Graftless sinus floor augmentation of the highly atrophic posterior maxilla before implant placement

GRAFTLESS SINUS FLOOR AUGMENTATION OF THE HIGHLY ATROPHIC POSTERIOR MAXILLA BEFORE IMPLANT PLACEMENT

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DISSERTATION

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CONTENTS

Voor mijn ouders.

CHAPTER 1

INTRODUCTION

INTRODUCTION

In surgical dentistry and maxillofacial surgery dental implantology has developed to an extremely reliable and predictable clinical routine treatment, especially for those patients with an adequate amount of bone with regard to height and width. Unfortunately, these conditions are not always met. At the same time, even patients whose initial bony situation does not permit the insertion of implants would like to see an improvement in function and aesthetics; they even expect it as a matter of course.

Implant based prosthetic rehabilitations are an integral part of modern dentistry today. Since its introduction on a scientific basis at the beginning of the 1960s, implantology has been continuously developed[1]. With increasing patient demands, better radiological diagnostics and virtual planning, various augmentation procedures have developed in parallel, which can make implant placement possible even in prosthetically difficult initial situations. Today, implant prosthetic reconstructions are often only possible thanks to different augmentation procedures[2].

Over the past 25 years, various techniques and materials have been recommended for the reconstruction of alveolar ridge defects, including autogenous, allogeneic, xenogeneic and alloplastic bone grafting[3]. Despite the progress in the development of allogeneic and alloplastic materials, despite the development of guided bone regeneration (GBR)-techniques, despite intensive research, an incredible number of publications and results in this field, the reproducibility of such techniques remains limited compared to autogenous bone, which is still considered the gold standard[4]. Autogenous bone offers both mechanical and osteoinductive properties that no allogeneic, alloplastic or xenogeneic material has been able to achieve to date[5-7].

Advancing research and a growing understanding of the biological processes involved in bone healing, regeneration and remodeling in conjunction with transplantation procedures have made it possible to treat almost every patient with an implant-prosthetic restoration. Today, the alveolar process can be restored functionally to such an extent that successful and correct implant placement is possible even in cases where the bone is highly atrophied. Long-term results of such implants placed in augmented bone differ only slightly from those in non-augmented bone[3].

Various techniques are available for augmentation[8]. Depending on the existing situation and indication and on the basis of an adequate diagnosis, the various possibilities range from minimally invasive procedures with locally harvested bone grafts under local anesthesia to complex reconstruction procedures based on 3D planning and restoration of the jaw or alveolar ridge with free or microsurgical tissue grafts[9].

The cells of bone metabolism

Processes of bone metabolism are complex. A multitude of mediators, hormones, cells and metabolic products are involved in these lifelong processes of bone apposition and resorption. The most important cell groups are osteoblasts, osteocytes and osteoclasts[10, 11] (Fig. 1).

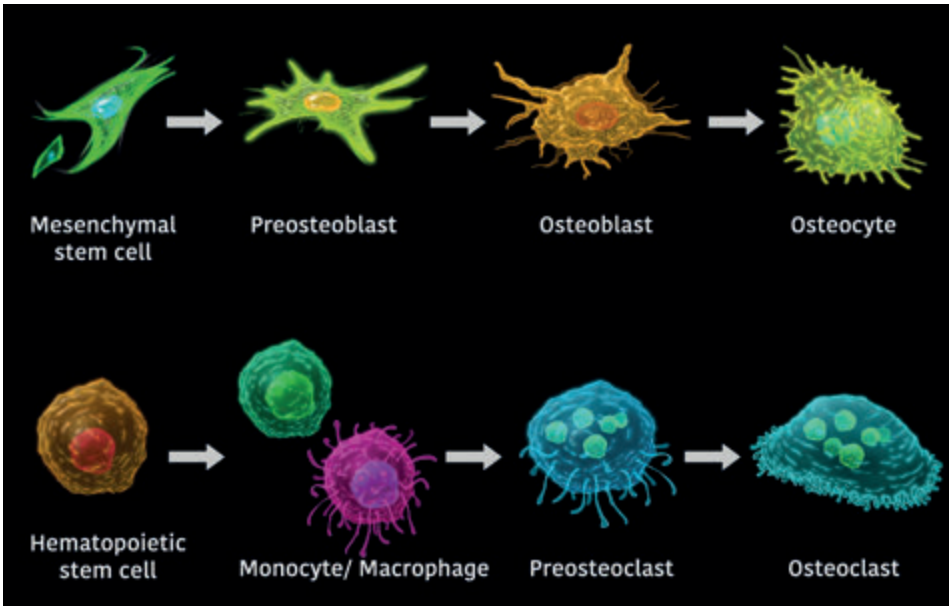

Figure 1. *Upper: Mesenchymal stem cell differentiation into an osteoblast and later in an osteocyte. Lower: Hematopoietic stem cell differentiation into an osteoclast.*

Osteoblasts

Osteoblasts arise from pluripotent mesenchymal precursor cells (Fig. 1). The differentiation is regulated by endocrine, paracrine and autocrine factors[10]. During bone formation they produce the bone matrix from which the hard substance is formed by mineralization processes. In the course of the bone remodeling processes

(Fig. 2), the osteoblasts are walled into the bone matrix and escape into metabolically less active osteocytes. As such, they do not lie in the bone dormant dependent on nutritional support by diffusion, but control ion transport via gap junctions of the cytoplasmic extensions. This is an indispensable factor for bone nutrition and various exchange processes, since a pure diffusion exchange through the mineralized matrix is not possible. The limitation of the ion transport to about 100µm limits the size of osteons to this distance. Thus osteons form not only a structural unit but also a metabolic unit. Flattened osteoblasts lying on the surface of the bone trabecula are also called 'resting osteoblasts' or 'bone lining cells'. In addition to their involvement in the metabolic activity of the bone, they are also thought to have a barrier function and to control the flow of ions between the bone and the extraosseous space. They also play a role in regulating bone resorption by releasing mediators which, in contrast with the resting bone lining cells, free the surface for the osteoclasts and activate them for resorption[12].

Osteocytes

Osteocytes constitute more than 90% of adult bone cells and play a crucial role in the determination and maintenance of bone structure[13, 14]. Cell biological examinations of the osteocytes are difficult because the osteocytes are embedded in hard bone tissue. A much greater focus is placed on investigations of the superficial bone-building and bone-destroying cells, the osteoblasts and osteoclasts. Mikuni-Takagaki[15] was one of the first to succeed in preparing osteocytes freely from the bone matrix. However, it was the cultivation of osteocyte cell lines that enabled the systematic investigation of these cells.

Osteocytes are terminally differentiated cells, derived from mature, matrix(osteoid)-producing osteoblasts. According to Manolagas[16], osteoblasts show three typical behaviors: They transform into osteocytes, become 'bone lining cells' or undergo apoptosis. Osteocytes surround themselves with a matrix of hydroxyapatite, a process we call mineralization beginning with osteoid deposition at the bone surface. During this process they develop their typical dendritic extensions, which remain in contact with other embedded osteocytes. This creates a lacuno-canalicular system typical for cortical and cancellous bone[13].

Knowledge has been gained from research efforts on osteoporosis and the medication related osteonecrosis of the jaw (MRONJ). Aging, but obviously also medication, leads to a decrease in the interconnection of osteocytes[17-20]. The loss of connectivity is probably due to cell death, apoptosis and autophagy. The loss of osteocytes leads to a loss of control in the activity balance between osteoblasts and osteoclasts. In

aging bones there is an excess of bone resorption, which goes far beyond the extent of bone growth. Farr et al.[21] found that osteocytes in aged mice express increased markers that lead to increased osteoclast activity with bone resorption.

Constant mechanical overloading of bone can also contribute to the expression of markers via micro trauma, resulting in increased bone resorption. On the other hand, osteocytes send out signals via the RANKL (receptor activator of nuclear factor-κB ligand) pathway to keep bone apposition and resorption in balance. Loss of RANKL communication leads to bone apposition[11].

It is now assumed that the long life span of osteocytes is also associated with their central function in bone metabolism. Via the dendrites, the osteocytes build up a finely branched network of sensors that can react sensitively to mechanical stress of all kinds. Considering that the total surface area of the lacuno-canalicular system is about 215m^2, the central role of osteocytes can also be understood in terms of calcium balance[22].

The control of the osteoclasts seems to take place via excretory functions, with RANKL again playing a role. RANKL is released via the dendritic extensions in close neighborhood to osteoclastic precursor cells stimulating cell differentiation and cell function. Furthermore osteoblastic-osteoclastic repair units are attracted by the secretion of osteocytic RANKL to remodel bone defects[23, 24].

The RANKL-mediated pathway controlling osteoclastic cell function by osteocytes directly, has an indirect effect on osteoblastic cell stimulation by osteoclastic-osteoblastic interaction. The direct effects of osteocytes on osteoblasts are mediated through the production and secretion of several stimulatory and inhibiting factors, among them growth factors as e.g. IGF-1 (insulin-like growth factor-1), glycoproteins as e.g. Wnt (Wingless-int), and nucleotides, such as ATP (adenosine triphosphate)[10, 25-29]. So osteoid formation, osteoblastogenesis, osteoblastic and osteoclastic activity are regulated by processes mediated by the osteocyte[30].

Osteoclasts

In contrast to the osteoblasts, the osteoclasts do not originate from mesenchymal, but from hematopoietic stem cells[10, 11, 30]. Their origin from granulocyte-macrophage progenitor cells seems particularly probable. Osteoclasts and their bone resorbing function are dependent on two key cytokines, RANKL and M-CSF (monocyte-colony stimulation factor). As mentioned before RANKL controls the differentiation process of osteoclasts. M-CSF plays a role in the proliferation of the osteoclast progenitors[10]. The osteoclasts form a group of giant cells specialized in the degradation of calcified

tissues. They are found in the so-called Howship lacunae, resorption lagoons in hard tissue, and show a positive acid-phosphatase reaction[31]. With a cell size of 30 to 100μm they have a number of about 3 to 30 nuclei. In the acidophilic cytoplasm, vacuoles indicate the active degradation process.

The marginal area of the osteoclasts, the clear zone, is located in the vicinity of the calcified tissue[12]. The central part of the giant cell shows an enlargement of the cell surface, the so-called 'ruffled border', which is caused by the invaginations of the cell membrane. At this enlarged surface, protons are released, which lower the pH value and thus can dissolve hard tissues. The collagen fibers exposed after the hydroxyapatite is dissolved are then broken down by lysosomal enzymes and collagenases[32].

Two different differentiation pathways have been identified for osteoclasts: One is dependent on interaction with osteoblasts and osteocytes and explains the alternating process of bone degradation and build-up, which occurs during physiological bone remodeling[12]. The second pathway is controlled by cytokines released during inflammation or trauma and is related to bone loss in pathological events. Of the inflammatory mediators, interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) are particularly relevant in oral and maxillofacial surgery[33, 34]. Investigations in recent years have shown that some patients suffer from an increased release of these mediators and thus increased bone resorption in response to inflammatory stimuli[35].

Bone remodeling – Physiological principles of bone formation and bone healing

During embryonic and post-embryonic development, the human skeleton consists of partially cartilaginous tissue and partially of connective tissue. The reason for the different preformation and phylogenetic development is that in the phylogenetic series from lower to higher developed animals, an apparent development from a cartilaginous to a more desmal ossification mode of the same skeletal part can be observed. The lower jaw is cartilaginous in the embryonic phase as part of the gill arch skeleton. In the human embryo the so-called Meckel's cartilage induces the development of an overlapping bone, the mandible[36]. Regardless of its primary structure, the bony maturation follows a desmal ossification mode, as do most of the other skeletal elements of the midface and especially the cranium.

Three types of embryological bone formation can thus be distinguished: 1) secondary-chondral osteogenesis with cartilaginous preformation and loading under pressure, 2) secondary-desmal bone formation with connective tissue preformation and loading under traction, and 3) primary angiogenic desmal osteogenesis in the absence of any preformative tissue or any form of mechanical influence on this tissue[37].

In case of bone healing, distance and size, as well as surrounding tissues, and the question of mechanical loading or immobilization play a decisive role in bone regeneration. The healing process follows a cascade of tissue differentiation. First vascular ingrowth is observed. Then the primary hematoma coagulates, forms a fibrin network and is replaced by granulation tissue. This primary healing substrate can originate from all those tissues that have been damaged by the trauma of a bony wound, i.e. bone marrow, cancellous and cortical bone, periosteum, surrounding peri-osseous soft tissues and, above all, smaller and larger blood vessels. This leads to cellular condensation, an accumulation of cells, also induced by site dependent transcription and growth factors, a highly reactive structure that has developed from the primary hematoma. This is the source for the repair of any bone defect. In the field of oral and maxillofacial surgery, the development of this early callus is often triggered by traumatic events of any form, e.g. tooth extractions, and leads to an inflammatory tissue reaction, which can end in repair, but also in degeneration. The primary cell mass is responsible for the potency of the tissue reaction. Therefore, there may be a discrepancy between the potency of the cell reaction and the extent of the defect to be repaired, resulting in a loss of bone volume.[38]

Local influencing factors, physical factors, but above all local signaling molecules, especially the so-called bone morphogenetic proteins (BMP) cause the osteogenetic differentiation of the cell masses. The cell differentiation means the final maturation for the cell and leads to full functionality. They create the cell types described above. Osteoblasts synthesize collagen, proteoglycans and glycoproteins in the growing or healing bone, from which a specific quaternary structure is formed in the extra-cellular space that is the model of all synthetic matrix constructs. The mineralization process takes place on this matrix. After the mineralization is complete, bone consists of approximately 65% inorganic substance, mainly hydroxyapatite, but also magnesia, potassium, chlorine, iron and carbonate, 25% organic substance and 10% water. The organic matrix is based on type I collagen (90%) as well as non-collagen proteins, e.g. osteonectin, osteocalcin, sialoproteins and others, and lipids (10%) together.

Bone remodeling consists of three consecutive phases: resorption by osteoclasts; reversal by surface mononuclear cells; and formation by osteoblasts (Fig. 2)[39].

Atrophy and bone regeneration

The maxillary sinus is already present in the fetal stage and is only a few millimeters in size[40]. During life the maxillary sinuses pneumatize, this process is slowed down when permanent dentition is erupting[41]. Tooth extractions result in more alveolar bone loss due to ridge resorption and pneumatization, especially in the area of the second molars[42-44].

