in routine annual examinations, only those with adequate follow-up (at least a minimum of five timepoints after dental implant placement) for radiological measurements were included, yielding a total of 92 patients at the start of the study. Among these, 54 patients were observed for up to 48 months and 40 patients were observed for up to 60 months. A total of 95 treatments were administered to the 92 patients, as three individuals underwent surgery on both

sites during two separate treatment sessions. All patients received autogenous graft material.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Medical Ethics Review Committee of VU University Medical Center (registration number: 2021.5723). The study is registered with the US Office for Human Research Protections (OHRP) as IRB00002991. The FWA number assigned to VU University Medical Center is FWA00017598.

Maxillary sinus floor elevation and bone harvesting procedures

All 92 patients underwent an MSFE procedure, according to Tatum's top-hinge trapdoor technique [2]. During the perioperative period, prophylactic procedures were carried out as previously published [21]. The maxillary tuberosity bone grafts were harvested with a mallet and an osteotome. The bone grafts from the mandible and chin (one patient) were harvested in a half-cylinder shape with explantation trephines (inner diameter 4.2 mm; Institute Straumann AG, Basel, Switzerland), with a drilling speed of 500 rpm, using sterile saline for copious irrigation. The bone grafts from the maxilla, mandible, or chin were positioned underneath the lifted trapdoor and Schneiderian membrane without exerting significant pressure on the lifted anatomical structures. No barrier membranes were used to cover the lateral window [27]. The wounds were closed with Gore-Tex® sutures (W.L. Gore & Associates, Newark, DE, USA). The sutures were removed after 10 to 14 days.

Dental implant placement

In all included 92 patients, 158 Straumann® SLA Soft Tissue Level dental implants with diameters of 3.3 mm or 4.1 mm and implant lengths of 10 or 12 mm were placed (Institut Straumann AG, Basel, Switzerland). According to the manufacturer's instructions, dental implant surgery was performed four months after MSFE. During the perioperative period, prophylactic procedures were carried out as previously published [21]. During the 3-month osseointegration period, the dental implants were not loaded, and the restorative dentist subsequently performed the prosthetic treatment.

Radiological evaluation

Considering regional differences in mechanical loading of the grafted bone and the effect of loading on alveolar bone height gain, bone height was measured at the distal positions of distal dental implants in gap situations and in free-end situations (Figure 1).

Panoramic radiographs were taken at the following timepoints: T0: patient intake, approximately two months prior to MSFE; T1: immediately after MSFE; T2: approximately one month prior to the dental implant placement; T3: immediately after dental implant placement; T4: after an osseointegration period of three months; and T5-T9: during annual follow-up recall visits up to 60 months after dental implant placement.

Bone heights were measured on the panoramic radiographs at the dental implant sites and 2-3 mm distally of the dental implant sites (as an inter-implant site, from now on referred to as gap situations, or as a free-end distal measurement site) and corrected for the magnification factor of 1.25, according to the method described by Zijderveld et al [20]. (Figure 1).

To prevent miscalculation of the cranial bone levels, a correction was made for the possibility of peri-implant bone loss in the cervical region.

Statistical analysis

The data are expressed as the mean and standard deviation between brackets. Because the bone heights of the same individual were measured multiple times (T0-T9) and 158 implants were measured in 92 patients, a one-way repeated measures (ANOVA) was used to account for the non-independence in the data. Maximum bone height loss was calculated at T8 (T1-T8) as well as T9 (T1-T9), and the difference between the two timepoints was examined using a paired *t*-test. In addition, differences between implant sites and distal to implant positions were also determined by a paired *t*-test. Differences between maxillary and mandibular bone, as well as gap- and free-end situations, were evaluated using an independent sample *t*-test; $p < 0.05$ was considered significant. Since patients were treated exclusively with either maxillary or mandibular bone, within-patient testing is not feasible. Version 28 of IBM SPSS was used for all statistical analyses.

This study is in compliance with the STROBE guidelines.

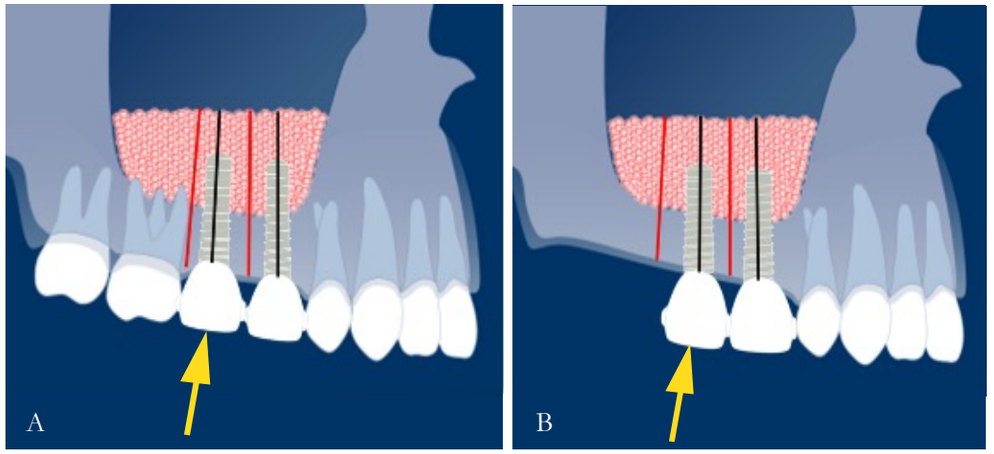


Figure 1.
This graphic shows the locations of the bone height measurements at the implant and distal to implant positions.

A: The black lines represent the measurement positions at implant sites; the red lines (2–3 mm distally) represent the "distal" or intermediate positions. The yellow arrows point to the most distal implant positions.

B: This graphic shows the locations of the bone height measurements at the implant and distal to implant positions (free-end situation). The black lines represent the measurement positions at implant sites, while the red lines (2-3 mm distally) represent the "distal" positions (free-end situation).
Graphics used with courtesy of the ITI Foundation, Basel, Switzerland.

RESULTS

Patient population

The patient data were divided into two groups: the first group with maxillary bone grafts consisted of 37 patients (17 males and 20 females with a mean age of 57 years) who received 64 dental implants, and the second group with mandibular bone grafts consisted of 55 patients (23 males and 32 females with a mean age of 54 years) who received 94 dental implants (Tables 1 and 2). At T8 and T9, 54 (60% of the total population) and 40 patients (44% of the total population), respectively, returned for regular follow-up.

Table 1. Patient data for maxillary sinus floor elevation (MSFE) is divided into two groups: maxillary bone grafts and mandibular bone grafts.

Grafts harvested from	Maxilla	Mandible
Number of patients	37	55
Number of dental implant sites	64	94
Gender	17 M, 20 F	23 M, 32 F
Mean age and range in years	57 (29–81)	54 (30-74)
Mean observation period in months	33	43

M: male; F: female.

Table 2. Number of available measurements at multiple time intervals up to 60 months of follow-up.

Time points	Months of observation	Maxillary bone grafts	Mandibular bone grafts	Total implants observed	Number of patients
T0	- 6	64	94	158	92
T1	- 4	58	94	152	88
T2	-1	54	83	137	81
T3	0	64	94	158	92
T4	3	44	89	133	82
T5	12	56	79	135	80
T6	24	42	78	120	70
T7	36	35	67	102	61
T8	48	24	70	94	54
T9	60	28	41	69	40

T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months. A part of the total patient population neglected to appear at various timepoints for a panoramic radiograph.

Maxillary and mandibular bone grafts

As shown in Figure 2 and Table 3, the mean alveolar bone height at T0 was larger in the maxillary bone graft group (6.0 mm) than in the mandibular bone graft group (4.4 mm) ($p < 0.001$). The initial bone height gain after MSFE at T1 was comparable (8.7 mm in the maxillary bone graft group versus 8.9 mm in the mandibular bone graft group, $p = 0.643$). The total bone height loss from T1 to T8 was similar in the maxillary and mandibular bone graft groups, with losses of 2.8 mm and 2.6 mm ($p = 0.652$), respectively. The total bone height loss at T9 was also similar in both bone graft groups: 2.9 mm in the maxillary and 2.3 mm in the mandibular grafts ($p = 0.155$).

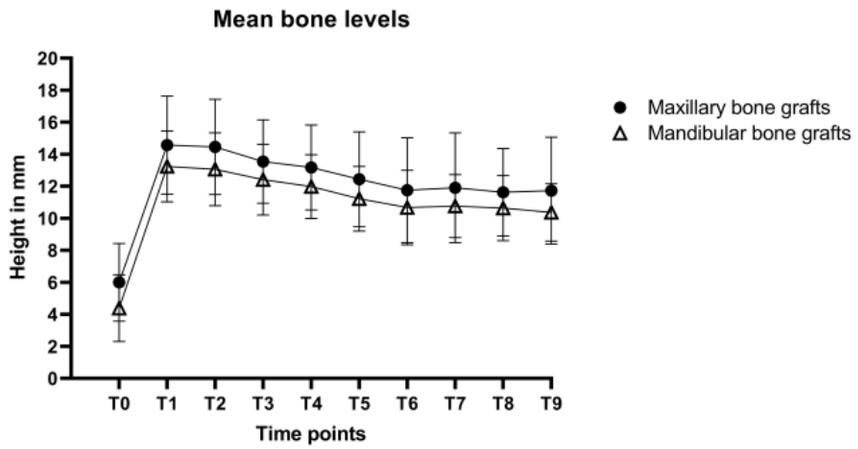


Figure 2.
Mean bone height measurements (and standard deviations) of maxillary sinus floor elevation (MSFE) with maxillary or mandibular bone grafts and 60-month follow-up after dental implant placement.
T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

Table 3. Radiographic bone height measurements (and standard deviations) of maxillary sinus floor elevation (MSFE) with maxillary bone grafts and mandibular bone.