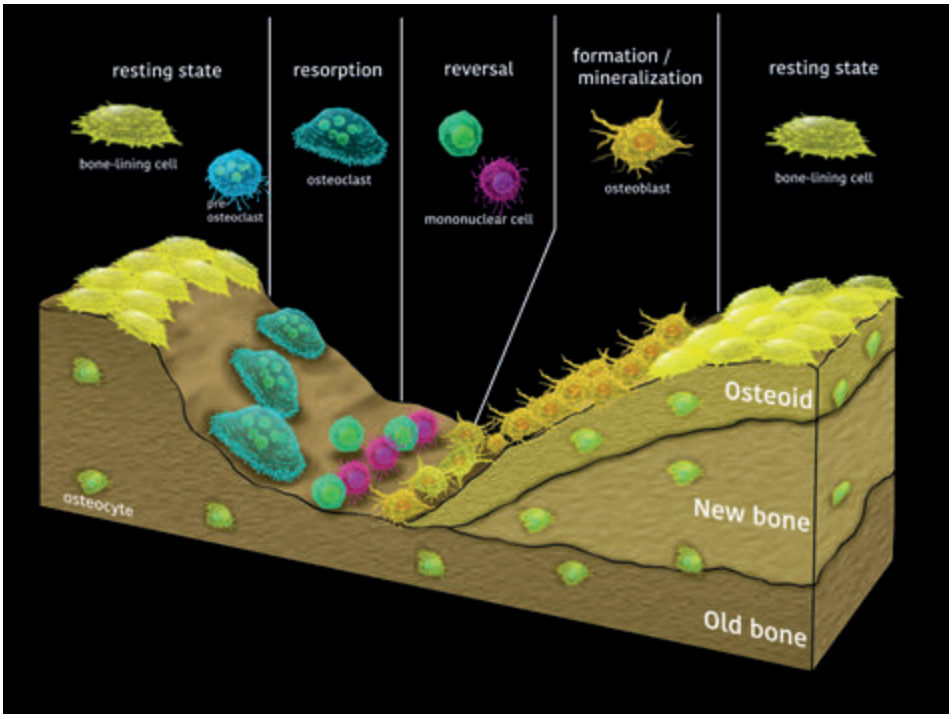

***Figure 2**. Bone remodeling process.*

The use of bone grafts is the standard to treat and to regenerate lost bone, as demonstrated by the large number of bone graft procedures performed by different surgical specialties worldwide. The most common still today are autogenous bone grafts[4]. However, the use of autografts can lead to complications and donor-site morbidity, such as infection, fracture, pain, scarring, blood loss, and hospital stay or even prolonged hospitalization[6]. Alternatively allografts can be used, but they lack the osteoinductive capacity of autogenous bone, carry the risk of an immune rejection and may even carry a risk of carrying infectious agents, if the material is of xenogeneic origin. Therefore, an enormous amount of bone substitute materials have been developed over the last decades[9]. The efficacy of bone substitute materials has been improved by incorporating bone progenitor cells and growth factors to stimulate bone growth. An ideal bone graft has not been found yet. It should mimic the structure and physical properties of natural bone, it should stimulate vascular ingrowth, bone growth based on osteoprogenitor cell-like characteristics and provide all the necessary environmental features found in autogenous bone. Despite enormous investments in the past such a material has not yet been developed.

The terms autogeneic, allogeneic and xenogeneic in conjunction with bone grafting have been introduced in science as early as the 18th century. In 1742 Duhamel coined these terms that are still used today[45]. Towards the end of the 19th century, medicine, and especially surgery, developed with great strides. Techniques of object magnification made it possible to examine details of bone healing under the microscope. Barth coined the term: 'Schleichender Ersatz' which is best translated by a process of creeping substitution in connection with bone transplants[46]. This term still describes processes of bone regeneration very vividly today. Creeping substitution describes the gradual resorption and replacement of bony transplants by newly formed local bone based on neovascularization from the local wound bed. Three main elements were found describing this process biologically: Axhausen stated that the periosteum as living tissue in the neighborhood of bone defects plays the essential role as bone grafts must be considered as non-vascularized, dead material, which must be resorbed and replaced. McEwan added that living osteoblasts within the bone graft support the process of regeneration. Finally Murphy used the term osteoconduction. According to him the bone graft simply acts as a scaffold for the growth of capillaries which transport osteogenic cells from the surrounding living tissues into the bone graft[45].

Osteoconduction

Osteoconduction is a three-dimensional phenomenon of bone regeneration based on a sprouting neovascularization from the surrounding bone bed. Extravasation creates extravascular tissues which contain osteoprogenitor cells[47]. According to Urist this process can also "occur within a framework of non-biologic materials such as glass, ceramics, and plastics, as well as within nonviable biologic materials such as autoclaved bone, deproteinized bone, demineralized-trypsinized bone, and frozen or freeze-dried allogeneic bone"[48]. This means that the process of osteoconduction is not necessarily linked to resorption of the underlying scaffold. In a biological, non-vascularized bone graft, the process of osteoconduction can be facilitated by remnants of vital osteoblasts. However, it must be clear that the process of osteoconduction starts from the material of the graft and not from living, bone-forming cells within the graft[49].

Osteoinduction

Groundbreaking research on BMP's has been conducted by Urist and co-workers in the last century[50-52]. Osteoinduction is a biological process of bone forming based on pluripotent mesenchymal stem cells which can be developed into bone forming cells by induction through BMP's. The results of the investigations of Urist led also to the conclusion that bone formation after implantation of demineralized bone tissue can

also be observed in heterotopic or ectopic localizations. This led to the hypothesis that free BMPs circulating in the blood may bind to scaffold structures and induce bone formation there regardless of the location. The definition of osteoinduction includes that the bone forming process is not linked to any kind of scaffold, but may also happen at heterotopic sites, if mesenchymal stem cells are available. This means that some typically osteoconductive scaffolds, as e.g. hydroxyapaptite matrices, might adapt osteoinductive properties, if the biological environment is considered to be favorable.

The developments in the field of bone regeneration will continue. At this moment particular attention is being paid to osteoconductive processes. The material composition, pore size, roughness, manufacturing method, surface structure, to name but a few, are the subject of numerous investigations today and will influence the definition of osteoconduction and osteoinduction in the future[49].

Approaching the posterior maxilla

In the developed countries the loss of the first teeth is shifting in ever later stages of life. This is basically a positive development and demonstrates the success of preventive strategies in dental clinical practice, but also in dental sciences. On the other hand, this development leads to a growing treatment demand, as more and more elderly patients complain about a pronounced vertical bone loss. It can be assumed that the onset of demographic change will exacerbate this situation[53, 54].

Especially in the lateral upper jaw tooth loss and vertical bone deficits can lead to challenging situations, if implant-based prosthetic repair is desired. In the early days of endosseous implantology, the posterior atrophic maxilla was considered an almost uncontrollable situation for the insertion of dental implants due to the poor bone quality in combination with crestal atrophy and the pneumatization process of the sinus. For some time, established therapies have been developed to increase the bone volume and supply in these regions to enable implantation at all[55, 56].

For the first time in 1976 Tatum reported on a new surgical method improving the vertical bone height in the sinus floor[57]. The most popular method to graft the maxillary sinus has been described by Boyne and James in 1980[55]. The so-called external sinus lift procedure based on a lateral antrostomy is still the standard method in maxillary sinus augmentation procedures today. However, in contrast to the original description, today only occasional use is made of autogenous bone material to augment the sinus floor. In 1986 Tatum again described a less invasive surgical procedure with the crestal access to the sinus floor, which was perfected

by Summers. In 1994 Summers described a minimally invasive procedure for the vertical elevation of the sinus floor. The internal sinus lift is using local bone which is condensed and carefully elevated into the floor of the sinus thus resulting in an improvement of the vertical bone height[56]. When using the internal sinus lift usually implants are placed simultaneously. Implants must have a sufficient primary stability. However, this elegant method has its limitations and the field of indication is limited.

Functionally relevant crestal atrophy can only be compensated for by augmentation with an onlay-osteoplasty or a segmental osteotomy with caudal dislocation of the alveolar process. In addition to the classical anatomically oriented classification (Fig. 3) according to Cawood and Howell[58] described in the literature, atrophy of the posterior maxilla can be classified as follows: 1, Vertical atrophy of the alveolar process due to: excessive pneumatization of the maxillary sinus, crestal vertical atrophy and a combination of both. 2, horizontal atrophy of the alveolar process. 3, complex forms of atrophy due to combinations of the first and second classifications.

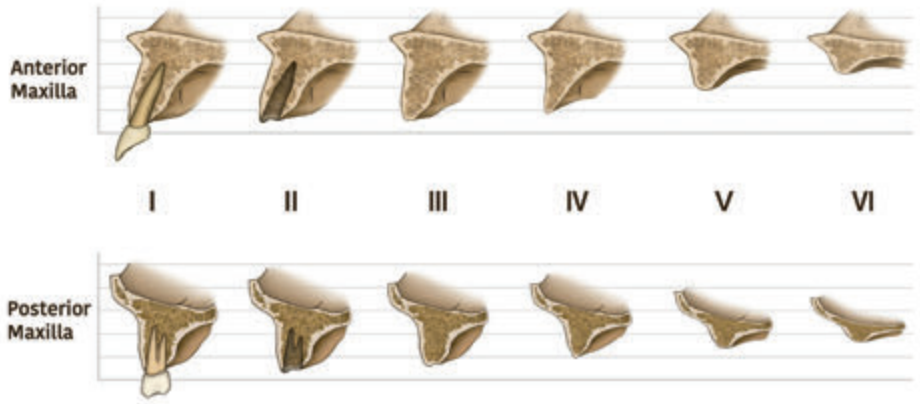

Figure 3. *Cawood and Howell classification of upper jaw atrophy.*

The reconstruction of complex atrophies requires knowledge and experience in almost all augmentation techniques. In addition, detailed anatomical, prosthetic and surgical knowledge is a basic prerequisite for the overall concept of fitting patients with implants in such situations.

Since 1980 a great variety of modifications of the basic techniques have been described. No technology seems superior to others. However, the rate of complications in implant placement in conjunction with sinus lifting procedures is higher than in patients without sinus lifting[59]. This led to the development of alternative concepts, which are becoming increasingly clinically relevant. Short and obliquely placed implants and zygoma screws, for example, appear to be a possibility for functional restoration of the posterior maxillary segment without the need for augmentation[60-63].

Based on the clinical experience of spontaneous bone formation in the maxillary sinus after removal of a cyst led to the development of another interesting modification of the external sinus lift procedure which has been published by Lundgren[64, 65]. A number of studies have shown the clinical success of this approach, at least for a short time[66-68].

Basic considerations – anamnesis

Some basic considerations are essential for the successful treatment planning in sinus lift procedures. Every patient must be interviewed on the history of medication use, allergies, and smoking and drinking habits. With regard to the maxilla one should ask about the reason for tooth loss and oro-antral fistulas which needed repair surgery. The intraoral inspection must focus on the remaining dentition, the periodontium, the soft tissues of the oral cavity and the intermaxillary relation. One should also ask for the presence of bruxism or other relevant habits related to the teeth or tongue. The preoperative diagnosis necessarily includes comprehensive x-ray diagnostics. A three-dimensional radiological analysis based on a cone-beam computed tomography (CBCT) should be considered as standard in the atrophied maxilla as this may include: information about the subantral residual bone substance, the periapical status of adjacent teeth, the anatomy of the sinus floor with possible signs of a present sinusitis or other pathological findings in the maxillary sinus can be obtained. Furthermore the CBCT data can be used for the 'backward planning' with regard to prosthetic rehabilitation. The number, position, length and width of dental implants needed for dental arch restorations can be determined with the help of the CBCT.

Anatomy and physiology

The maxillary sinuses were first described and illustrated by Leonardo da Vinci in 1489 and later documented by the British anatomist and surgeon Nathaniel Highmore in 1651[69]. The maxillary sinus is an air-filled cavity of the upper jaw bone lined with epithelium in the shape of a 4-sided pyramid with a base to the lateral nasal wall. The paired maxillary sinuses are lying within the bilateral maxillae, lateral to the nasal cavity, superior to the maxillary teeth, inferior to the orbital floors, and anterior

to the infratemporal fossa. These sinuses are the largest of the paranasal sinuses, measuring an average of 12.5 mL in volume. The sinus can be divided by septa and communicates regularly with the middle nasal passage via a natural ostium. Functionally it reduces the weight of the maxilla, protects the base of the skull from injury through its geometry, moistens and warms the inhaled air and is a resonating body during phonation. The pneumatization of the maxilla progresses from birth to adulthood and can lead to a progressive pneumatization of the sinus floor after tooth extractions.

The 2-layered lining of the sinus, in oral and maxillofacial surgery often referred to as Schneider's membrane, consists of a ciliated cylindrical bi-layer epithelium. Basal and goblet cells are superimposed on a thin lamina propria with multiple seromucous glandular cells. The ciliated columnar respiratory epithelium is based on a single-cell cambium layer on the bone side which is considered to have periosteal properties.

The sinus secretion produced therein is transported towards the ostium naturale at a flow rate of about 1 cm^3 per minute. This muco-ciliary clearance renews and cleans the sinus in a period of about 30 minutes. Histologically the membrane consists of a bilaminar layer of ciliated columnar epithelial cells on the cavernous side and basal membrane, which is considered to function as periosteum on the osseous side.

The arterial blood supply to the sinus and the mucosa consists of regular intra-bony vessels and an additional extra-bony anastomosis supplied by the infraorbital artery, the lateral nasal posterior artery and the superior posterior alveolar artery, all of which are originating from the maxillary artery.

The functioning self-cleaning mechanism, combined with the intact osteo-meatal unit formed by the hiatus semilunaris, the bulla ethmoidalis and the processus uncinatus, is of utmost importance for the success of a sinus floor elevation. Under the conditions described above, NO-(nitric oxide)synthase can maintain a bacterial and viral NO-concentration that turns the sinus into a sterile cavity. Under these conditions, a sufficient oxygen partial pressure can be achieved, which is then involved in osteoneogenesis in the sinus floor as a co-determining cofactor.

If the function of the Schneider membrane is severely restricted and if the middle nasal meatus is constricted, pathological changes in the area of the paranasal sinuses occur[70].

Scientific Background

The indication for the internal sinus lift is limited and certain anatomical conditions must be met to perform an internal sinus lift at all. The alveolar process must have a sufficient width in relation to the number, diameter and position of the implants needed. The vertical and transversal intermaxillary relation must be sufficient for later prosthetic rehabilitation. To perform an internal sinus lift the remaining vertical height of the alveolar process should be at least 5 mm. If these conditions are fulfilled an internal sinus lift could be indicated. The overall morbidity in comparison to the external sinus lift is much lower.

With the internal sinus lift, the implant bed is prepared with small diameter bits until just before the sinus floor. The bone condensers or osteotomes are used to condense the bone laterally and vertically leading to the perforation of the floor of the maxillary sinus. Bone of the alveolar process is elevated into the maxillary sinus, whereas the sinus membrane should not be perforated[56]. This procedure enables simultaneous implant placement. Important is the use of instruments with concave working ends for the perforation and elevation of the sinus floor. To fill the gap between the floor of the sinus and the sinus membrane sufficiently autogenous bone or bone replacement material can be used facultatively. This material has to be placed carefully under the sinus membrane using the osteotomes. The assumption is that the augmentation keeps the elevated sinus floor in a cranial position over the healing phase. Next an implant of desired length can be placed. To exclude a perforation of the sinus membrane a Valsalva maneuver can be executed before placement of the augmentation material. If a perforation of the sinus membrane has happened the treatment can be switched to an external sinus lift[71].

For augmentation of the sinus floor a great variety of materials from various manufacturers is available. Bone replacement materials can be of different origin: autogenous, allogenous, xenogenous or alloplastic materials are offered. The exact healing mechanism of all these diverse materials is not yet fully understood. Additionally the effect of these materials on implant healing and integration is unclear. The successful insertion of implants after internal sinus lift without augmentation has also been described in literature (Tent-Pole-Technique)[64, 65]. In this technique, the implants are used like tent posts to clamp the sinus membrane. This results in a bone gain in the area of the implants without augmentation material.

Alternatively a two-step procedure may be considered, if the existing bone quality and quantity or defect size suggest this. The two-step procedure has not yet been scientifically investigated and represents the research topic of this work[72].

Augmentation of the maxillary sinus

Sinus augmentation is a routine surgical procedure in pre-implantological bone reconstruction today. Success rates for dental implants of 90% and more are reported from literature in several long-term studies[73,74]. Due to its biological qualities and osteoconductive and osteoinductive properties autogenic bone is still considered to be the gold standard material for bone replacement[75-77]. However, any harvesting site will create additional morbidity[6]. Limitations are longer operating time and costs, morbidity-related pain, unpredictability of resorption and limited tissue availability[78]. For these reasons, ongoing research efforts are investigating the performance of other biomaterials to be used as bone replacement in oral surgery. Among the synthetic materials, bioactive glasses, resorbable hydroxyapatite (HA), β-tricalcium phosphate (TCP) and their combinations have been proposed and widely used due to their similarity to the bony mineral matrix[79]. Resorbable calcium phosphates have osteoconductive properties and are gradually replaced by new bone according to their resorption rates[80], whereas some HA bone replacement products can be considered as non-resorbable. These materials share a common disadvantage in comparison with autogenic bone grafts as they lack extracellular organic molecules playing a dual role by providing both structural support for the mineral phase and stimulating signals to the resident cells to promote graft remodeling and bone regeneration. Furthermore, as they are similar in composition and structure to autogenic bone, xenogeneic, but also homogenic grafts are associated with the risk of inflammatory and foreign body reactions, and for these reasons they are usually processed in such a way that they lose their immunogenic properties which make the product biologically inert, but also inactive[81, 82]. Homogenic bone is interesting, but ethical constraints, costs, safety and availability issues have limited its use in oral surgery[83]. Therefore, bovine deproteinized inorganic bone matrix has become the most popular graft material for maxillary floor augmentation due to its high availability and reduced costs. In such a diverse biomaterial scenario, where new grafts and their combinations with synthetic biomaterials are proposed as scaffolds for sinus lift procedures, the best clinical choice can be challenging[84].

Hypothesis

Bone repair in a sinus lift procedure, like in any bone wound, is a coordinated response that includes molecular factors, multiple cell types, such as bone cells, immune cells, cells of surrounding tissues, and vascular structures. The overall tissue response is similar to any general wound healing response. Physiologically the tissue response on trauma, in this case an iatrogenic trauma in the floor of the maxillary sinus, resembles an inflammatory reaction, which is important for host defense against infection, but also for starting the regeneration process with forming of a hematoma[85]. Like the

mucous membrane of the maxillary sinus, periosteum consists of two layers: an outer fibrous layer comprised primarily of fibroblasts and an inner cambium layer carrying multiple cells and tissue structures including nerves, capillaries, osteoblasts, and undifferentiated progenitor cells[86, 87]. Within the periosteum, but also in the surrounding bony walls, reside mesenchymal stem cells which facilitate wound healing in response to the trauma[88].

The augmentation cavity in the floor of the maxillary sinus is surrounded on all sides by potentially bone-forming structures. In the presence of BMPs and other cell-differentiating proteins, periosteal but also bone marrow-derived stromal cells can differentiate into osteoblasts and form new bone. In addition to natural bone healing, it is known that periosteal stromal cells can stimulate bone formation even in ectopic implant sites, even in contact with augmentation materials[89].

These were the basic considerations that served as prerequisites for developing the split-mouth model for sinus augmentations on humans, the design which will be described in the next chapters in detail.

Aims and Review of the Thesis

The overall objective of this dissertation was to quantitatively, qualitatively and functionally assess the independent, spontaneous osseous regenerative forces in the wall and floor region of the maxillary sinus without augmentation material. Dental implants were to prove the functional loading capacity and stability of the bone regenerate in the maxillary sinus.

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CHAPTER 2

Elevation of the maxillary sinus membrane for de-novo bone formation: First results of a prospective study in humans

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ABSTRACT

Purpose

Sinus floor elevation via the lateral window approach represents a reliable technique for bone augmentation in the atrophic posterior maxilla. It is known that sinus membrane elevation leads to new bone formation. This prospective clinical study compared a specific technique in sinus membrane elevation with a conventional sinus floor augmentation (xenogenous/autogenous bone) in a human split mouth model.

Methods

Five edentulous patients with highly atrophic posterior maxillae were included in this study. On one maxillary side a degradable PDLLA-membrane was placed to create a space underneath the sinus membrane. Contralateral a mixture of autogenous and xenogenous bone was used for sinus floor augmentation. A two-stage procedure was carried out. The following variables were assessed: bone regeneration on cone-beam computed tomography (cone-beam CT), implant success, prosthetic comfort and patient satisfaction. Bone biopsies were taken with simultaneous implant placement. The samples were histologically analyzed.

Results

Cone-beam CTs revealed new bone formation on both sides. Thirty implants were placed, 15 in the augmented region and 15 in the non-augmented side. Thirty bone biopsies were taken and evaluated. Vital new bone was detected on the experimental side (osteoinductivity). On the conventional side a mixture of autogenous and residual bone substitute material was seen (osteoconductivity). Implant survival was 100% so far. Patient's satisfaction was high and prosthetic complications were not encountered.

Conclusion

As it provides the highest rate of bone formation, autogenous bone in combination with bone substitute material can be considered as a very reliable standard procedure in sinus floor augmentation. The specific sinus membrane elevation technique as presented here showed satisfying results and might be a suitable alternative for maxillary sinus augmentation.

INTRODUCTION

Atrophy of the maxilla is often seen in edentulous patients and causes problems with retention of conventional prosthesis. Functional and esthetic rehabilitation of the edentulous atrophic posterior maxilla requires bone suited for the long-term stability and survival rate of dental implants. Prior to implant insertion an augmentation of the maxillary sinus is mandatory, if the remaining bone height is not sufficient for immediate implant placement. Various substitutes have been used to fill the resulting space of the sinus, including autogenous bone, allografts, xenografts, synthetics, and mixtures of various materials [1, 2]. Despite clinical establishment of the operation technique, the search continues for the optimal bone substitute or graft for sinus floor augmentation. Ideally, augmentation with bone substitute materials would include good bone tissue integration, osteoinduction, and long-term stability. However, such a bone substitute material in its pure form does not yet exist. The variety of available materials make things increasingly difficult for the user to keep an overview [2-4]. When autogenous bone is harvested, there will always be donor site morbidity with additional surgical risks and postoperative complaints[5].

The aim of the following study was the clinical and histological investigation of bone regeneration and integration of a well characterized anorganic bovine bone substitute material (Bio-Oss™; Geistlich Biomaterials GmbH, Wolhusen, Switzerland) mixed with autogenous bone in comparison to elevation of the sinus membrane alone. It is known that sinus membrane elevation in the atrophic maxilla will lead to new bone formation. The elevation can be accomplished by using the implants directly as a pillar under the membrane in a one-stage implant procedure [6-9]. Another option is to use a spaceholder above the implants[10] or a spaceholder for sinus elevation in a two-staged implant procedure[11]. In comparison to the existing literature (Table 1) our study is the first one referring to totally edentulous patients, where the space of the pneumatized sinus is larger than in the partially dentulous patients. Furthermore the elevation membrane and technique vary from the methods described in literature. To create a comparable initial situation, a two-stage procedure with an external approach was carried out. The primary outcome of the study was the newly formed bone in the non-augmented area in comparison with the conventionally augmented side. Secondary outcomes were implant survival, patient satisfaction and prosthetic comfort.

Table 1: *Literature on sinus membrane elevation.*

Author/year	Species	Spaceholder
Cricchio et al. 2011a[12]	Capuchin primates (n=6)	H-shaped or star-shaped device (polylactide)
Palma et al. 2006[13]	Capuchin primates (n=4)	2 implants
Cricchio et al. 2009[14]	Capuchin primates (n=8)	Space making device (polylactide)
Hatano et al. 2007[9]	Humans (n=6)	Implants
Lundgren et al. 2008[7]	Humans (n=10)	Implants
Cricchio et al. 2011b[8]	Humans (n=84)	Implants
Cricchio et al. 2014[15]	Humans (n=10)	Implants
Jungner et al. 2014[16]	Capuchin primates (n=9)	Implants
Lundgren et al. 2004[6]	Humans (n=10)	Implants
Felice et al. 2009[11]	Humans (n=10)	Resorbable rigid Inion barrier
Kaneko et al. 2012[10]	Humans (n=11)	Titanium bone fixation device
Kim et al. 2010[17]	Dogs (n=6)	Implant

	Immediate implantation	Outcome	Note
	No	Histology	- Osteoinductive properties sinus membrane
	Yes	Histology	- Osteoinductive potential sinus membrane
	Split mouth	Histology	- Minor bone formation space-making device only (displacement?)
	Yes	Radiology	- Mean gained bone height 10 mm - 1 of 14 failed
	Yes	Radiology	- Bone formation and osseointegration
	Yes	Radiology	- 5.3 mm new bone formation - 98.7% implant survival
	Yes + immediate loading	Radiology	- 5.7 mm new bone formation
	Yes	Histology	- No osteoinductive potential sinus membrane
	Yes	Radiology	- New bone formation
	No	Radiology Histology	- Comparison with Bio-Oss - New bone formation
	Yes	Radiology	- New bone formation
	Yes	Radiology Histology	- Blood clot not stable enough for elevated position of membrane

MATERIALS AND METHODS

The study design represents a pilot trial in a split mouth model to compare the efficacy of two different techniques for the augmentation of highly atrophic maxillae in ten edentulous patients. This study was approved by the medical ethics committee of the Maastricht University Clinic: azM/UM: NL41286.068.12/METC 12-2-066. The test sides of the maxillae were independently randomized to their surgical procedure. The allocation was performed at random immediately before surgical intervention. The main coordination of the study including enrollment and assignment of the patients was performed by the first author. In January 2013 we started our pilot study under the condition to split the test group in half for an interim evaluation of the elevation technique before continuing the study. The duration of the study from first intake until the last follow-up is 24 months/patient.

The results of this study will be analyzed descriptively. These results can be used for the sample size calculation of a next study, a randomized controlled clinical trial.

After obtaining informed consent, five edentulous patients with bilateral highly atrophic maxillae enrolled the study. The operations took place in general anesthesia. All patients received 2,200 mg amoxicillin/clavulanic acid peri-operatively; this was continued for 7 days post-operatively (oral dosage, 625 mg amoxicillin/clavulanic acid, 3x/day). One maxillary side was augmented using the standard augmentation procedure with a mixture of autogenous and xenogenous bone. On the contralateral side the Schneiderian membrane of the maxillary sinus was lifted and stabilized with a degradable perforated membrane (Fig. 1).

In detail: the sinus was approached by the lateral window technique. The Schneiderian membrane was exposed and lifted from the sinus floor. The resorbable membrane made of poly(D,L)-lactide (PDLLA) (Resorb X™, KLS Martin, Tuttlingen, Germany) commonly used in oral and maxillofacial surgery was placed as shown in Fig. 1. The membrane measured 40 x 40 x 0.2 mm and is perforated. When the membrane is heated, it can be formed to the ideal shape to create a stable support for the elevated sinus membrane. For fixation two resorbable pins of the Sonic Weld™ system were used (SonicWeld™, KLS Martin, Tuttlingen, Germany). The space created in the sinus was filled with autogenous venous blood. Finally the wound was closed tightly (Fig. 2a-e). With this technique a stable elevation of the sinus membrane is provided to support bony ingrowth in the created space.

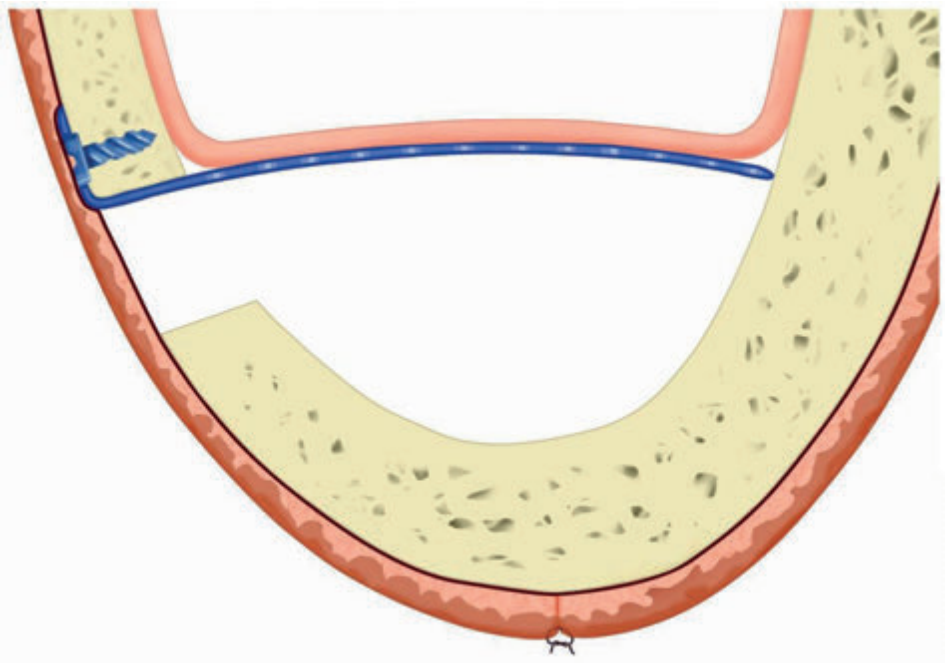


Figure 1. *Schematic drawing of sinus membrane elevation with a resorbable membrane.*

According to the study protocol six implants of appropriate width and length were placed six months after sinus floor augmentation. A total of 30 implants were placed.