Time Points	Months of observation	Maxillary bone grafts in mm (mean ± SD)	Mandibular bone grafts in mm (mean ± SD)
		Mean bone height levels	Mean bone height levels
T0	-6	6.0 (2.4)	4.4 (2.1)
T1	-4	14.6 (3.1)	13.2 (2.2)
T2	-1	14.5 (3.0)	13.1 (2.3)
T3	0	13.5 (2.6)	12.4 (2.2)
T4	3	13.2 (2.7)	12.0 (2.0)
T5	12	12.4 (3.0)	11.2 (2.0)
T6	24	11.8 (3.3)	10.7 (2.3)
T7	36	11.9 (3.5)	10.8 (2.0)
T8	48	11.6 (2.8)	10.6 (2.0)
T9	60	11.7 (3.4)	10.4 (1.8)

T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

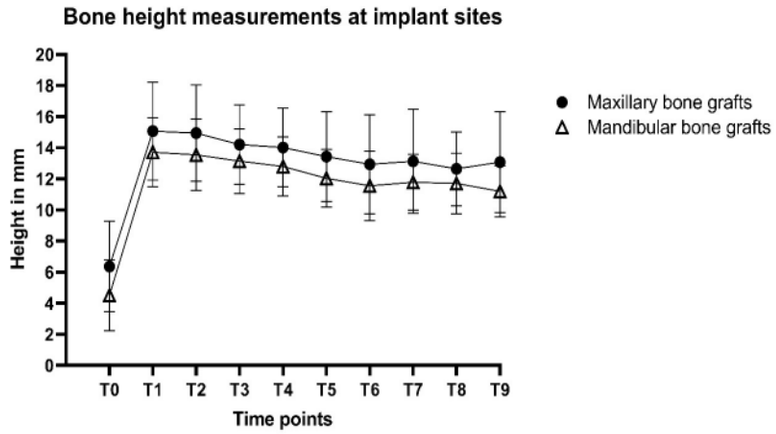


Figure 3.
Mean bone height measurements at implant sites (and standard deviations) of maxillary sinus floor elevation (MSFE) with maxillary or mandibular bone grafts and 60-month follow-up after dental implant placement. T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

Table 4. The radiographic bone level measurements (and standard deviations) of 158 maxillary sinus floor elevations (MSFE).

Time Points	Months of observation	Autogenous bone grafts implant sites in mm (mean ± SD)		Autogenous bone grafts distal to implant positions in mm (mean ± SD)	
		Maxillary	Mandibular	Maxillary	Mandibular
T0	-6	6.4 (2.9)	4.5 (2.3)	5.6 (2.2)	4.3 (2.2)
T1	-4	15.1 (3.2)	13.7 (2.2)	14.1 (3.1)	12.8 (2.3)
T2	-1	14.9 (3.1)	13.5 (2.3)	14.0 (3.0)	12.6 (2.3)
T3	0	14.2 (2.6)	13.1 (2.1)	12.9 (2.8)	11.7 (2.5)
T4	3	14.0 (2.5)	12.8 (1.9)	12.3 (3.0)	11.2 (2.2)
T5	12	13.4 (2.9)	12.0 (1.9)	11.4 (3.2)	10.4 (2.3)
T6	24	12.9 (3.2)	11.6 (2.3)	10.6 (3.7)	9.8 (2.6)
T7	36	13.1 (3.4)	11.8 (1.8)	10.7 (3.9)	9.7 (2.3)
T8	48	12.6 (2.4)	11.7 (1.9)	10.6 (3.4)	9.6 (2.3)
T9	60	13.1 (3.3)	11.2 (1.7)	10.4 (3.7)	9.5 (2.1)

T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months; initial height gain is T1-T0; final height gain is T9-T0.

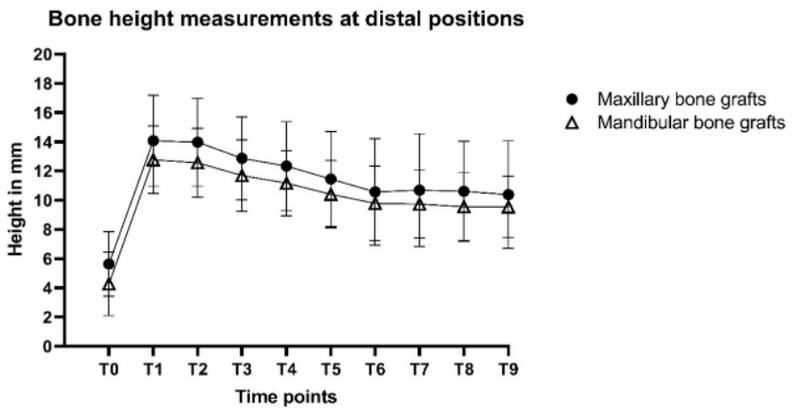


Figure 4.
Mean bone height measurements at distal to implant positions (and standard deviations) of maxillary sinus floor elevation (MSFE) with oral bone grafts with a 60-month follow-up after dental implant placement. T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

Dental implant sites and distal to implant positions

The total bone height loss at dental implant sites calculated at T8 (T1-T8) did not differ significantly between the two groups ($p = 0.487$), with a mean of 2.5 mm for the maxillary bone graft group and 2.0 mm for the mandibular bone graft group (Figure 3 and Table 4). At T9 (T1-T9), the total bone height loss at dental implant sites (both maxillary and mandibular) was not statistically significant, with a mean of 2.0 mm in the maxillary group and 2.5 mm in the mandibular group ($p = 0.968$). The total bone height loss at the distal to implant position at T8 was not statistically different between the two groups ($p = 0.882$), with a mean of 3.5 mm in the maxillary bone graft group and 3.2 mm in the mandibular bone graft group (Figure 4 and Table 4). Statistically, the total bone height loss at distal to implant positions was significantly different between

Table 5. Absolute number of maxillary sinus floor elevations with maxillary and mandibular bone grafts according to the number of gap and free-end situations and dental implants. (*95 treatments were administered to 92 patients.)

	Gap situation /dental implants	Free-end situation/ dental implants	Total of MSFE/ dental implants
Maxillary bone graft	7/11	33/53	40/64
Mandibular bone graft	17/30	38/64	55/94
Total	24/41	71/117	95(*)/158

*95 treatments were administered to 92 patients.

the two groups at T9 (p = 0.023), with a mean of 3.7 mm in the maxillary bone graft group and 3.3 mm in the mandibular bone graft group.

Gap and free-end situation

Table 5 shows the total number of dental implants placed in gap situations (24 patients) and free-end situations (71 patients) after MSFE with maxillary or mandibular bone grafts.

Total bone height loss was not different for maxillary versus mandibular bone grafts in gap situations for both T8 and T9 (T8: 2.3 versus 2.0 mm, p = 0.768; T9: 3.7 versus 1.9 mm, p = 0.07) (Figure 5 and Table 6). Similar patterns were observed for free-end situations with losses at T8 of 3.5 and 3.8 mm (p = 0.808) and at T9 of 3.9 and 3.0 mm (p = 0.335) in maxillary and mandibular bone grafts, respectively (Figure 6 and Table 6).

Table 6. Bone level measurements (and standard deviations) at distal to implant sites in gap situations and in free-end situations.