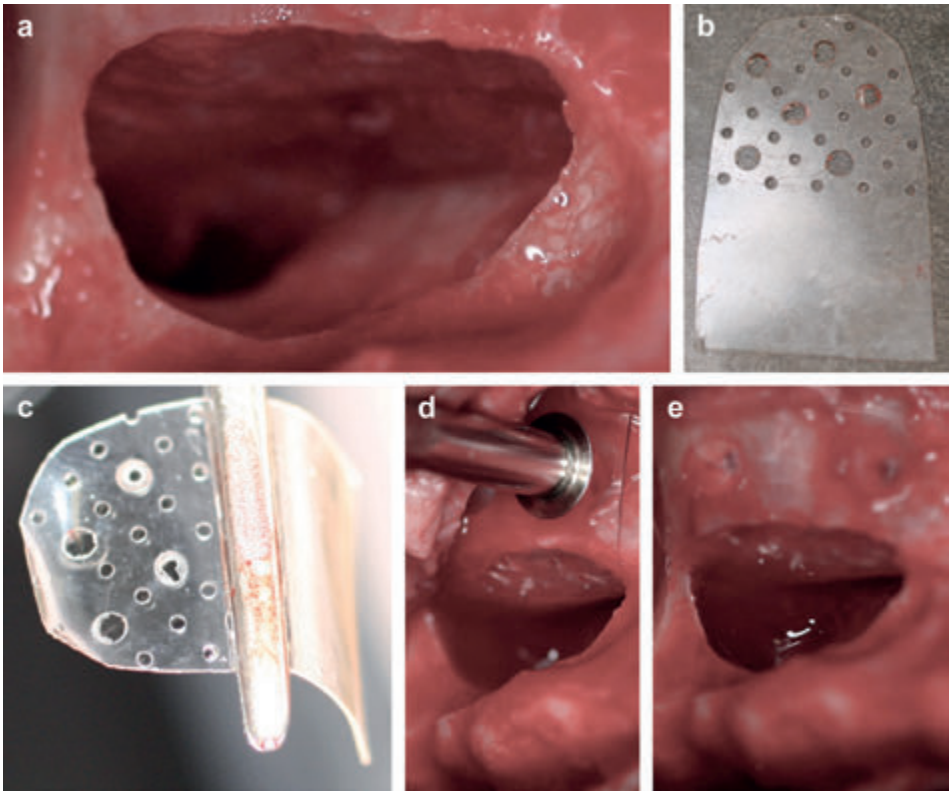
Radiological follow-up

Cone-beam computed tomography (cone-beam CT) was applied pre-operatively, immediately postoperatively and six months later[18]. On the radiographs gain in bone height in the regions of interest in the posterior maxilla were measured. The gain in bone volume on the Cone-beam CTs was measured using the iCatVision (Imaging Sciences International, Hatfield, PA, USA) program on three different locations on each side of the maxilla in the regions 17, 15, 14, 24, 25, 27. Only descriptive statistical analysis was possible, because of the small number of probes.

Histology

During the regular procedure of implant insertion the implant bed must be prepared. Instead of using a solid twist drill for the preparation, we used a trephine bur of 3 mm diameter (outer diameter 3.0 mm, inner diameter 2.0 mm, length 14 mm; Hager & Meisinger GmbH, Neuss, Germany). A trephine bur allows us to take cylindrical bone probes from the center region of the augmented maxilla for histological evaluation

before implant placement. No extra defects were created. We avoided a sinus perforation by limiting the length of the bone specimens to 8 mm. The biopsies were placed in paraformaldehyde, then dehydrated in graded alcohol at room temperature in a dehydration unit (Shandon Citadel 1000®; Shandon GmbH, Germany) and embedded in a methacrylate-based resin (Technovit® 9100 New; Haereus Kulzer, Germany). The embedded bone samples were prepared for histological evaluation according to established cutting and grinding methods[19-22]. Then the bone samples were cut on the median longitudinal axis and ground into thin sections of 120 µm (Exakt Apparatebau GmbH, Norderstedt, Germany). The haematoxyline-eosine staining was used for histological evaluation of the bone biopsies. The biopsies were analyzed by a specialist in osteology (H.-A.M.).



Figures 2a-e. *Intraoperative procedure: (a) creating a lateral window, (b) the PDLLA membrane, (c) forming of the membrane, (d) adapting the membrane to the maxillary sinus wall, (e) fixed membrane before wound closure.*

Implant survival, Prosthetic survival and Patient Satisfaction

Implant survival and patient comfort with the bar retained overdentures were documented. We defined implant success according to the criteria described by Albrektsson[23] et al. Implant loss was defined as failure. Patients were asked to fill out a form based on a visual analog scale (VAS) to report about their satisfaction with the prosthetic rehabilitation six months and one year after placement of the prosthesis.

RESULTS

Radiology

After six months sufficient bone volume was present for implantation on the non-augmented, as well as the augmented side (Table 2). However, the non-augmented side showed less opacity, which suggested less bone density or less presence of mature bone (Fig. 3a-d).

Table 2: *The vertical bone gain was measured on the cone-beam CTs in the regions 17, 15, 14, 24, 25, 27.*

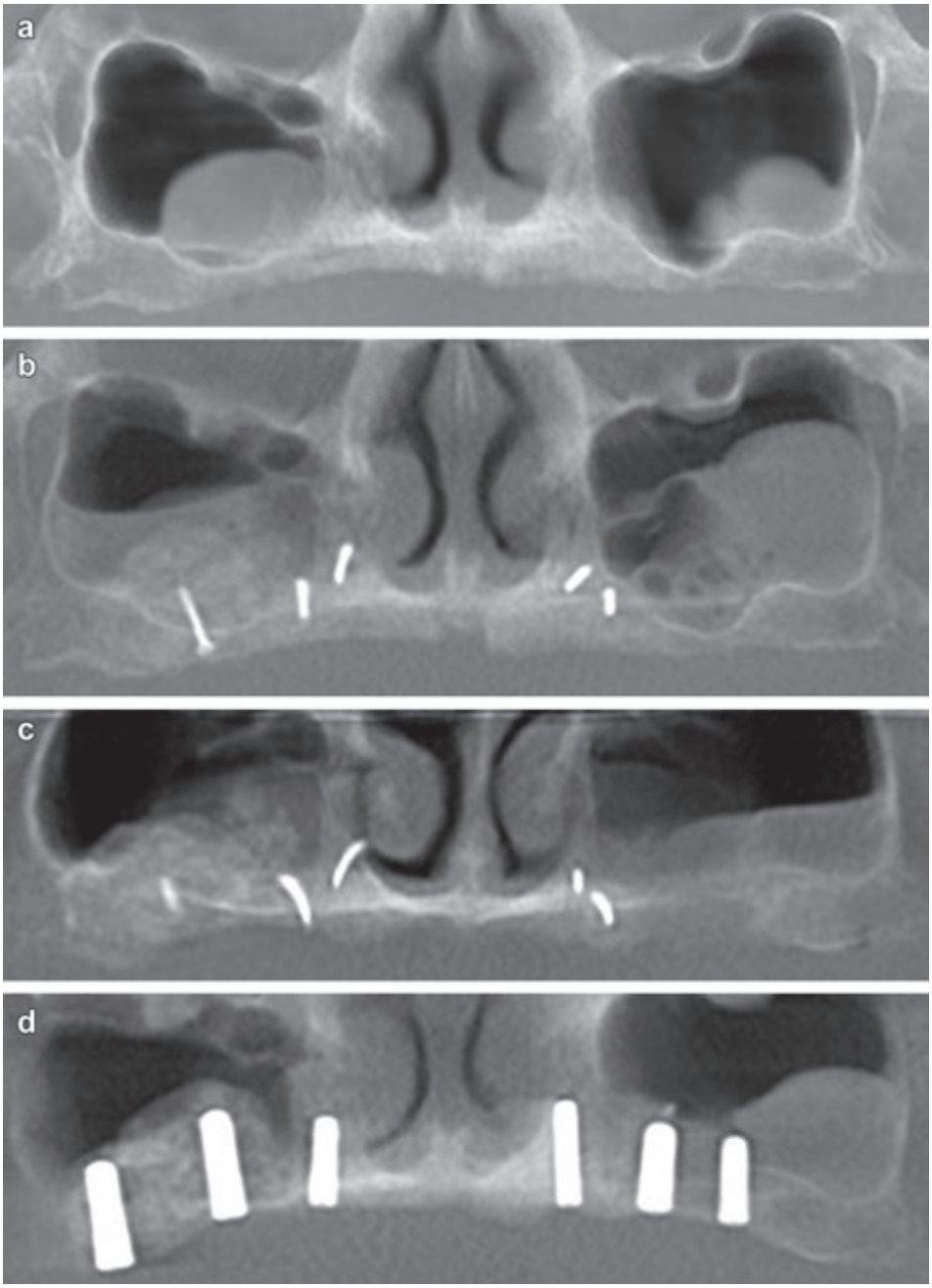
Five patients, measured on cone beam CT pre- and 6 months postoperatively	*Non-augmented* ***Mean (sd)***	*Augmented* ***Mean (sd)***
Vertical bone gain in mm	7,78 (3,65)	9,99 (3,82)

Histology

All bone specimens showed new bone formation. The bone probes were taken after deflection of the mucoperiosteal flap. As we tried not to perforate the augmented site, the residual bone was located at the bottom of the bone specimens. This criterion was used for orientation prior to histological evaluation. The transition from residual to augmented bone was detected in most cases, especially in the probes following augmentation bone substitute material. In the non-augmented bone specimens exhibited a smooth transition between residual bone and bone formed by osteoinductivity.

However, the bone of the experimental side was less organized and immature (Fig. 4). The bone biopsies of the conventional side showed as expected the combination of Bio-Oss™, embedded in bone marrow and newly formed bone (Fig. 5). The biopsies from the experimental side showed new bone formation and osteoblast and osteoclast activity as signs of an active bone forming and remodeling process (Fig. 6).

Implant success rates were 100% on both sides after six months and after one year after completion of the prosthodontic rehabilitation. All implants could be loaded by prostheses in a conventional way (bar retained overdentures) and are successful at this stage of the study. All patients reported comfort with the dentures and were fully satisfied. Based on the randomization patients did not mention differences between both sides of the maxilla. Prosthetic follow up differed from 12 months post-loading in the first study patient to 6 months post-loading in the last patient.



Figures 3a-d. *Conebeam CTs, (a) preoperative, (b) one day postoperative, (c) six months postoperative, (d) after implantation.*

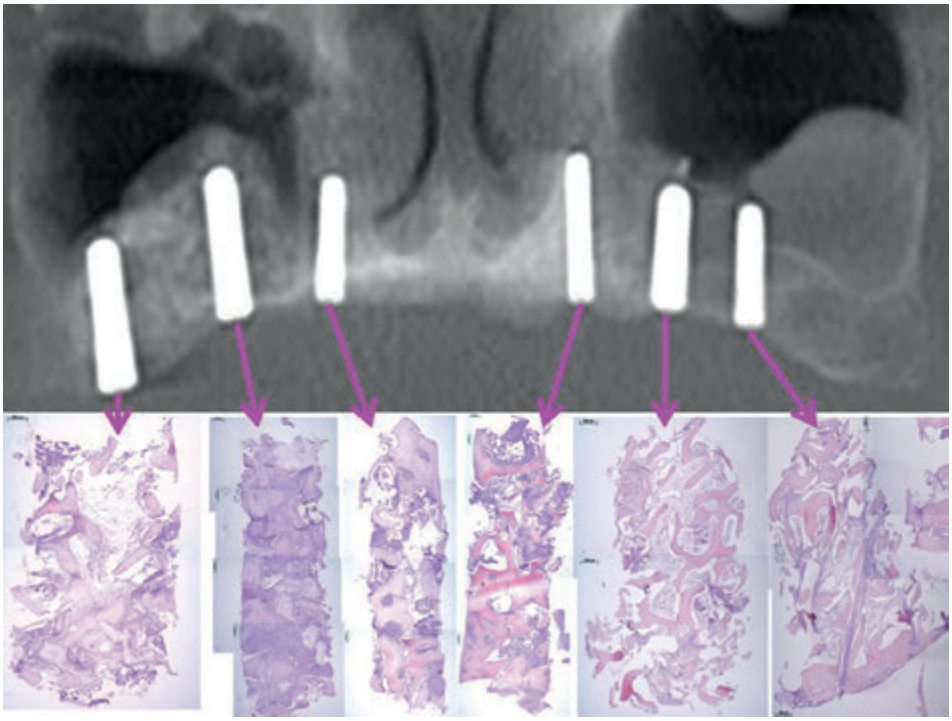
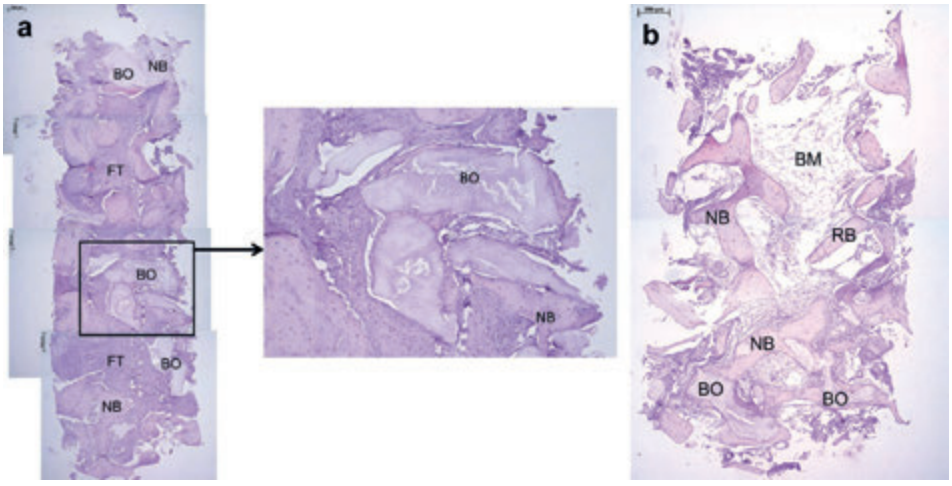
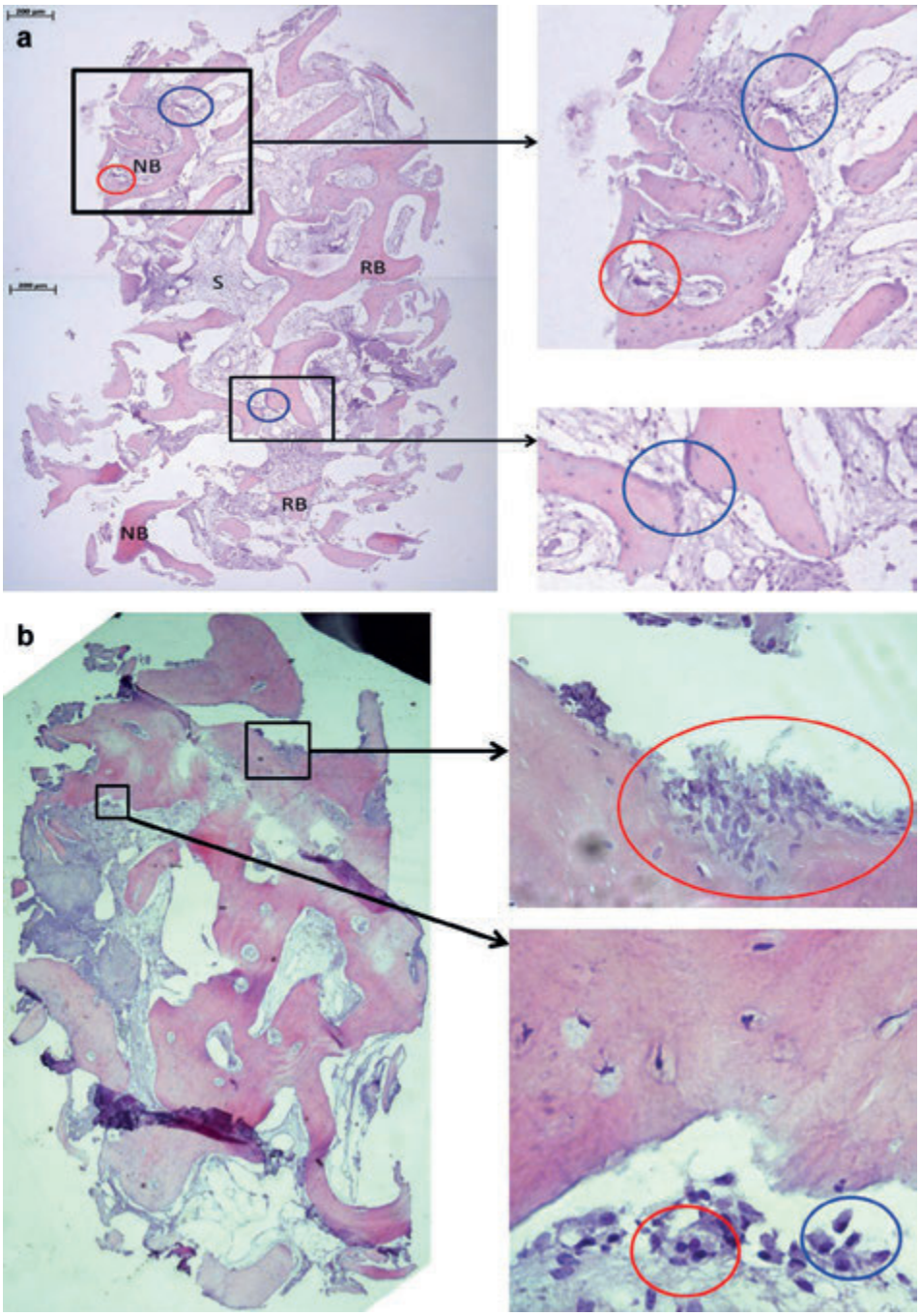


Figure 4. *Overview: the right side presents bone biopsies of the augmented maxillary sinus, the left side of the experimental, non-augmented sinus.*



Figures 5a-b. *Augmented side: BO = Bio-Oss™, NB = new bone, RB = residual bone, BM = bone marrow, FT = fibrous tissue.*



Figures 6a-b. *Non-augmented side: NB = new bone, RB = residual bone, S = stroma, blue circle = osteoblast activity, red circle = osteoclast activity.*

Implant survival, Prosthetic survival and Patient Satisfaction

DISCUSSION

Augmentation of the maxillary sinus is a well-established standard procedure in preprosthetic surgery. Various techniques have been described with high success rates for creating a sufficient amount of bone for stable placement of dental implants[22, 24, 25].

This pilot study compared a sinus membrane elevation technique with a control intervention consisting of augmentation with a mixture of autogenous and xenogenous bone. Both techniques resulted in sufficient newly formed bone for later implantation.

Harvesting bone can be associated with additional complaints at the donor site[5, 26]. Bone substitutes share a common disadvantage: Only their osteoconductive effect is scientifically proven[27]. The inductive potential of these materials is mostly based on speculation or wishful thinking. Besides this xenogenous and allogenous materials share a small, yet incalculable remaining risk of carrying possibly infectious proteins or protein fragments. Allogenic bone substitutes could be the best compromise regarding their absolute biological inertness. However, the degradation characteristics are less favorable and advantageous than of those materials based on biological bone[28].

Lundgren et al. (2004)[6] were the first to report about an osteoinductive potential by elevation of the Schneiderian membrane in combination with implant placement. Later especially the publications of Felice et al., Cricchio et al. and Kaneko et al. added up to this knowledge [6-9, 11].

The major advantage of the technique presented here is the absence of any kind of donor site morbidity (autogenous bone) and there is no risk of infectious proteins (xenogenous bone substitutes). The bone forming process resembles a callus-based bone formation in a space surrounded by bony walls. The hematoma forming in this artificially created space seems to have sufficient stability and potential to transform into new bone.

The membrane we used was a standard product that was originally designed for different indications. It is a material of great interest because of its proven biocompatibility and high initial mechanical strength and was tested in numerous clinical studies[29]. PDLLA has the advantage of degradation without generation of any crystalline remnants[30]. The degradation process has obviously not interfered with the bone forming process. The ideal membrane has maybe yet to be found. It must

have the following properties: sufficient stability combined with a short degradation time, no negative effects on the bone forming process in the space between the Schneiderian membrane and the surrounding tissues[12]. A perforated mesh design seems to be logical to allow vascular ingrowth.

If we compare the cone-beam CTs of both sides, less opacity on the experimental side was seen. The question, if this is immature bone or a problem related to the missing bone substitute material can only be answered in the long-term follow-up. The histology presented an active bone forming process with osteoid forming osteoblasts and bone remodeling. The so-called distance problem of bone ingrowth into a cavity could be the explanation for the lesser bone density on the test side.

Primary stability of the implants was achieved in all cases independent of the augmentation technique applied; the identity of the implantation side was not clinically relevant at the time of implantation. Based on this investigation, we are unable to make a statement regarding the long-term stability of the dental implants and the augmented region, but these issues will serve as the subjects for future reports.

CONCLUSION

Bone formation by sinus membrane elevation has been proven in several studies[6-8, 12, 13, 15, 16].

The combination of autogenous bone and a bone substitute material, however, can still be looked upon as a standard procedure with regard to newly formed bone in the region of interest. In a test setting with sinus membrane elevation on both maxillary sides less patient morbidity could be an advantage for this technique.

The resorbable membrane proved to be a good and reliable technique to create a stable elevation of the sinus membrane. The PDLLA-membrane seems not interfere with the bone forming process.

The newly formed bone on the experimental side resembles a callus-like structure.

The long-term success of the implant-retained prostheses and the stability of the augmented maxillary regions remain tasks of further investigation. Future research has to ascertain whether or not the properties of this specific technique of the sinus membrane elevation in a two-staged procedure in totally edentulous patients will have clinical relevance.

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CHAPTER 3

Pre-implantological bone formation in the floor of the maxillary sinus in a self-supporting space

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ABSTRACT

Introduction
In edentulous patients the form and size of the maxillary sinus vary greatly. Therefore sinus floor augmentation is a standard procedure for implantological purposes. As the sinus membrane cannot be characterized as periosteum, various augmentation materials are used.

Hypothesis
An artificially generated space underneath the sinus membrane in the floor of the sinus will lead to spontaneous callus forming and a stable bony consolidation without augmentation material.

Methods
Ten edentulous patients with highly atrophic maxillae were selected. Augmentation of the sinus floor was carried out in a split-mouth study design: On one side a combination of autogenous and xenogenous bone was used, and on the contralateral side a sinus membrane elevation was performed without using any substitutes. After a 6-month interval bone specimens from the test regions were harvested during implant placement.

Results
Clear histological evidence of new bone formation was found in all human bone specimens. An active bone remodeling process could be proven by the presence of Haversian systems (osteons) displaying osteoblastic and osteoclastic activity.

Conclusion
In the maxillary sinus of edentulous patients a spontaneous callus-derived de-novo bone formation is possible by elevating the sinus membrane without using augmentation materials.

INTRODUCTION

Bone healing can be influenced decisively by mechanical forces. The functional stressing in fracture healing has widely been examined and can constitute in a trophic stimulus for the tissues to heal[1-3]. On the contrary, in certain circumstances, a permanent mechanical stressing, such as it is provoked by muscular tension and by body weight when standing or walking, can exert an extremely damaging effect on the biology of the bony tissue. If it is assumed that the formative tissue of bone is a polyvalent tissue consisting of pluripotent cells, one has to understand that it is able to develop in different directions and definitively arrives at maturity as easily as connective tissue, as cartilage or as bony tissue. The formation of the different types of tissue should be considered as an adaptation of the formative tissue to the function demanded of it in the sense of Roux's law concerning the action of functional adaptation. Functional loading, however, is totally absent when discussing bone formation in the maxillary sinus [4].

The form and size of the maxillary sinus varies greatly. In some individuals the maxillary sinus may be limited to the maxillary bone, in others a variety of bulges may exist. One can differentiate alveolar bulges from zygomatic, infraorbital and palatal bulges. Following loss of teeth, the alveolar bulges can expand into the alveolar process of the maxilla leading to highly atrophic situations in the upper jaw.

With regard to augmentative pre-implantological procedures in the maxilla, the sinus floor augmentation occupies a prominent position [5, 6]. It is by far the most commonly used technique [7]. To augment the floor of the sinus, autogenous bone, xenogenous bone substitutes or a mixture of both are used. When autogenous bone is harvested, there will always be donor site morbidity with additional surgical risks and postoperative complaints [8, 9]. Despite substantial progress in recent years based on numerous controlled clinical and experimental studies the optimal material for augmenting the floor of the sinus has obviously not yet been found [10-12]. Ongoing research in this area centers on the design of matrices mimicking active biological qualities of natural materials such as bone [13]. Matrices or particulate bone substitute materials impart two main biological aspects by creating a space being filled with materials that maintain osteoconductive, and if possible osteoinductive characteristics [14]. The physical properties to the implanted material must be of a kind to allow for bony regeneration and later implant placement. A vast amount of resorbable and non-resorbable materials are on the market.

The hypothesis of the clinical study presented here was that a periosteal or bone-induced callus forming in an artificial space in the region of the floor of highly atrophic maxillae is able by itself to ensure sufficient volume and stability for bony consolidation and later implant placement [15, 16].

MATERIAL AND METHODS

The study design for testing in humans has been described in extenso earlier [17]. The study represents a pilot trial in a split mouth model to compare the efficacy of two different techniques for the augmentation of highly atrophic maxillae in ten edentulous patients. This study was approved by the medical ethics committee of the Maastricht University Clinic: azM/UM: NL41286.068.12 / METC 12-2-066. The test sides of the maxillae were independently randomized to their surgical procedure. The main coordination of the study including enrollment and assignment of the patients was performed by the first author. Two techniques were used in the split-mouth model for augmentation of the maxillary sinus: 1) A combination of autogenous bone of the iliac crest and bovine xenogenous bone (Bio-Oss®, Geistlich, Wolhusen, Switzerland) and 2) sinus membrane elevation using a Resorb-X® mesh (KLS-Martin, Tuttlingen, Germany) as spaceholder without the use of any bone substitute. After augmentation of the maxillary sinus floor in ten patients and a 6-month interval, bone specimens from the test regions were harvested during implant placement. In all patients six implants were placed, and six bone specimens were taken accordingly. Instead of using a solid twist drill for the preparation, we used a trephine drill of 3 mm diameter (outer diameter 3.0 mm, inner diameter 2.0 mm, length 14 mm; Hager & Meisinger GmbH, Neuss, Germany). A trephine drill allows us to take cylindrical bone probes from the center region of the augmented maxilla for histological evaluation before implant placement. No extra defects were created. We avoided a sinus perforation by limiting the length of the bone specimens to 8 mm. The biopsies were placed in paraformaldehyde, then dehydrated in graded alcohol at room temperature in a dehydration unit (Shandon Citadel 1000®; Fisher Scientific GmbH, Schwerte, Germany) and embedded in a methacrylate-based resin (Technovit® 9100 New; Kulzer, Hanau, Germany). The embedded bone samples were prepared for histological evaluation according to established cutting and grinding methods [17-21]. Then the bone samples were cut on the median longitudinal axis and ground into thin sections of 120μm (Exakt Apparatebau GmbH, Norderstedt, Germany). The haematoxylin-eosin staining was used for histological evaluation of the bone biopsies. The biopsies were analyzed by a most experienced specialist in osteology (H.-A.M.).

RESULTS

All human bone specimens showed new bone formation. The bone probes were taken after deflection of the mucoperiosteal flap. As we tried not to perforate the augmented site, the residual bone was located at the bottom of the bone specimens. This criterion was used for orientation prior to histological evaluation. The transition from residual to augmented bone was detected in most cases, especially in the probes following augmentation with bone substitute material. The non-augmented bone specimens exhibited a smooth transition zone between residual bone and newly formed bone by osteoinductivity.