		Distal mean bone levels in gap situations in mm (mean ± SD)		Distal mean bone levels in free-end situation in mm (mean ± SD)	
Time points	Months of observation	Maxillary bone grafts	Mandibular bone grafts	Maxillary bone grafts	Mandibular bone grafts
T0	-6	4.4 (1.3)	4.6 (2.1)	5.4 (1.9)	4.4 (2.3)
T1	-4	12.6 (1.5)	12.0 (1.9)	13.0 (2.6)	13.2 (2.7)
T2	-1	12.6 (2.5)	11.8 (2.0)	12.9 (2.5)	13.1 (2.7)
T3	0	10.9 (1.7)	11.5 (1.9)	11.7 (2.0)	11.9 (2.7)
T4	3	9.4 (1.8)	11.1 (1.9)	11.0 (2.0)	11.5 (2.3)
T5	12	9.3 (1.2)	10.8 (1.6)	9.9 (2.1)	10.4 (2.3)
T6	24	8.3 (1.9)	9.3 (3.4)	9.3 (2.4)	9.8 (2.3)
T7	36	9.0 (2.0)	9.7 (1.6)	9.4 (2.9)	9.7 (2.5)
T8	48	9.2 (1.0)	10.1 (1.3)	8.8 (2.1)	9.4 (2.3)
T9	60	8.0 (1.2)	9.4 (1.7)	9.1 (2.5)	9.4 (2.2)

T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

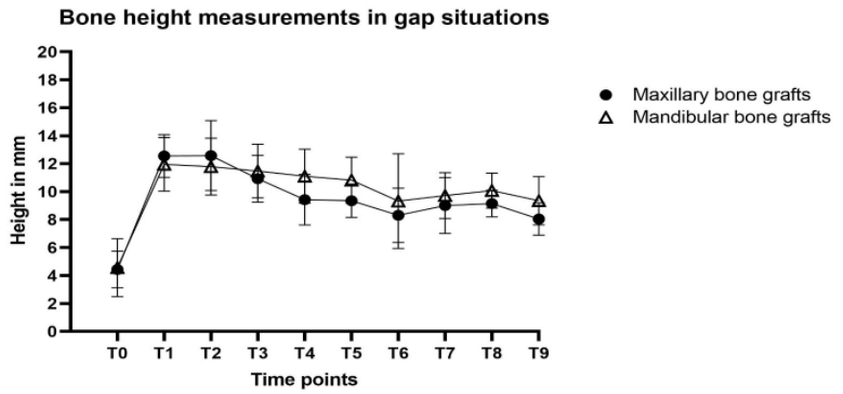


Figure 5.
Mean bone height measurements in gap situations (and standard deviations) of maxillary sinus floor elevation (MSFE) with maxillary or mandibular bone grafts and 60-month follow-up after dental implant placement. T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

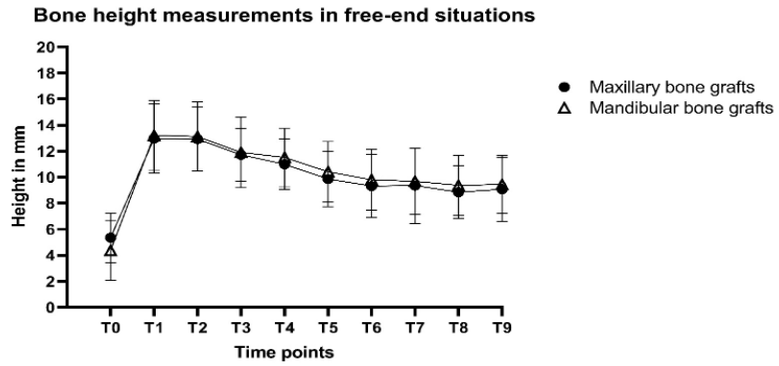


Figure 6.
Mean bone height level measurements in free-end situations (and standard deviations) at distal to implant sites. T0: patient intake; T1: maxillary sinus floor elevation; T2: ridge mapping; T3: dental implant placement; T4: prosthetic loading; T5: follow-up visit after 12 months; T6: follow-up visit after 24 months; T7: follow-up visit after 36 months; T8: follow-up visit after 48 months; T9: follow-up visit after 60 months.

DISCUSSION

This study evaluated the changes in bone height after MSFE using two types of autogenous bone grafts, one taken from the retromolar area of the mandible and the other from the maxillary tuberosity, over a prolonged period of time. This study showed that 48 and 60 months after MSFE, the total bone height, measured on panoramic radiographs, did not differ between maxillary or mandibular bone grafts at dental implant sites as well as at distal to implant sites. For distal to implant sites, bone height was comparable in both free-end and gap situations. The total bone height was lower at distal positions compared to implant positions.

Our findings demonstrate a general trend of gradual bone height loss following the initial increase after the MSFE procedure, up to 60 months for both intraoral donor sites, which is consistent with our hypothesis. A similar pattern was observed in a study that used calcium phosphate ceramics as graft material [21]. In that study, three types of calcium phosphate ceramics were compared after MSFE (β-TCP, BCP (20/80) 20% hydroxyapatite (HA)-80% β-TCP, and BCP (60/40) 60% HA-40% β-TCP), which revealed that after initial settling of the bone substitute particles in the maxillary sinus was followed by resorption of the grafted material for all three types of calcium phosphate ceramics, of which the majority of resorption occurred within the first 24 months and then appeared to slow down [21]. A gradual height loss after the initial increase was also observed by radiographic assessment with two other types of bone substitutes (Bio-Oss® and Cerabone®), but they showed the greatest vertical resorption after 12 months (55–65% of tissue height loss) and an annual height loss of approximately 10-12% over a total of 48 months [28]. Height loss of grafted material due to the pressure from respiratory airflow in the maxillary sinus is unavoidable, according to some authors [22, 23]. Whether this is an additional explanation for the height loss (resorption) of the autogenous bone grafts used in the present study remains unclear. Nevertheless, as previously stated, autogenous bone is still the preferred material for MSFE and the "gold standard". HA bone substitutes are widely used due to their limited solubility and because they are widely and easily commercially accessible. This characteristic is believed to prevent excessive graft resorption, thereby reducing the risk of dental implant apices becoming exposed.

In general, the MSFE procedure is performed to increase the height of the posterior

maxilla, eventually facilitating the placement of dental implants. In our study, in all cases, sufficient bone height was achieved to allow the planned placement of dental implants with lengths of 10 mm or 12 mm. The reduction in bone height, after the initial increase, never reached a point in the course of 5 years where the dental implants were exposed or subsequently lost, which demonstrates that the intended purpose of the augmentation procedure was fulfilled.

Overall, our findings did not support a preferential origin of the autogenous bone grafts since differences could not be detected. In contrast, Wu et al. argue that based on histological investigation of the bone biopsies harvested at dental implant surgery four months after MSFE, maxillary bone grafts may perform better than mandibular bone grafts in MSFE due to enhanced vascularization, osteoid deposition, and active bone remodeling. The grafts were compared using histology and histomorphometry, which revealed the better vascularity of the maxillary bone grafts. However, this does not prove that the material is superior for dental implant placement in the long-term. Due to the histological nature of the Wu et al. study, the influence of clinical aspects like bone density was not taken into account. The density of the graft material, which was omitted from this study, could have a substantial effect on the primary stability of dental implants placed after MSFE [29].

Our findings indicate that total bone height loss is greater at distal to implant positions compared to implant positions, regardless of the type of bone graft used. The higher bone loss probably occurs as a result of the lack of dental implant load on the graft material. These results emphasize the importance of ongoing monitoring and evaluation in implant dentistry to make informed decisions regarding graft material and implant location, ultimately optimizing the long-term success and stability of dental implants.

The bone height in the maxillary and mandibular groups was significantly different at baseline. This difference could have influenced the final bone height. When MSFE requires a considerable quantity of autogenous bone graft for space expansion, the choice of graft is usually mandibular bone because the mandible provides a greater quantity of accessible bone compared to the maxilla. This difference is therefore unavoidable, but since both maxillary and mandibular bone grafts were used for native bone heights of at least 4 mm, taking into account the patient's anatomical conditions, the effect on the final bone height is probably rather small. The decisive factor was the targeted volume increase, which depended on whether there was sufficient bone

available from the maxilla or whether bone from the mandible was required.

In the present study, bone heights were measured on panoramic radiographs. The relevance of radiographic measurements of MSFE with bone substitutes for the stability and longevity of dental implants is limited since they do not reveal the amount of vital implant-supporting bone. Radiographic analysis does have the advantage of repeated measurements over time within one individual. This gives the opportunity to obtain data on bone height loss for a prolonged follow-up.

A limitation of our study is the low number of measurements during the 60-month follow-up due to patient withdrawal. For this reason, an extra data collection point was chosen because fewer than 50% of the patients participated in the annual examination after 60 months. After 48 months, 60% of the patients remained in the population. Studies with a 48- to 60-month follow-up period are rare, and this study has yielded important insights regarding the use of autogenous bone grafts in MSFE procedures and dental implant placement. Another limitation of this study was that panoramic radiography was used. Cone beam computed tomography (CBCT) is currently more routinely used in research and clinical practice. CBCT provides three-dimensional imaging of structures and other advantages over the traditional two-dimensional panoramic view imaging, particularly for complex diagnostic and surgical applications. In particular, the resorption pattern of maxillary bone grafts in gap situations was discernible after prosthetic loading. Only nine patients who underwent MSFE with maxillary bone grafts were observed for the entire 60-month period. Bone harvesting from the mandible for MSFE was performed more frequently based on the patient's anatomical condition. Despite the choice of bone grafts, there was no correlation between patient non-attendance at the various time points and loss of bone height due to resorption.

The origin of the bone graft (maxilla or mandible) did not significantly affect the preservation of bone height around the implant site over a long-term follow-up. However, solely assessing bone height may not suffice to assess the longevity of dental implants after MSFE procedures.

CONCLUSIONS

This radiologic study showed that over a long-term period there is a similar bone height pattern at dental implant sites and at distal to implant sites when maxillary or mandibular bone grafts are used in MSFE.

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7

General discussion

This thesis evaluated the regenerative performance of calcium phosphate ceramics, with emphasis on the use of biphasic calcium phosphate (BCP) and β-tricalcium phosphate (β-TCP), as well as autogenous bone grafts in maxillary sinus floor elevation (MSFE). The evaluation was based on clinical, radiological, histological, and histomorphometric outcomes at different postoperative time points up to five years. The primary objective was to assess the quality and quantity of bone formation at 6, 9, and 12 months, with a particular focus on graft integration, bone remodeling dynamics, and the preservation of vertical tissue height.