Self-supporting space in the floor of the maxillary sinus (Resorb X® mesh, KLS Martin, Tuttlingen, Germany)

The histological preparations concerned human decalcified bone specimens from the sinus floor region displaying spontaneous bone regeneration in an artificially created submucous cavity after elevation of the sinus floor membrane. Thin slice preparations were used for evaluation (microtome preparations on slides). The bony regenerate appears to be crossed by vital bone trabeculae which cover the whole specimen (figs. 1-5). The bone trabeculae are organized in a diffuse pattern typical for bone regeneration without functional loading. The inter-trabecular space is mostly filled with undifferentiated primary bone marrow consisting of stromal tissues rich in vasculature and an abundancy of stromal cells. Histologically fibroblasts and fibrocytes are dominant in this granulation tissue (fig. 3). In the more cranial aspect of the preparation close to the submucous layers, sparse primary ossification centers can be detected. Osteoblastic activity can be proven. There are also regions displaying functional remodeling indicated by osteoclastic activity that can be demonstrated by higher image magnification (figs. 1, 2).

Augmented space in the floor of the maxillary sinus (Bio-Oss®, Geistlich, Wolhusen, Switzerland)

The stained thin slice preparations show all relevant structures clearly differentiable (figs. 6a,b). A strong bony "ceramo-osseous" regenerate crossed by strong bony trabeculae is visible covering the full length and width of the preparation. The truncated newly formed bone trabeculae are interspersed with vital osteocytes. Rows of vital osteoblasts guiding the bone trabeculae indicate an ongoing process of appositional bone growth. Furthermore, nests of ossicles dispersed over the whole thin slice preparation, act as a histological indicator of a continuing bone forming process. Based on the staining, a clear differentiation between newly formed bone and remaining transplanted autogenous bone particles (cancellous bone) is not possible.

However, the structure of the bone regenerate displays no clear histomorphological evidence for the existence of transplanted bone chips, as e.g. the cement lines between osteonal structures cannot be seen. The surface of the trabeculae shows a mostly osteo-anabolic activity being lined with osteoblasts. This can be interpreted as full substitution. One can conclude that the transplanted bone has already been completely substituted. Other proof for the bone substitution process (creeping substitution) [22] is the only sporadically visible absorption lacunae.

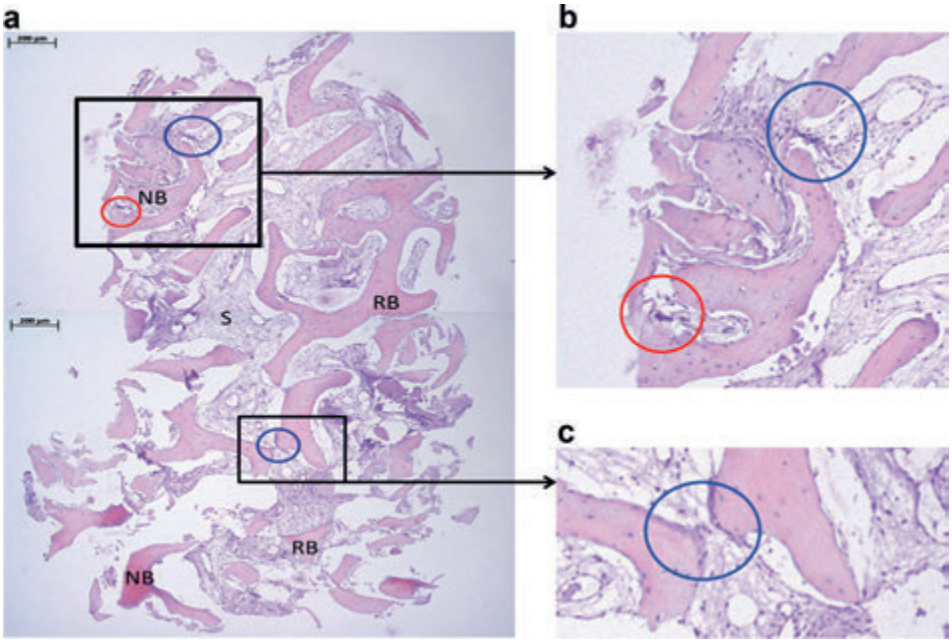

Figure 1. a) *120 µm thin section and a width of about 3 mm. The bone regenerate is vital, bone trabeculae cover the whole specimen organized in a diffuse pattern. The inter-trabecular space is mostly filled with undifferentiated primary bone marrow consisting of stromal tissues rich in vasculature and an abundancy of stromal cells.* ***b)*** *In the blue encircled field osteoblastic activity is documented and in the red encircled field osteoclastic activity.* ***c)*** *Osteoblasts are lined up on both sides of the inter-trabecular gap.*

NB = new bone, RB = residual bone, S = stroma, blue circle = osteoblast activity, red circle = osteoclast activity.

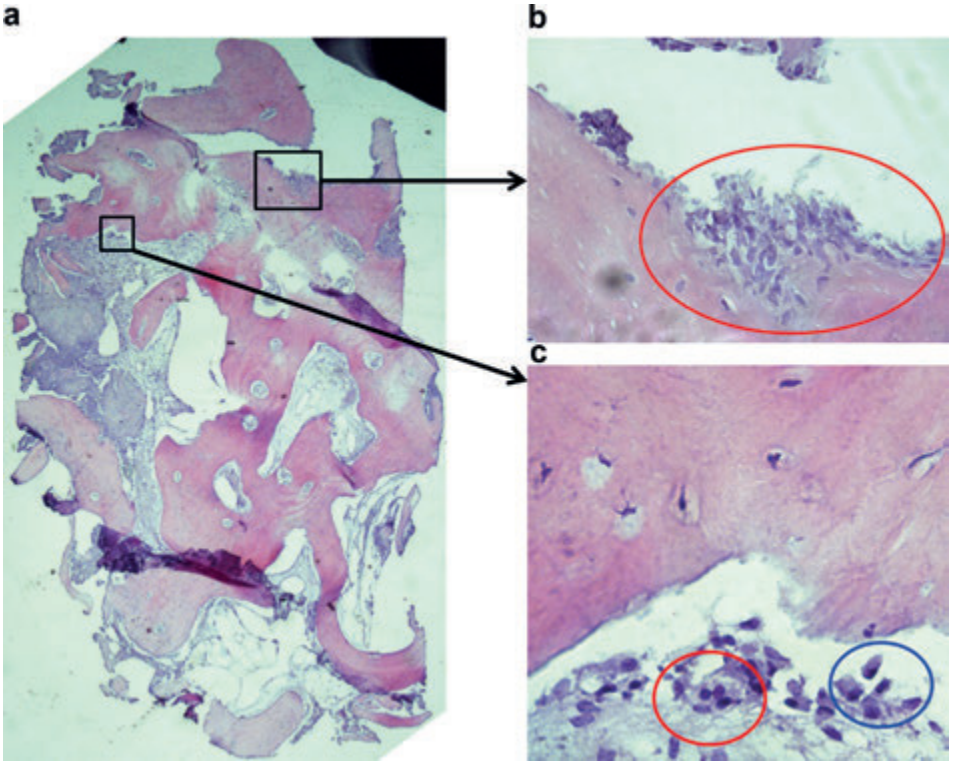

Figure 2. a) *Active bone remodeling is defined by the presence of osteoblastic and osteoclastic activity.* ***b)*** *The red circle shows osteoclastic activity.* ***c)*** *In the blue encircled field osteoblastic activity is documented, in the red encircled field osteoclastic activity.*

The engrafted bone filling material does not yet show any form of resorption or osseous remodeling. The bone substitute granules are covered by thin newly formed trabeculae directly attached to the surface of this material. In higher image magnification the ankylosing effect of the intergranular osseous union is visible leading to stable and compact bone in the sinus floor augmentation. In contrast to the vital bone trabeculae the bone substitute material does not hold any vital osteocytes. Histologically no inflammatory reaction is seen in the neighborhood of the xenogenous bone material. There seems to be no immunological reaction as there are no lymphocytes or other round cells visible.

The intergranular soft tissue is well vascularized without proof of cell material which could lead to a disturbance of the osteo-anabolic bone healing process. Intermittent macrophages are visible in close neighborhood to the Bio-Oss® particles.

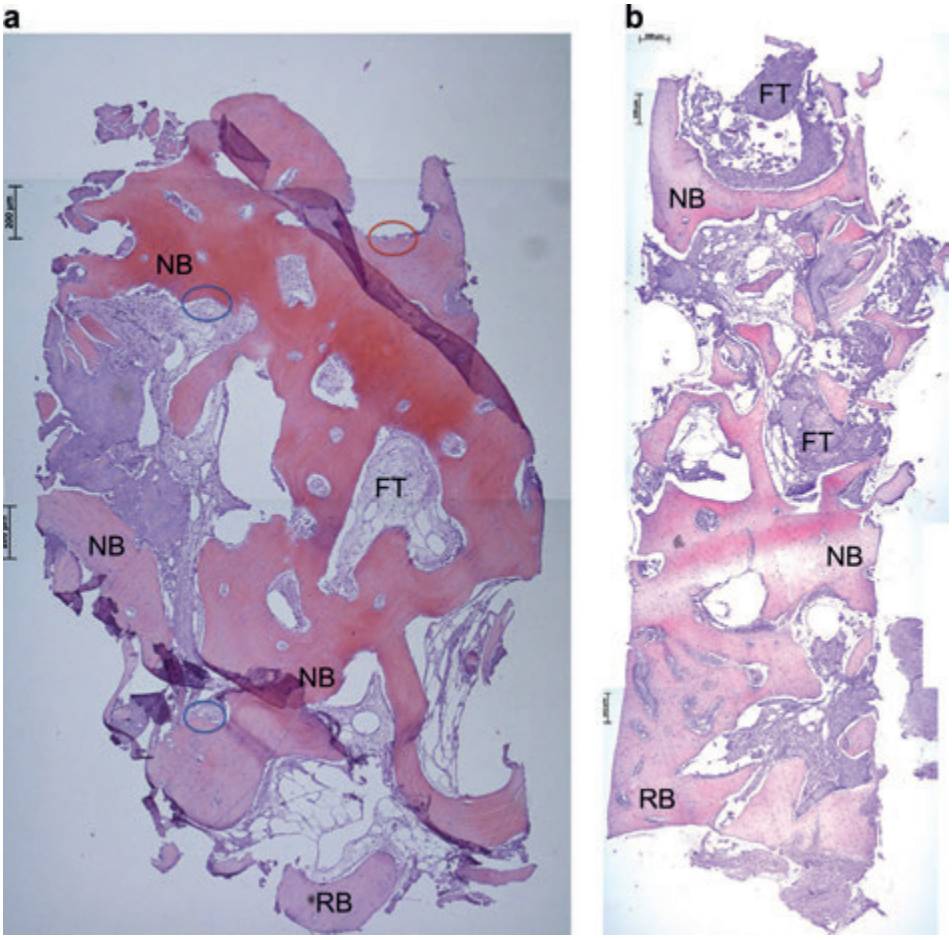

Figure 3. a) and b) *The inter-trabecular space is mostly filled with undifferentiated primary bone marrow. Histologically fibroblasts and fibrocytes are dominant in this granulation tissue.*

NB = new bone, RB = residual bone, FT = fibrous tissue, blue circle = osteoblast activity, red circle = osteoclast activity.

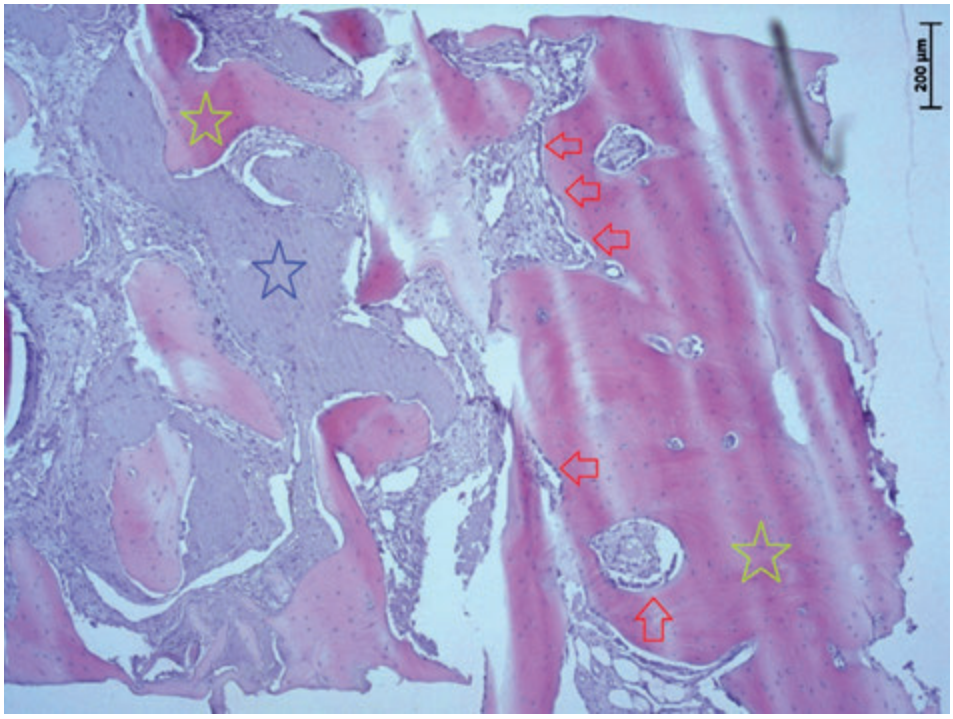

Figure 4. *This histological image shows evidence of persistent neo-ossification and a well-vascularized, cell-rich presence of trabeculae and bone marrow. There are both old trabeculae (blue star) as newly formed (yellow star), but still less calcified and less fiber-rich cells. Osteoid trabecular structures are formed and seen near the osteoblasts (red arrow) linked by tight junctions, which speaks for an intense new bone formation.*