It was demonstrated that BCP, whether used pure or in combination with autogenous bone, integrates with native bone from the floor of the maxillary sinus and functions effectively as a stable, osteoconductive scaffold. Histological analysis at 6, 9, and 12 months revealed distinct phases of bone regeneration following the use of BCP grafts. At 6 months, active bone modeling was evident through the presence of woven bone and osteoid tissue. By 9 months, a clear transition to mature lamellar bone was observed, accompanied by the highest levels of vital bone volume, indicating that this healing time is optimal for dental implant placement. At 12 months, both osteoid volume (OV) and bone volume (BV/TV) fraction declined, while residual BCP remained, suggesting a shift from active osteoblastic bone formation to balanced remodeling. These findings challenge the assumption that longer healing times lead to better outcomes for both quantity and quality of bone tissue, and highlight the importance of carefully timing dental implant placement. The persistent presence of BCP particles throughout all time points confirms its role as a long-term osteoconductive scaffold supporting gradual bone regeneration.

Comparative analyses across graft materials further elucidated differences in performance. BCP demonstrated stable integration with native bone and consistent remodeling behavior over time, supporting its use as a reliable osteoconductive scaffold. Autogenous bone grafts facilitated rapid bone formation during early healing stages but exhibited greater variability in resorption rates, which may allow earlier dental implant placement to benefit more from the mechanical loading [1, 2]. Mixed grafts, consisting of BCP combined with autogenous bone, offered the most balanced profile, achieving both improved spatial bone distribution and greater structural integrity, factors critical to optimizing bone-to-implant contact and primary stability. The presence of osteoid

islands and the ongoing replacement of BCP with vital bone tissue align with previous findings [3, 4], reinforcing the concept that BCP facilitates time-dependent, sustained bone regeneration.

The present thesis contributes to the existing literature on the radiological follow-up of various graft materials used in MSFE by providing long-term data with a follow-up period of up to five years. No dental implants were lost during the five-year follow-up. All graft materials exhibited a gradual loss in augmented tissue height over longer periods. Nevertheless, after a five-year follow-up, we observed that tissue height was best maintained at dental implant sites, whereas more pronounced resorption was observed at inter-implant and free-end locations. This may be explained by a higher degree of resorption in the non-loaded areas compared to the loaded areas with dental implants. Among the materials evaluated, BCP grafts containing hydroxyapatite (HA) demonstrated superior long-term dimensional stability compared to β-TCP-based substitutes, particularly in the context of functional loading by dental implants. Another explanation for the higher tissue level at dental implant sites might be the so-called push-up of tissue during bed preparation. The radiological behavior of bone surrounding dental implants thus reinforced the histological findings, indicating that BCP offers reliable and predictable bone or tissue volume preservation in mechanically loaded regions. These findings confirm the biocompatibility and structural stability of BCP as a grafting material, aligning with the results of previous studies [5-7]. Collectively, these data contribute valuable evidence supporting the clinical utility of BCP in MSFE procedures and highlight the significance of healing duration and dental implant timing in optimizing regenerative capacity and maintaining tissue height.

In this thesis, several bone substitutes were compared on bone quantity and quality, always considering autogenous bone as the gold standard. However, the performance of autogenous bone grafts is not uniform across all cases and varies significantly based on harvesting site, technique, and procedural context [8]. This thesis showed that, over the long term, a similar pattern of bone height loss is observed at both dental implant sites and sites distal to dental implants, when maxillary or mandibular bone grafts are used in MSFE. However, the location of the autogenous bone donor sites may have influenced the quality of the newly formed bone tissue. Cortical and trabecular bone differ significantly in structure and remodeling behavior, which directly influences

graft performance after MSFE. Cortical bone is dense and primarily provides structural stability, undergoing slow remodeling, whereas trabecular bone is porous, highly vascularized, and remodels faster, allowing quicker integration. Clinical studies show that mixed grafts combining cortical and cancellous bone balance these properties by providing both stability and faster bone turnover, with outcomes such as augmented bone height, new bone formation, and dental implant survival rates comparable to autogenous bone, bovine substitutes, and other allografts [5]. This disparity could be due to the difference in vascularization capacity of the newly formed bone tissue.

Although blood vessels play an important role in bone regeneration [9], the studies in this thesis did not include vascularization in the analysis of newly formed bone. Vascular networks not only enable cellular exchange but also deliver oxygen, nutrients, and signaling molecules essential for osteogenesis. As shown by Wu et al., autogenous bone grafts that have better blood vessel growth, like tuberosity bone, show better health and ability to heal than denser graft types like retromolar mandibular bone. These findings highlight the critical role of angiogenesis in facilitating effective bone regeneration [10]. Revascularization and long-term remodeling in bone regeneration following MSFE are significantly influenced by the thickness of autogenous bone grafts. Thin cortical or cancellous grafts (≤1 mm) facilitate rapid vascular ingrowth and reach deep enough to support bone cell survival, while thicker grafts (>3 mm) often may receive insufficient vascular supply, which can lead to tissue death and poor healing results. On the other hand, thicker autogenous blocks (over 3 mm), particularly those made of cortical bone, take longer to develop blood vessels in the center, which raises the chances of tissue death and poor healing results. Ingrowth of blood vessels is also dependent upon anatomical and biological factors in the recipient site, e.g. the degree of vascularization of the surrounding tissues [11-13].

Unexpected histological outcomes in bone volume were observed in the 9- and 12-month healing time groups. We expected higher bone volume in the 12-month healing time group, but a steady state in bone volume is present from nine months healing time onward. This variation may be attributed to differences in initial native bone height between patients treated with a 9-month versus a 12-month healing period following MSFE. Patients in the 9-month group had, on average, a larger baseline bone height than those in the 12-month group (6.4 mm vs. 4.4 mm). This greater baseline

bone height provided more native alveolar bone beneath the graft, which therefore contained more biologically active cells and growth factors that may have influenced the osteogenic response to the grafting material and improved the overall regenerative capacity of the augmented site.

Although the 12-month healing time group achieved a larger increase in tissue height in the grafted area compared to the 9-month healing time group (9.3 mm vs. 7.5 mm), histological analysis revealed a lower percentage of vital bone volume (28.2% vs. 35.2% in the 9-month healing group). Clinically, this highlights the importance of dental implant placement timing, since placing dental implants during peak osteogenic activity, when vital bone mass is highest, may enhance osseointegration and improve long-term dental implant placement success. An aspect that was not investigated and will obviously be difficult to determine is the effect of the drilling for dental implant placement. This mechanical trauma to the bone, blood vessels, and bone substitute might provide a new impulse for bone formation [14, 15].

In this thesis, a standard procedure for MSFE was applied, in which the Schneiderian membrane was elevated and tilted inward and upward. It remains uncertain whether the Schneiderian membrane contributes to new bone formation. The Schneiderian membrane, which lines the maxillary sinus, has been identified as playing a limited yet active role in osteogenesis [16]. Rather than acting solely as a passive barrier, the Schneiderian membrane contains cells and structures that actively contribute to bone regeneration. It can support new bone formation in MSFE even in the absence of graft material [17]. However, its osteogenic capacity is significantly lower compared to that of the surrounding bony walls of the maxillary sinus. Studies in animal models have consistently shown that relocated bony trapdoor and newly formed bone originate primarily from, and are most robust near, the maxillary sinus bone walls [16, 18, 19]. In contrast, bone formation adjacent to the maxillary sinus mucosa, the Schneiderian membrane, is minimal and does not increase over time, indicating only a modest contribution from the membrane.

In this thesis, a mixture of BCP and autogenous bone with a ratio of 50/50 was used in MSFE. In five patients, the addition of autogenous bone did not increase overall bone formation compared with pure BCP, but it did result in a more homogeneous distribution of newly formed bone, which may ultimately improve bone-to-implant

contact. In MSFE procedures, various ratios of autogenous bone to bone substitute have been investigated to balance regenerative effectiveness with clinical feasibility. While 100% autogenous bone provides rapid osteogenesis, its use is limited by possible donor site morbidity and availability [20]. On the other hand, using only bone substitute materials such as BCP offers favorable volume stability and biocompatibility but may delay remodeling due to limited osteoinductivity. As a result, many clinicians employ composite grafts combining autogenous bone with a substitute in ratios ranging from 20/80 to 50/50. A 50/50 ratio is especially common, offering a compromise between the osteogenic properties of autogenous bone and the space-maintaining characteristics of the substitute [21]. Lower ratios of autogenous bone, such as 20/80, have also demonstrated satisfactory outcomes, especially when sufficient healing time is allowed prior to dental implant placement [22]. Ultimately, the choice of ratio depends on clinical parameters, including the volume of augmentation, the availability of sufficient bone graft volume, timing of dental implant placement, and desired balance between regeneration speed and stability. Stability is crucial for successful outcomes in bone augmentation procedures. Therefore, careful consideration of these factors will help clinicians tailor their approach to optimize both the healing process and the functional integration of dental implants.

Beyond the calcium phosphate materials evaluated in this thesis, substantial advances have been made over the past decade in the development of next-generation synthetic bone substitutes. In recent years, calcium phosphate-based bone substitutes for MSFE prior to dental implant placement have advanced substantially. Whereas HA and β-TCP were previously used primarily as relatively passive osteoconductive materials [23], attention has shifted toward BCPs, in which the ratio of HA to β-TCP is carefully adjusted to achieve an optimal balance between volume stability and controlled resorption [23]. Recent systematic reviews have demonstrated that BCPs used in MSFE procedures result in bone formation that is at least comparable to, and in some cases, superior to that achieved with xenogenic graft materials [24, 25]. In addition, new generations of octacalcium phosphate (OCP) and OCP-collagen composites have been developed. Due to their biomimetic structure, these materials mimic the natural transformation to biological apatite and actively promote angiogenesis and osteoblast differentiation [26-28]. Furthermore, injectable calcium phosphate cements and three-dimensional

printed scaffold structures, for example, those enriched with magnesium, strontium, or silicon, have made it possible to precisely optimize both porosity and biological activity [29]. Functionalization with growth factors and stem cells has further shifted these materials from purely osteoconductive fillers to bioactive and partially osteoinductive regenerative systems [30, 31]. As a result, synthetic calcium phosphates have emerged as a predictable and safe alternative to autogenous bone grafts, offering reduced donor-site morbidity and increasing clinical applicability in oral implantology.

LIMITATIONS OF THE STUDIES

In the histological evaluation, the sample sizes of the 6-, 9-, and 12-month healing time studies were small, which may have affected the reliability of the histomorphometric data. However, multiple dental implant placement within each participant provided sufficient material for meaningful evaluation. The 12-month interval between MSFE and dental implant placement is considered relatively long, and most patients are unwilling to wait that long, making such bone samples rare but particularly valuable for long-term analysis. A further limitation of the long-term studies is the reliance on panoramic radiography rather than cone-beam computed tomography (CBCT), which has since become widely adopted in clinical practice. At the time these studies were initiated, panoramic radiographs were the standard of care, and CBCT was not yet routinely available. From today's perspective, this represents a methodological limitation, as CBCT provides considerable advantages, including three-dimensional visualization, improved diagnostic accuracy, more precise surgical planning [32]. It should also be noted that early CBCT and especially CT scans involved substantially higher radiation doses than contemporary CBCT, which may have further restricted their clinical applicability at the time. Consequently, while panoramic radiography allowed for consistent longitudinal evaluation, the absence of CBCT may have limited the precision of vertical height measurements and the detailed assessment of structural bone changes.

In general, the impact of factors such as patient lifestyle, systemic health conditions, and postoperative care on bone graft performance should not be underestimated. Recent literature highlights the role of systemic diseases like diabetes and osteoporosis in influencing bone remodeling and dental implant success rates [33, 34]. To ensure a controlled analysis and minimize confounding variables, most of our studies

implemented inclusion and exclusion criteria. Factors such as smoking, drug use, poor-quality radiographs, complete edentulism, a history of jaw radiation, heart valve prostheses, and endocarditis were carefully considered in the histological studies to reduce bias and improve the reliability of the findings. In the radiological follow-up studies these demographic data were not available, therefore for example, smoking could not be excluded.

CONCLUDING REMARKS

The studies described in this thesis confirm that BCP, whether used as pure BCP or in combination with autogenous bone grafts, is a safe and effective alternative to autogenous bone grafting. The optimal timing for dental implant placement following BCP grafting appears to be nine months, when vital bone volume peaks, at least from a histological and histomorphometric perspective. Adding autogenous bone to BCP improves the uniform distribution of newly formed bone throughout the grafted area, although it does not substantially increase the overall bone volume. Long-term outcomes favor BCP materials with a higher HA ratio because of their superior resistance to resorption compared with β-TCP. While autogenous bone remains biologically superior because of its osteogenic potential, its disadvantages limit its universal application. The findings of this thesis support the increasing use of synthetic bone substitutes as clinically equivalent alternatives. Clinically, these findings also support the wider use of BCP to reduce patient morbidity and surgical complexity while maintaining high dental implant survival rates.

FUTURE PERSPECTIVES

Future research should primarily address the biological and methodological limitations identified in this thesis. The findings presented in this thesis highlight the importance of incorporating histological evaluations into clinical trials assessing grafting materials for MSFE. Histological analysis, feasible without additional patient discomfort through trephine drilling during implant placement, offers important details about bone quality that radiographic assessments alone cannot capture. Future research should prioritize well-designed clinical studies that ideally compare grafting outcomes directly with autogenous bone, the current reference standard, and include histomorphometric data as a key endpoint. This would generate data not only on bone mass but also on

osteoblastic bone formation, osteoclastic bone resorption, and new vessel formation. At the biological level, systematic integration of vascular parameters into MSFE research is imperative. Advanced histological and imaging techniques (e.g. immunohistochemistry for endothelial markers, micro-CT with contrast perfusion) can be used to quantify angiogenesis and correlate vascular density with spatiotemporal patterns of new bone formation, residual graft presence, and dental implant stability.

Methodologically, future clinical studies should move from two-dimensional panoramic assessment towards standardized CBCT-based three-dimensional volumetric analyses with rigid registration, enabling precise quantification of graft resorption, vital bone volume, and localized scalloping around dental implants in both loaded and non-loaded regions. Coupling these imaging data to longitudinal histomorphometry could clarify how radiological "tissue height" can be translated more accurately into biologically meaningful "vital bone height".

Optimizing healing and loading protocols represents another critical avenue. The present data indicate that 9 months may coincide with maximal vital bone volume, whereas 12 months represents a transition towards steady-state remodeling rather than further quantitative gain. Future trials should therefore systematically compare early, conventional, and delayed loading strategies (e.g. 3 vs. 6 vs. 9 months after dental implant placement), stratified by graft type (pure BCP, mixed grafts, autografts) and baseline bone height, and powered for both survival and surrogate endpoints such as marginal bone loss, primary stability, and changes in vital bone fraction. Adaptive loading concepts, in which the decision to load is guided by individualized thresholds (e.g. CBCT-derived bone volume, or biochemical markers of bone turnover), should be explored to replace the current "one-size-fits-all" time-based protocols. In parallel, experimental studies should elucidate the biological impact of early functional loading on graft remodeling and BCP resorption, distinguishing beneficial mechanotransduction from overload-induced microdamage.

In parallel, the development and evaluation of next-generation biomaterials hold considerable promise. Future graft development should focus on "next-generation" ceramics with tunable HA/β-TCP ratios, micro- and macro-porosity, and surface chemistry will be able to better balance resorption with bone formation, possibly in combination with biologics (e.g. bone morphogenetic proteins) or cell-based strategies.

Dedicated studies on the biomechanical and biological impact of implant bed preparation (microfracturing, bleeding, secondary osteogenic stimulus) and the actual osteogenic contribution of the Schneiderian membrane are warranted. Addressing these questions will enable a more individualized, biology-driven planning of graft choice, graft volume, and dental implant timing, thereby mitigating the current shortcomings and optimizing long-term functional and structural outcomes.

Clinically, future efforts should focus on translating these findings into pragmatic, structured treatment protocols for MSFE. Rather than relying on fixed healing intervals, graft selection and timing of dental implant placement and loading should be guided by baseline anatomy (native bone height, maxillary sinus configuration), graft type (BCP, mixed graft, autograft), systemic risk factors, and objective indicators of graft maturation such as ISQ values and CBCT-based volumetric analyses. Prospective comparative studies are needed to define evidence-based thresholds for safe early or immediate loading in grafted maxillary sinuses, while maintaining long-term stability. Ultimately, the clinical objective should be a personalized yet reproducible MSFE workflow in which graft choice, healing duration, and loading strategy are biologically justified, time-efficient, and optimized for long-term function and patient-reported outcomes.

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8

Summary

Samenvatting

SUMMARY

Loss of teeth in the posterior maxilla results in resorption of the alveolar ridge, a physiological process that is further exacerbated by pneumatization of the maxillary sinus. This combination of factors frequently reduces alveolar bone height to the extent that dental implant placement is no longer possible without prior augmentation. Maxillary sinus floor elevation (MSFE) is a widely used and predictable surgical technique to restore sufficient bone volume enabling dental implant placement. Traditionally, autogenous bone grafts are regarded as the gold standard for grafting because of their osteogenic, osteoinductive, and osteoconductive properties. However, considerable disadvantages, including donor site morbidity, restricted availability of harvestable bone, and unpredictable resorption rates, have led to the search for synthetic alternatives. Calcium phosphate ceramics, especially biphasic calcium phosphate (BCP), consisting of hydroxyapatite (HA) and β-tricalcium phosphate (β-TCP), are considered viable alternatives. Their chemical resemblance to natural bone, biocompatibility, and space-maintaining capacity make them ideal for use in MSFE procedures.