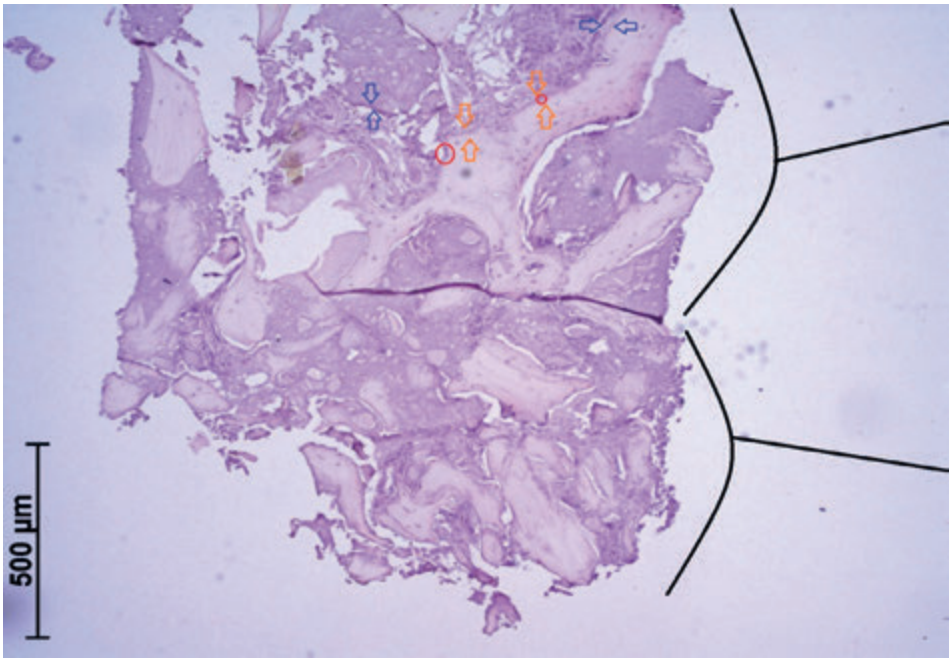

Figure 5. The upper part *shows neo-trabeculae with evidence of osteoblasts (blue arrow) and osteoid forming matrix (yellow arrow) with embedded osteocytes (red circle).*

The lower part *shows residual bone of the sinus wall with a dense trabecular structure and well-vascularized inter-trabecular internal spaces with sporadic evidence of osteoclasts and missing osteoblastic activity.*

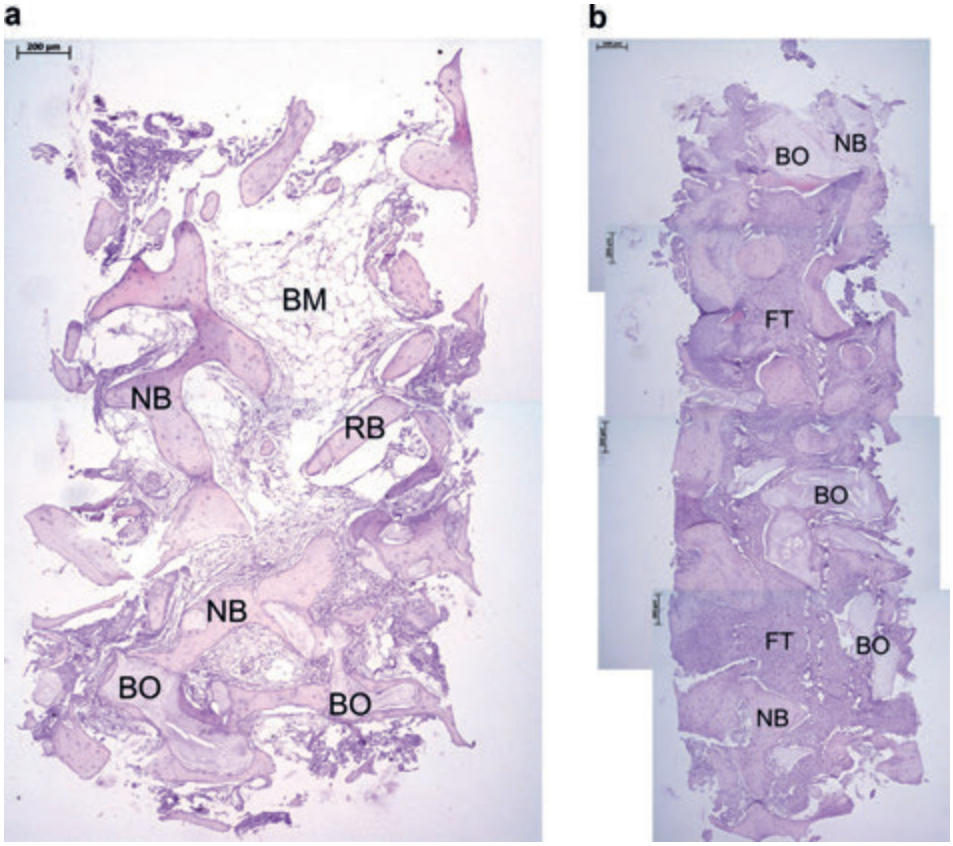

Figure 6. *Augmented side:* ***a)*** *The bone biopsies of the conventional side show a combination of Bio-Oss® embedded in bone marrow and newly formed bone.* ***b)*** *The respective augmentation compartments BO : FT : NB are at ratio of 30 : 40 : 30 percent.*

BO = Bio-Oss®, NB = new bone, RB = residual bone, BM = bone marrow, FT = fibrous tissue.

DISCUSSION

Several studies have already proven new bone formation after maxillary sinus lift procedures follwed by leaving a space filled with blood. In most studies direct implant placement helped to create a submembraneous space in the sinus with the implant as a spaceholder [23-25]. All these studies were performed in partially dentate patients resulting in a more extended bone-to-callus contact area than in the case series presented here. The effect of the implant surface as stimulus for bone regeneration cannot be neglected and is one of the major differences the study set-up compared to our study.

In this study on edentulous patients with highly atrophic maxillae bone-to-callus contact was only possible on the palatal side and in the floor of the sinus. For proper bone regeneration we had to wait with implant placement for six months. Due to the relatively long healing period a transformation of the red bone marrow into secondary marrow of the yellow type (yellow bone marrow) could already be seen in the basal regions of the histological thin slice preparation close to the originating bone of the maxillary floor. Thus, according to our theory these regions of the specimens belonged to the bone layers forming the primary originating bone in the bone generation process. This indicates that the bone formation process starts at bone-callus junction like in distraction osteogenesis. The rich vascularization of the interosseous soft tissues indicates a primary angiogenic bone formation which was described by Stefan Krompecher already in the thirties of the last century [26]. One can assume that the bone formation and remodeling process in the floor of the maxillary sinus is promoted by the surrounding bony tissues.

Apparently the bone formation process had reached a steady state as the spontaneous bone generation seemed to be depleted. Rounded trabeculae extending into the submembranous space are corresponding signs of an exhausted bone generation process. An osteoconductive reaction cannot be expected due to the lack of bone substitute material. So the generation of new bone comes to a still stand after having created a certain bone volume (so called "distance problem in bone regeneration").

Bio-Oss® is a natural bone substitute material derived from the mineral portion of bovine bone. The remarkable similarity to human bone makes Bio-Oss® an important and predictable material in the regenerative regimen in oral surgery [27, 28]. Due to the material characteristics and lacking functional loading, an osteonal reorganization of the newly formed bone cannot be seen. The attachment of newly formed trabeculae to the surface of the bone substitute granules indicates the guiding function of the

bone substitute material in the scope of new bone formation (implant hopping). This effect is typically seen in osteoconductive bone remodeling and has been described in numerous studies before. In due consideration of the generally accepted postulation of at least 20 to 35% of bony reorganization in sinus floor augmentations, the histological examination of the bone specimens is in rough estimation also valid for the present preparations [29]. The respective augmentation compartments BO : FT : NB are at ratio of 30 : 40 : 30 percent (fig. 6b). (BO = Bio-Oss®, FT = fibrous tissue, NB = new bone).

Two phenomena are well known in maxillary sinus pathology: The one is the 'silent sinus syndrome' which is defined as a rare disease with collapse of the maxillary sinus caused by chronic hypoventilation [30-32]. Negative pressure forms in the sinus as a result of obstruction of the maxillary sinus ostium. This syndrome is also related with enophthalmos, chronic sinusitis and thinning of the sinus walls [33]. Even a total collapse of the sinus walls has been described. The other phenomenon is often seen in edentulous patients. The volume of the maxillary sinus tends to expand to the alveolar process, also combined with an extreme thinning of the bordering walls. However, the aeration of the sinus remains intact and this is essential to avoid maxillary sinus diseases. So the sinus remains healthy, but extreme atrophy, especially in the floor of the maxillary sinus, causes problems with dentures and makes placement of implants impossible. From the standpoint of a healthy maxillary sinus, callus formation affecting the sinus walls with reduction of the sinus volume must be regarded as unfavorable, as this might lead to obstruction and sinus diseases. The "distance problem" in bone regeneration in healthy sinuses seems to block the risk of total obstruction of the sinus by new bone formation.

For the explanation of the results discussed here one should not forget about the complications of the classical Caldwell-Luc operation. The Caldwell-Luc operation has been employed for about 90 years for various indications of intra-sinus diseases, mostly chronic maxillary sinusitis. There is an abundance of literature citing the complications and morbidity associated with this technique. And these were far greater than mostly realized. Among others, thickening of the sinus walls with contraction of the affected lateral midface could be observed leading to facial disfigurement, chronic neurological pain, ocular dystopia and dental problems [34]. An aerated paranasal sinus which is deprived of its function by total or sub-total resection of the respiratory epithelium will be filled by a hematoma. The hematoma will be organized and partly be ossified or transformed into connective tissue. The sinus walls may thicken as a result of reactive bone formation; the sinus walls may also collapse, narrowing the antral cavity. Postoperative synechiae may develop within the antral cavity, possibly

causing compartmentalization of the cavity and formation of postoperative mucocele. The pathophysiology described in combination with the Caldwell-Luc operation might be the key to the explanation of the success of the clinical study presented here with only limited intra-maxillary exposition of bone and preservation of the functional matrix of the sinus membrane.

Complex but nevertheless common implantological and pre-implantological procedures with bone augmentation can sometimes impact on sino-nasal homeostasis and require intervention. The maxillary sinus floor augmentation requires a peculiar evaluation of potential candidates, since the procedure permanently modifies the maxillary sinus anatomy. Any present or potential obstruction of the sinus drainage has to be avoided during the augmentation procedure. Pre-existing ostiomeatal obstructions and sinus conditions or poorly executed pre-implantological procedures (e.g. rupture of sinus membrane) may lead to immediate and long-term infective complications, both acute and chronic.

In contrast to periosteal and medullary callus formation in fracture models, the callus formed in a natural body's cavity cannot be regarded as sensitive to mechanical stress as this is absent during osteoneogenesis. By implanting a resorbable, perforated elevation mesh we tried to create a kind of tension on the surrounding tissues, at least a barrier function directed at the sinus membrane. The position of the elevation mesh was deliberately planned to avoid any obstruction of the natural meatus to guarantee sufficient aeration to avoid sinusitis or a 'silent sinus syndrome'.

Shirley et al. demonstrated in bone fracture models that bone marrow stem cells are systematically mobilized and attracted to fracture sites from remote cell depots. The same effect can be postulated for a clinical model where a similar callus forming can be observed as in fracture healing [35]. The effect of a stable callus forming on osteoneogenesis in the floor of the maxillary sinus is decisive above all because this callus protects the sensitive, essential medullary healing process, which hesitantly follows, against damaging stimuli as they are well known in fracture or distraction models [2]. The lack of interfering bending, shearing and compressive forces on the augmentation site in the sinus can be interpreted as one factor protecting the callus, despite the fact that mechanical stress in appropriate doses might also have stimulating effects.

A callus is protective to the surrounding tissues. We called the callus formed in the maxillary sinus a periosteal and medullary callus. These termini are used in fracture and bone distraction research. The callus formed in the artificial cavity in the floor

of the sinus by tenting the sinus membrane must be regarded as different. It is to the nearly complete lack of formation of any periosteal callus as only at the lateral aspect of the defect periosteum is covering the wound (window approach). The primary hematoma is formed by creating a bone wound by removing sinus membrane from the floor of the sinus, the lateral and medial sinus walls. The denudation of the bony walls on at least three sides of the sinus obviously leads to the formation of a stable hematoma which later is transformed in a bone forming callus. In this context harmful mechanical forces exerting their specific action freely on the sensitive tissues of regeneration must be absent. Thus all conditions are fulfilled that ensure that no disturbing forces can exert a decisive influence on the stability of the callus.

In the literature the role of the sinus membrane with regard to bone formation remains somewhat unclear. Scala et al. did not find bone formation originating from the respiratory epithelium in their elevation study based on implants [36]. Rong et al. state in their publication [37] on an animal experiment that the sinus membrane has bone forming capacity, but weaker than that of the surrounding bony walls of the maxillary sinus [38, 39]. Srouji et al. and Graziano et al. isolated and cultured osteoprogenitor cells from mucosa of the human maxillary sinus and confirmed its bone forming potential [16, 40]. Srouji et al. also transplanted the sinus membrane in ectopic locations in nude mice and found that new bone formed, confirming the osteogenetic potential of sinus membrane. Own studies proved that a bone generation process originating from the sinus membrane can be definitively excluded. Animal experiments in Göttingen minipigs showed this in fluorescence microscopic analyses [41].

The small number of patients could be regarded as a limitation of the study. The constant results of de-novo bone formation in all patients independent of their individual disposition is indicative of low inter-individual variations and a stable, predictive physiological tissue reaction on sinus membrane elevation.

CONCLUSION

A de-novo bone formation in the bottom bulges of the maxillary sinus in edentulous patients is possible by elevating the sinus membrane without filling the gap with bone, matrices or bone substitute material. Bone generation in artificially created spaces in the maxillary sinus starts from the bony walls surrounding the defect. In the beginning a spontaneous bone formation can be seen which later will be followed by a true new bone generation based on angiogenic ossification [26]. In a self-supporting space without bio-functional loading the amount of unidirectional bone formation originating from the bony walls of the maxillary cavity will exhaust. The limiting factor of bone formation in the artificially created functional "dead space" will be defined by the "distance problem" of spontaneous bone generation. Future perspective: In pre-prosthetic implant placement short implants are common. The use of these short implants has been increased in the last years [42]. These so called "shorties" could be an ideal option in atrophic maxillae with a limited amount of newly generated bone. To gain an optimum of bone volume in spontaneous bone generation it is of utmost interest to plan the insertion of implants at the right moment. If the right moment for inserting implants is missed out, the newly generated bone might resorb as "resorption blockers" like engrafted bone substitutes, e.g. Bio-Oss®, and a functional impact are missing.