In Chapter 1, a general introduction to this topic, including background information and the outline of this thesis, is provided. The studies described in this thesis investigated the performance of BCP, autogenous bone, and a combination of both in MSFE procedures. The combination of clinical, radiological, histological, and histomorphometric analyses was chosen to determine bone quality, quantity, and dimensional stability at different time points, ranging from six to twelve months, as well as long-term radiological outcomes up to five years.

In Chapter 2, we evaluated the quality and quantity of bone formation in MSFE using a fully synthetic BCP (60% HA and 40% β-TCP). A unilateral MSFE procedure was performed in six patients using 100% BCP. Biopsy retrieval for histological and histomorphometric analyses was carried out before dental implant placement after a 6-month healing period.

Uneventful healing was observed in all cases. Radiological evaluation after 6 months showed maintenance of the vertical tissue height gained immediately after MSFE. All dental implants showed good primary stability and appeared to be well osseointegrated after a 3-month healing period. Histological investigation showed no signs of inflammation. Newly formed mineralized tissue was observed cranial to the native alveolar bone. Also, osteoid islands as well as connective tissue were seen around the BCP particles, cranial to the front of newly formed mineralized tissue. Close bone-to-substitute contact was observed. Bone maturation was evident from the presence of lamellar bone. Histomorphometric analysis showed an average bone volume fraction of 27.3% (SD ± 4.9), bone surface to volume ratio 4.5 mm^2/mm^3 (SD ± 1.1), trabecular thickness 132.1 μm (SD ± 38.4), osteoid volume/bone volume 7.5% (SD ± 4.3), osteoid surface/bone surface 41.3% (SD ± 28.5), osteoid thickness 13.3 μm (SD ± 4.7) and number of osteoclasts per total area 4.4 $1/mm^2$ (SD ± 5.7).

This study provides radiological and histological evidence confirming the osteoconductive properties of BCP and its ability to provide a scaffold for new bone formation, allowing subsequent dental implant placement after a 6-month healing period.

In Chapter 3, we evaluated the clinical, radiological, histological, and histomorphometric aspects of BCP (60% HA and 40% β-TCP) used in an MSFE procedure with 9- and 12-month healing times. A unilateral MSFE procedure using 100% BCP was performed in two series of five patients with healing times of 9 and 12 months, respectively. Clinical and radiological parameters were measured up to 5 years postoperatively. Histological and histomorphometric analyses were performed on bone biopsies retrieved during dental implant placement.

Uneventful healing was observed in all cases. All dental implants appeared to be well osseointegrated after 3 months. Radiological evaluation showed less than 1 mm of tissue height loss from MSFE to the 5-year follow-up examination. No signs of inflammation were detected on histological examination. Newly formed mineralized tissue was found cranial to the native bone. The BCP particles were surrounded by connective tissue, osteoid islands, and newly formed bone. Mineralized bone tissue was in intimate contact with the BCP particles. After 12 months, remnants of BCP were still present. The newly formed bone had a trabecular structure. Bone maturation was demonstrated by the presence of lamellar bone. Histomorphometric analysis showed that, at 9 and 12 months, respectively, the average vital bone volume was 35.2% and

28.2%, the bone surface fraction was 4.2 mm^2/mm^3 and 8.3 mm^2/mm^3, the trabecular thickness was 224.7 μm and 66.7 μm, the osteoid volume/bone volume was 8.8% and 3.4%, the osteoid surface/bone surface was 42.4% and 8.2%, and the osteoid thickness was 93.9 μm and 13.6 μm.

It was concluded from this study that MSFE with BCP resulted in new bone formation within the augmented sinus floor and allowed the osseointegration of dental implants in both groups. At nine months, the biopsies showed the highest vital bone tissue volume and a transition from woven to lamellar bone, suggesting a nine-month healing time as the optimal moment for dental implant placement. After twelve months, bone tissue volume stabilized, osteoid fractions declined, and remodeling progressed over areas of active bone formation, while residual BCP particles remained present. These results challenge the assumption that longer healing times necessarily improve regenerative outcomes and highlight the importance of timing dental implant placement when osteogenic activity is at its peak.

In the study described in Chapter 4, it was evaluated whether autogenous bone 1:1 mixed with BCP (60% HA and 40% β-TCP) used in an MSFE procedure leads to improved bone formation compared with the use of pure BCP. In five patients a unilateral MSFE was performed. Histological and histomorphometric analyses were performed on bone biopsies obtained 6 months after MSFE during dental implant surgery.

The average vital bone volume was 29.9% of the total volume (SD ± 10.1), of which 7.1% was osteoid volume (SD ± 4.8). The osteoid surface covered 26.0% (SD ± 13.4) of the bone surface. The bone surface fraction was 4.7 mm^2/mm^3 (SD ± 2.3). Compared with the previous studies, the analyses showed differences in trabecular thickness and osteoid surface, but not in bone volume, osteoid volume, or the number of osteoclasts.

It was concluded from this study that MSFE using autogenous bone mixed with BCP showed an amount of newly formed bone that is comparable with the findings from the previously published 6-month study with pure BCP (Chapter 2). However, a more uniform distribution of new bone throughout the entire biopsy was observed, which may enhance dental implant integration and long-term stability.

In Chapter 5, a study is presented evaluating the radiological changes in tissue height after MSFE using three types of calcium phosphate ceramics over a period of up to 5 years after dental implant placement. In 163 patients MSFE was performed. Three groups of patients were distinguished and treated based on the type of calcium phosphate ceramic used and radiologically evaluated: 40 patients with 100% β-TCP, 76 patients with BCP (20% HA and 80% β-TCP), and 47 patients with BCP (60% HA and 40% β-TCP). Radiological measurements were performed on panoramic radiographs at different time points up to 5 years after dental implant placement.

After MSFE, a slow decrease in tissue height measured over time was observed in all three study groups. Resorption of the grafted bone substitutes was more prominent in β-TCP than in BCP ceramics with an HA component (60/40 and 20/80). Tissue height loss after 5 years was lowest in the BCP 60/40 group and highest in the 100% β-TCP group.

This radiological study showed a predictable and comparable pattern with a slow decrease in tissue height over time for all three types of calcium phosphate ceramics used in MSFE, demonstrating a natural remodeling process. However, β-TCP resorbed more rapidly, leading to greater tissue height loss, whereas BCP with 60% HA and 40% β-TCP exhibited superior dimensional stability, particularly at dental implant sites. The fraction of HA in calcium phosphate ceramics and dental implant loading, seems to be beneficial for tissue height maintenance after MSFE and for long-term performance.

The study described in Chapter 6 aimed to assess the impact of maxillary and mandibular autogenous bone grafts on maxillary bone height in patients who underwent MSFE. Ninety-two patients were included in this study divided into two groups: 37 patients receiving maxillary bone grafts for MSFE and 55 patients receiving mandibular bone grafts for MSFE. Bone height after MSFE was measured on panoramic radiographs at different time points up to 60 months postoperatively, with comparisons made across different positions and clinical situations.

In general, both maxillary and mandibular bone grafts resulted in an increase in bone height directly after the MSFE procedure, followed by a gradual bone height loss over

time, with no significant differences between the two groups at gap and free-end positions. However, at distal to the implant positions, mandibular bone grafts showed less bone loss. Despite the gradual bone height loss, all dental implants remained fully covered by bone without exposure or subsequent loss, indicating successful MSFE procedures.

It was concluded from this radiologic study that over a long-term period there is a similar bone height pattern at dental implant sites and sites distal to the dental implants when maxillary or mandibular bone grafts are used in MSFE. At all follow-up time points, dental implants placed after MSFE demonstrated full survival rates with no dental implant losses reported.

In Chapter 7, the results of the studies described in this thesis (Chapters 2-6) and their clinical relevance are discussed from a broader perspective in relation to the existing literature, and recommendations for further research are presented.

The studies described in this thesis confirm that BCP, whether used as pure BCP or in combination with autogenous bone grafts, is a safe and effective alternative to autogenous bone grafting. The optimal timing for dental implant placement following BCP grafting appears to be nine months, when vital bone volume peaks, at least from a histological and histomorphometric perspective. Adding autogenous bone to BCP improves the uniform distribution of newly formed bone throughout the grafted area, although it does not substantially increase the overall bone volume. Long-term outcomes favor BCP materials with a higher HA ratio because of their superior resistance to resorption compared with β-TCP. While autogenous bone remains biologically superior because of its osteogenic potential, its disadvantages limit its universal application. The findings of this thesis support the increasing use of synthetic bone substitutes as clinically equivalent alternatives. Clinically, these findings also support the wider use of BCP to reduce patient morbidity and surgical complexity while maintaining high dental implant survival rates.

Future research should focus on enhancing biomaterial performance by incorporating biologically active molecules or stem cells, improving increased vascularization, and

accelerating the replacement of graft material with vital bone. Advanced imaging techniques, such as cone-beam CT and micro-CT, have the potential to improve longitudinal assessment of graft integration. Ultimately, large multicenter trials with standardized protocols are essential to establish definitive clinical guidelines.

In conclusion, based on the studies presented in this thesis, BCP appears to be a reliable and predictable grafting material (although not the gold standard) for MSFE procedures, providing outcomes comparable to those achieved with autogenous bone grafts while avoiding their associated disadvantages. These findings emphasize the importance of graft composition, healing time, and dental implant loading in determining long-term success and contribute to contemporary maxillary sinus augmentation procedures.

SAMENVATTING

Verlies van gebitselementen in de zijdelingse delen van de bovenkaak leidt tot fysiologische resorptie en daarmee tot een volumevermindering van de processus alveolaris. Een afname van de alveolaire bothoogte die ook nog kan worden versterkt door pneumatisatie van de sinus maxillaris, verhindert het plaatsen van tandwortelimplantaten. De verhoging van de bodem van de sinus maxillaris, een zogenaamde sinusbodemelevatie (SBE), is een veel toegepaste en gestandaardiseerde chirurgische techniek om voldoende kaakbothoogte te verkrijgen om het plaatsen van tandwortelimplantaten wel mogelijk te maken. Traditioneel geldt autoloog bot als de gouden standaard voor bottransplantatie vanwege de osteogene, osteo-inductieve en osteoconductieve eigenschappen. Daartegenover staan echter nadelen, zoals de morbiditeit ter plaatse van de donorplaats, de beperkte beschikbaarheid van donorbot en de onvoorspelbare mate van resorptie van het bottransplantaat. Deze nadelen hebben geleid tot de ontwikkeling van synthetische botsubstituten. Calciumfosfaatkeramieken, met name bifasisch calciumfosfaat (BCP), bestaande uit hydroxyapatiet (HA) en β-tricalciumfosfaat (β-TCP), worden beschouwd als geschikte alternatieven voor autologe bottransplantaten. Hun chemische overeenkomst met natuurlijk bot, biocompatibiliteit en ruimtebehoudend vermogen maken ze bijzonder geschikt voor toepassing bij het uitvoeren van een SBE.

In hoofdstuk 1 wordt een algemene introductie gegeven op het hierboven beschreven onderwerp en wordt de opzet van dit proefschrift nader uiteengezet. In de studies die in dit proefschrift worden beschreven, werd het biologische gedrag van een BCP, autoloog bot en combinaties ervan onderzocht, waarbij de SBE als onderzoeksmodel werd gebruikt. Hierbij werden klinische, radiologische, histologische en histomorfometrische analyses met elkaar gecombineerd om de botkwaliteit, botkwantiteit en dimensionale stabiliteit te bestuderen op verschillende tijdstippen, variërend van zes tot twaalf maanden. Ook de radiologische uitkomsten op de langere termijn, tot vijf jaar na de behandeling, werden onderzocht.

In hoofdstuk 2 wordt een onderzoek beschreven, waarin bij zes patiënten de kwaliteit en kwantiteit van botvorming werden geëvalueerd zes maanden na een SBE met een volledig synthetisch BCP bestaande uit 60% HA en 40% β-TCP. Voorafgaande aan de plaatsing

van de tandwortelimplantaten werden met behulp van een trepaanboor botbiopten uit de geaugmenteerde regio's genomen voor histologische en histomorfometrische analyses.
Bij alle patiënten verliep de genezing ongecompliceerd. Beeldvorming na zes maanden toonde aan dat de direct na de SBE gerealiseerde verticale weefselhoogte behouden bleef. Alle tandwortelimplantaten lieten na een genezingsperiode van drie maanden een goede stabiliteit en integratie zien. Histologisch onderzoek toonde geen tekenen van ontsteking. Nieuwgevormd gemineraliseerd botweefsel werd waargenomen craniaal van het oorspronkelijke kaakbot. Daarnaast werden eilanden van osteoïd en bindweefsel rondom de BCP-partikels gezien, vóór het front van nieuwgevormd gemineraliseerd weefsel, evenals direct contact tussen bot en botsubstituut. De aanwezigheid van lamellair bot wees op voortgaande botmaturatie. Bij histomorfometrisch onderzoek werd het volgende waargenomen: een gemiddeld botvolumepercentage van 27,3% (SD ± 4,9), een botoppervlak-volumeverhouding van 4,5 mm^2/mm^3 (SD ± 1,1), een trabekeldikte van 132,1 µm (SD ± 38,4), een osteoïdvolume/botvolume van 7,5% (SD ± 4,3), een osteoïdoppervlak/botoppervlak van 41,3% (SD ± 28,5), een osteoïddikte van 13,3 µm (SD ± 4,7) en een aantal osteoclasten per totaal oppervlak van 4,4/mm^2 (SD ± 5,7).
Deze studie levert radiologisch en histologisch bewijs voor de osteoconductieve eigenschappen van bovengenoemd type BCP en geeft aan dat het materiaal een geschikte matrix vormt voor nieuwe botvorming na een SBE-procedure, hetgeen het plaatsen van tandwortelimplantaten mogelijk maakt na een genezingsperiode van zes maanden.

In hoofdstuk 3 wordt een onderzoek beschreven, waarin de klinische, radiologische, histologische en histomorfometrische aspecten van BCP (60% HA en 40% β-TCP) werden onderzocht na een SBE-procedure, met een genezingsperiode van negen en twaalf maanden. Twee series van ieder vijf patiënten ondergingen een unilaterale SBE met 100% BCP, gevolgd door negen respectievelijk twaalf maanden genezing. Klinische en radiologische parameters werden gevolgd tot vijf jaar postoperatief. Histologische en histomorfometrische analyses werden uitgevoerd op botbiopten die voorafgaande aan de plaatsing van de tandwortelimplantaten werden verkregen.
Bij alle patiënten verliep de genezing ongecompliceerd. Alle tandwortelimplantaten lieten na drie maanden een goede integratie zien. Radiologische evaluatie, vijf jaar na

de SBE, toonde een verlies van minder dan een millimeter weefselhoogte. Histologisch werden geen tekenen van ontsteking waargenomen. Nieuwgevormd gemineraliseerd weefsel werd aangetroffen craniaal van het oorspronkelijke alveolaire bot. De BCP-deeltjes waren omgeven door bindweefsel, eilanden van osteoïd en nieuwgevormd bot. Gemineraliseerd bot stond in direct contact met de BCP-partikels. Na twaalf maanden waren nog restdeeltjes van BCP aanwezig. Het nieuwgevormde bot had een trabeculaire structuur en toonde kenmerken van maturatie door de aanwezigheid van lamellair bot.
Histomorfometrische analyse liet zien dat na respectievelijk negen en twaalf maanden het gemiddelde vitale botvolume 35,2% en 28,2% bedroeg, het botoppervlak 4,2 mm^2/mm^3 en 8,3 mm^2/mm^3, de trabekeldikte 224,7 µm en 66,7 µm, het osteoïdvolume/botvolume 8,8% en 3,4%, het osteoïdoppervlak/botoppervlak 42,4% en 8,2%, en de osteoïddikte 93,9 µm en 13,6 µm.
Er werd geconcludeerd dat een SBE met BCP resulteerde in nieuwe botvorming binnen het geaugmenteerde gebied en integratie van tandwortelimplantaten mogelijk maakte, zowel na negen als na twaalf maanden. Na negen maanden werd het hoogste volume vitaal bot waargenomen, met een overgang van gevlochten naar lamellair bot en van snelle botvorming naar botremodellering, hetgeen suggereert dat een genezingsperiode van negen maanden optimaal lijkt te zijn voor het plaatsen van tandwortelimplantaten. Na twaalf maanden stabiliseerde het botvolume, namen de osteoïdfracties af en zette de botombouw zich voort, terwijl restdeeltjes van BCP aanwezig bleven. Deze resultaten tonen aan dat een langere genezingsduur niet noodzakelijkerwijs leidt tot een verbeterde botregeneratie en benadrukken het belang van het juiste tijdstip voor het plaatsen van tandwortelimplantaten tijdens de piek van osteogene activiteit.

In hoofdstuk 4 wordt een studie beschreven, waarin werd onderzocht of autoloog bot gemengd in een verhouding van 1:1 met BCP (60% HA en 40% β-TCP) leidt tot meer botvorming in vergelijking met 100% BCP. Bij vijf patiënten werd een unilaterale SBE uitgevoerd. Histologie en histomorfometrie zes maanden na de ingreep toonden een gemiddeld vitaal botvolume van 29,9% van het totale volume (SD ± 10,1), waarvan 7,1% osteoïdvolume was (SD ± 4,8). Het osteoïdoppervlak bedroeg 26,0% (SD ± 13,4) van het botoppervlak. De botoppervlakfractie bedroeg 4,7 mm^2/mm^3 (SD ± 2,3). Vergeleken met eerdere studies werden verschillen gevonden in trabekeldikte en

osteoïdoppervlak, maar niet in botvolume, osteoïdvolume of het aantal osteoclasten.
Er werd geconcludeerd dat een SBE met een mengsel van autoloog bot en BCP een vergelijkbare hoeveelheid nieuwgevormd bot opleverde als de eerder gepubliceerde zesmaandenstudie met 100% BCP. Dit nieuwgevormde bot had wel een meer homogene verdeling in het geaugmenteerde gebied, hetgeen mogelijk gunstig is voor de integratie van tandwortelimplantaten en de stabiliteit op de langere termijn.

In hoofdstuk 5 wordt een studie gepresenteerd, waarin bij 163 patiënten de radiologische veranderingen in weefselhoogte werden geëvalueerd na een SBE met drie typen calciumfosfaatkeramieken, te weten: β-TCP, BCP (20% HA en 80% β-TCP) en BCP (60% HA en 40% β-TCP) gedurende een periode van vijf jaar na het plaatsen van de tandwortelimplantaten. Drie patiëntengroepen werden onderscheiden: 40 patiënten met 100% β-TCP, 76 patiënten met BCP (20% HA en 80% β-TCP) en 47 patiënten met BCP (60% HA en 40% β-TCP). De weefselhoogte werd gemeten op panoramische röntgenopnamen op verschillende tijdstippen tot vijf jaar na het plaatsen van de tandwortelimplantaten.
Na een SBE werd in alle drie patiëntengroepen een geleidelijke afname van de weefselhoogte waargenomen. Na vijf jaar was het verlies aan weefselhoogte het kleinst in de BCP 60/40-groep en het grootst in de groep met 100% β-TCP.
Deze studie toonde een voorspelbaar en vergelijkbaar patroon van geleidelijke afname van de weefselhoogte bij het gebruik van de drie bovengenoemde materialen, passend bij het natuurlijke botombouwproces. β-TCP resorbeerde echter sneller, hetgeen leidde tot meer hoogteverlies, terwijl BCP 60/40 de grootste dimensionale stabiliteit vertoonde, met name ter plaatse van de tandwortelimplantaten. Een groter aandeel van HA in calciumfosfaatkeramieken en de fysieke belasting van tandwortelimplantaten lijken gunstig te zijn, als het gaat om het behoud van weefselhoogte na een SBE en voor de uitkomsten op langere termijn.

In hoofdstuk 6 wordt een onderzoek beschreven, waarin de invloed van autologe bottransplantaten, afkomstig van de maxilla en mandibula, op de bothoogte van de bovenkaak na een SBE werd onderzocht. In deze studie werden 92 patiënten geïncludeerd: 37 patiënten kregen een bottransplantaat uit de maxilla en 55 patiënten kregen een bottransplantaat afkomstig van de mandibula. De bothoogte werd gemeten

op panoramische röntgenopnamen op verschillende tijdstippen tot zestig maanden na plaatsing van de tandwortelimplantaten.
Over het algemeen resulteerden beide typen bottransplantaten in een toename van de bothoogte direct na de SBE, gevolgd door een geleidelijk verlies van bothoogte in de tijd. Er werden geen significante verschillen gevonden tussen beide groepen ter plaatse van "gap"- en vrij-eindigende posities. Distaal van de tandwortelimplantaten toonden mandibulaire bottransplantaten echter minder botverlies. Ondanks het geleidelijke verlies van bothoogte bleven alle tandwortelimplantaten volledig door bot bedekt, zonder blootstelling of verlies van de betreffende implantaten, hetgeen wijst op succesvolle SBE-procedures.
Uit deze studie werd geconcludeerd dat op lange termijn een vergelijkbaar patroon van bothoogte bestaat ter plaatse van de tandwortelimplantaten en distaal van de tandwortelimplantaten, wanneer bottransplantaten afkomstig van de maxilla of mandibula worden toegepast bij SBE-procedures. Tijdens alle follow-upmomenten toonden de tandwortelimplantaten een hoog succespercentage.

In hoofdstuk 7 worden in een algemene discussie de belangrijkste resultaten van de studies die zijn beschreven in de hoofdstukken 2 tot en met 6, en de klinische relevantie ervan besproken. Tevens worden aanbevelingen voor toekomstig onderzoek gedaan.

De studies in dit proefschrift bevestigen dat BCP, zowel toegepast als puur materiaal als in combinatie met autoloog bot, bij een SBE een veilig en effectief alternatief vormt voor autologe bottransplantaten. Het optimale tijdstip voor het plaatsen van tandwortelimplantaten na toepassing van BCP bij een SBE lijkt vanuit histologisch en histomorfometrisch perspectief rond negen maanden te liggen, wanneer het vitale botvolume zijn maximum bereikt. Het toevoegen van autoloog bot aan BCP bevordert een meer gelijkmatige verdeling van nieuwgevormd bot binnen de geaugmenteerde regio, maar leidt niet per se tot een substantiële toename van het totale botvolume. Op lange termijn tonen BCP-materialen met een hogere HA-fractie een betere stabiliteit door hun grotere weerstand tegen resorptie in vergelijking met β-TCP. Hoewel autoloog bot biologisch gezien superieur blijft vanwege zijn osteogene potentieel, beperken de praktische nadelen de universele toepasbaarheid ervan.
Vanuit klinisch perspectief ondersteunen deze bevindingen een bredere toepassing van

BCP ter vermindering van patiëntmorbiditeit en chirurgische complexiteit, bij hoge succespercentages van tandwortelimplantaten.

Toekomstig onderzoek dient zich te richten op verdere verbetering van biomaterialen door toevoeging van biologisch actieve moleculen of stamcellen, stimulering van de (micro)vascularisatie en versnelling van de omzetting van het transplantatiemateriaal in vitaal bot. Geavanceerde beeldvormingstechnieken, zoals cone-beam CT en micro-CT, bieden mogelijkheden voor een betere longitudinale beoordeling van de integratie van transplantatiematerialen. Uiteindelijk zijn grootschalige multicenterstudies met gestandaardiseerde protocollen noodzakelijk om uniforme klinische richtlijnen vast te stellen.

Concluderend toont dit proefschrift aan dat BCP een betrouwbaar en voorspelbaar transplantatiemateriaal is voor SBE-procedures, met klinische resultaten die vergelijkbaar zijn met het gebruik van autologe bottransplantaten, maar zonder de daaraan verbonden nadelen. De bevindingen benadrukken het belang van de samenstelling van het transplantatiemateriaal, de genezingsduur en de belasting van tandwortelimplantaten voor het succes op de lange termijn, en dragen bij aan de verdere ontwikkeling van de hedendaagse SBE-procedures.



9

List of abbreviations
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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
ASBMR	American Society for Bone and Mineral Research
ASC	Adipose-derived stromal/stem cells
BCP	Biphasic calcium phosphate
BIC	Bone-to-implant contact
BPM	Bone perimeter
cm^3	Cubic centimeter
CaP	Calcium Phosphate
CBCT	Cone beam computed tomography
CE	Conformité Européenne (European Conformity)
CT	Computed tomography
DBBM	Demineralized bovine bone mineral
g	Gram
h	Hour
HA	Hydroxyapatite
mg	Milligram
mL	Milliliter
mm	Millimeter
mm^2	Square millimeter
mm^3	Cubic millimeter
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cells
MSFE	Maxillary sinus floor elevation
NA	Not available
ns	Not significant
p-value	Null hypothesis significance testing
SBC	Straumann® Bone Ceramic
SD	Standard deviation ±
SLA	Sandblasted, large grit, acid-etched
SVF	Stromal vascular fraction
TCP	Tricalcium phosphate

TRAP	Tartrate-resistant acid phosphatase
w/w	Weight-based
β-TCP/beta-TCP	β-tricalcium phosphate
µm	Micrometer

Histomorphometric indices

BV	Bone volume
BV/TV	Bone volume/total volume
BS	Bone surface
BS/TV	Bone surface /total volume
N.Oc	Number of osteoclasts
N.Oc/Tar	Number of osteoclasts/total area
O.Th	Osteoid thickness
OS/BS	Osteoid surface/bone surface
OV/BV	Osteoid volume/bone volume
OS	Osteoid surface
OV	Osteoid volume
Tb.Th	Trabecular thickness

CHAPTER INFORMATION AND CONTRIBUTING AUTHORS

Chapter 2

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Bouwman WF, Bravenboer N, ten Bruggenkate CM, Frenken JWFH, Schulten EAJM. The use of a biphasic calcium phosphate in a maxillary sinus floor elevation procedure: a clinical, radiological, histological, and histomorphometric evaluation with 9- and 12-month healing times. International Journal of Implant Dentistry 2017; 3(1): 34

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OVER DE AUTEUR

Wilhelmus Franciscus Bouwman
Geboren op 7 januari 1954

Na het afronden van de middelbare school aan het Keizer Karel College in Amstelveen studeerde Wilhelmus Franciscus Bouwman geneeskunde en tandheelkunde aan de Vrije Universiteit Amsterdam. Tijdens zijn studie tandheelkunde en na zijn afstuderen als tandarts was hij werkzaam op de afdeling Mondziekten, Kaak- en Aangezichtschirurgie en op de operatiekamer van het ziekenhuis in Leiderdorp. Na enkele jaren als tandarts en OK-assistent te hebben gewerkt, volgde hij aan de Vrije Universiteit Amsterdam de opleiding tot mond-, kaak- en aangezichtschirurg (MKA-chirurg). Opleider prof. dr. I. van der Waal.

Na zijn pensionering op 1 januari 2024 bleef hij als waarnemend MKA-chirurg werkzaam op verschillende locaties.

Naast zijn werk heeft hij een grote belangstelling voor muziek en autosport. Na jarenlang actief te zijn geweest in de kartsport, richt hij zich tegenwoordig op het rijden van rally's met een youngtimer-rallyauto.