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CHAPTER 4

Non-grafted versus grafted sinus lift procedures for implantation in the atrophic maxilla: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

The aim of this systematic review and meta-analysis was to critically evaluate the currently existing clinical evidence on the efficacy of graftless maxillary sinus membrane elevation for implantation of the atrophic posterior maxilla. A search protocol without limitations to November 2020 was followed by two independent researchers. Randomized controlled trials using the lateral window approach for graftless sinus membrane elevation were included. Uncontrolled, retrospective, non-comparative studies, case reports and experimental studies in animals or cadavers were excluded. The search identified 2777 studies, this was followed by a critical selection by two independent researchers who eventually included a total of nine studies. A risk of bias assessment was applied using the Revised Cochrane risk-of-bias tool for randomized trials. A meta-analysis was conducted for seven studies. Results show a high overall implant survival rate in both the graftless and bone grafted sinus lift groups (respectively 97.92% and 98.73%). The graftless sinus lift group shows a significant lower vertical bone height gain with a mean difference of -1.73 mm ($P=0.01$) and a significant lower bone density with a mean difference of -94.7 HU ($P<0.001$). The Implant Stability Quotient values showed no significant differences between the test and control group ($P=0.07$).

INTRODUCTION

Dental implants require a certain amount of peri-implant bone. The primary goal in dental implantology must remain the complete and stable integration of an implant in local bone. Treatment of highly atrophic alveolar ridges is still challenging. To increase local bone volume, lateral and vertical bone augmentation procedures are performed[1-4]. Autogenous bone grafts are still regarded as the gold standard for all kinds of horizontal and vertical bone augmentation[5, 6]. Common intraoral donor regions are, for example, the chin region and the retromolar area[7, 8]. Another option is the use of extra oral donor sites, such as the cranium or pelvic bone from the anterior or posterior iliac crest[9, 10].

Its osteogenic properties make autogenous bone grafts superior to bone substitute materials[6, 11]. However, when using autogenous transplants, there are drawbacks such as unavoidable donor morbidity and the limited availability of bone volume, especially from intraoral donor sites, and additional costs[12-14].

To avoid the use of autogenous bone, bone substitutes are used as an alternative[15]. Bone substitute materials are a valid alternative and often used in combination with membranes, in the sense of guided bone regeneration[3, 16].

Most augmentation procedures in the atrophic posterior maxilla are combined with elevation of the maxillary sinus membrane. The basal linings of the sinus membrane cannot be considered as pure periosteum, nevertheless numerous studies show new bone formation underneath the sinus membrane after elevation without using any bone grafts[16-19].

The lateral window technique to approach the maxillary sinus for increasing bone volume in the posterior maxilla is a well-established and documented surgical procedure allowing for simultaneous or staged dental implant placement[4, 20-23]. Graftless sinus membrane elevation for later implant placement avoids donor site morbidity after harvesting autogenous bone and prevents the use of any kind of bone replacement material. This would mean less discomfort for the patient with regard to sinus floor augmentation[9, 10, 12-14].

According to earlier systematic reviews that described the graftless sinus lift, this procedure leads to a high implant survival in the atrophic maxilla[24-29]. However, no systematic review is performed that included only prospective randomized controlled trials using the lateral window technique for graftless sinus floor augmentation.

The aim of this systematic review was to critically evaluate the currently existing clinical evidence on the efficacy of graftless maxillary sinus membrane elevation using the lateral window approach for implantation of the atrophic maxilla.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews (PRISMA) statement for reporting systematic reviews[30]. The focused questions were: Is the de-novo bone formation in graftless maxillary sinus membrane elevation comparable to sinus floor augmentation with the use of bone grafts? Is implant survival in the graftless sinus lift comparable to the sinus lift with the use of bone grafts?

Search strategy

A search of MEDLINE (PubMed), Cochrane Library, Embase (Elsevier) databases and recent journal review was performed. Search terms were: "sinus membrane elevation" OR "sinus floor augmentation" OR "maxillary sinus lift" OR "Sinus Floor Augmentation"[MeSH Terms]. No search limitations were applied. The search period was performed until the 1st of November 2020. An additional hand-search or grey literature search was performed.

Study selection and data extraction

We used the population, intervention, control, outcome and study (PICOS) guidelines to define eligible studies. In the population (P) were patients with maxillary atrophy in need for a sinus floor augmentation for immediate or staged implant placement. The intervention (I) was tenting of the maxillary sinus membrane without the use of any bone substitutes. The comparison (C) was made with the sinus floor augmentation using bone grafts. Eligible outcomes (O) were implant survival, bone height gain and bone density measured on radiographic images, implant stability and histology. The study designs (S) were prospective randomized controlled trials with an observation period of at least six months.

We have accepted a minimum number of five comparative sinuses in the included studies. Staged or simultaneous implantation were both included, as long as a tenting technique of the sinus membrane was performed and the sinus was approached using the lateral window technique.

The osteotome technique, the use of growth factors, case reports, retrospective studies, non-comparative studies, technical notes, animal studies, cadaver studies and reviews were excluded.

Two reviewers (NL and CL) contributed to the elaboration of the systematic review through research, reading, critical article selection and data extraction. All references were transferred to and screened using Rayyan (Rayyan, Qatar Computing Research Institute, Qatar Foundation)[31]. After screening the titles and abstracts potential studies were selected. A critical selection was made after reading full texts of the potential studies according to the inclusion and exclusion criteria. In case of disagreement a group discussion with a third reviewer (PK) led to a decision whether to select an article or not. A meta-analysis of the included studies was performed.

Data information that was extracted by the reviewers were: year of publication, study design, number of patients, tenting technique, used grafts in control group, immediate or two-phased implantation, number of placed implants, follow-up, partially dentate or complete edentulous patients, residual bone height, outcome method, implant survival, vertical bone height gain, bone density, Implant Stability Quotient (ISQ), other used outcomes and complications.

Risk of bias assessment

The risk of bias was assessed independently by the two researchers (NL and CL) according to the "Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)"[32, 33]. The tool classifies five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported result. The excel tool to implement RoB 2 was used for this assessment.

Statistical analysis

The means and standard deviations (SD) of vertical bone height gain, bone density, ISQ values and implant survival were extracted from the included studies. When the mean or SD values were not mentioned in the article, these could be calculated from the available data. For continuous data the inverse variance method was used. The Mantel-Haenszel method was used for dichotomous data. Study heterogeneity was assessed using DerSimonian and Laird method and I-square index. I^2 values are interpreted as follows: at 0-40% might not be important, from 40-60% were classified as moderate heterogeneity, from 60-80% were classified as substantial heterogeneity and values from 80-100% may represent considerable heterogeneity[32]. If moderate, substantial or considerable heterogeneity was found, the random-effects model was chosen to minimize any bias caused by methodological differences among studies. The fixed effects method was chosen when there was no evidence of heterogeneity. Outcomes were expressed as weighted mean difference (WMD) and the 95% confidence interval (CI) was used for the meta-analysis. The level of significance was determined by a

P-value of 0.05. Forest plots were generated to graphically represent the difference in outcomes for all included studies. Extracted data were analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA). Publication bias was assessed via a funnel plot.

RESULTS

Study selection and characteristics of the studies

The search strategy identified 2777 studies after de-duplication. There were 44 articles potentially relevant for inclusion. After a full-text read and a critical selection, eventually 9 articles were included for this review (Fig. 1)[16, 34-41], 7 articles were eligible for meta-analysis[16, 34-37, 39, 40]. A total of 160 patients were included in these selected studies. The tenting technique without the use of any bone graft was performed in 112 maxillary sinuses and this was compared to the sinus floor augmentation in 104 maxillary sinuses with autografts, allografts, xenografts, alloplasts or a mixture of these bone substitutes. A total of 426 implants were placed. The characteristics of the articles are described in table 1.

Different tenting techniques were used: in some studies implants were used as a space holder to keep the sinus membrane elevated[34, 35, 37-40] and other studies used a resorbable material to keep the membrane lifted[16, 36, 41]. The three studies that did not use an implant as space holder planned a two-staged procedure, where implants were placed six months after the sinus floor augmentation. These three studies took the opportunity to take bone biopsies right before placing the implants with a small trephine drill for histological research. One study[38] even retrieved implants, six months after placing them, to analyze bone-to-implant-contact. Table 2 describes the outcome methods and results of the 9 selected studies.

Risk of bias assessment

The risk of bias assessment is summarized in figure 2 and 3. Six articles were assessed at low risk of bias[16, 35-37, 39, 40]. Three articles had some concerns in risk of bias[34, 38, 41], these three did not describe if the randomized allocation was blinded until the day of the intervention. One article[38] described the loss of an implant. However, this implant was not included in the results. No studies with high risk of bias were analyzed.

Data synthesis and meta-analysis

Implant survival

Of the 9 selected articles, 7 could be analyzed with regard to implant survival[16, 34-37, 39, 40]. In one study[38], two different test groups and a control group were used. In the first test group one implant was lost. The exact number of implants in each group was not described. Scarano et al.[41] did not mention implant survival of the 34 implants placed in the test and control groups.

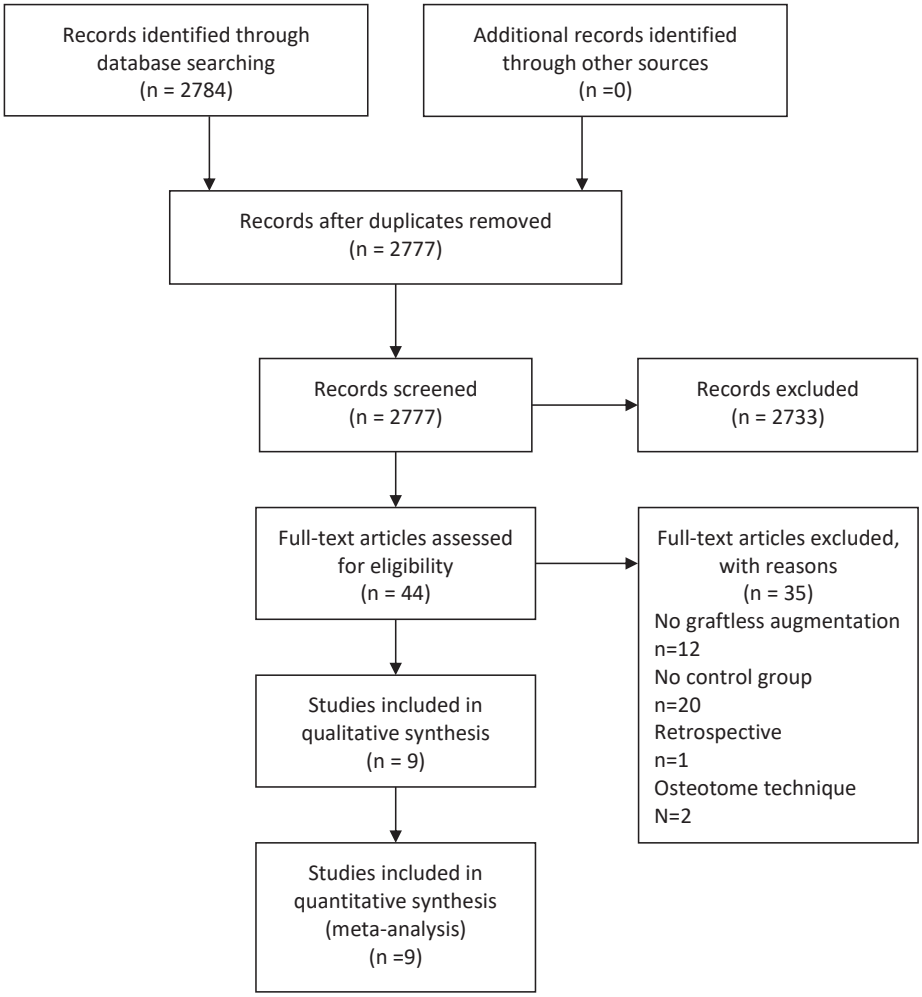

Figure 1. *PRISMA flow diagram of the study selection process.*

Table 1. Articles included for review: characteristics. ND, not determined; PDLLA, poly(D,L-lactic acid); RCT, randomized controlled trial.

Author year	Study Design	Patients (n=)	Test group (n=)	Control group (n=)	Graftless side: tenting technique	Graft side
Altintas 2013 [34]	RCT	14	10	10	Implant	Allograft
Borges 2011 [35]	RCT, split mouth	15	15	15	Implant	Autograft
Felice 2009 [36]	RCT, split mouth	10	10	10	Resorbable barrier (Inion)	Xenograft
Fouad 2018 [37]	RCT	17	10	10	Implant	Xenograft
Johansson 2013 [38]	Randomized, three groups	24	10 / 10	10	Implant (with bone window replacement / collagen membrane)	Autograft
Khaled 2019 [39]	RCT	19	10	10	Implant	Alloplast
Lie 2015 [16]	RCT, split mouth	5	5	5	Resorbable membrane (PDLLA)	Mixture of autiograft and xenograft
Ranaan 2018 [40]	RCT	33	18	20	Bovine pericardium membrane + implant	Allograft
Scarano 2018 [41]	RCT	23	14	14	Heterologous cortical lamina	Xenograft
TOTAL: 9		160	112	104	Graftless	Autografts, Allografts, Xenografts, Alloplasts

	Implant placement	Implants test (n=)	Implants control (n=)	Follow-up (mo)	Patients included: partial / fully edentulous	Residual bone height (mm)
	Immediate	12	12	6	Both	4-6
	Immediate	28	26	6	Both	5.89 (test) / 5.34 (control)
	After 6 months	24 (-3)	24	5 (after loading)	Partial	3.4 (test) / 2.8 (control)
	Immediate	17	17	6	Partial	4-6
	Immediate	101 (total)	101 (total)	7	Partial	4.3 (test) / 3.5 (test) / 4.3 (control)
	Immediate	13	12	6	Partial	4-6
	After 6 months	15	15	6 (post-loading)	Fully	ND
	Immediate	36	40	6, 8 and 24	Partial	5.48 / 4.69
	After 6 months	34 (both groups)	34 (both groups)	6	Both	2-3
		229 (-3)	197			

Table 2. *Articles included for review: outcomes. BIC, bone-to-implant contact; CBCT, cone beam computed tomography; CT, computed tomography; ISQ, implant stability quotient; ND, not determined; NS, no significance.*

Author	**Outcome method**	**Implant survival (test/ control) (%)**	**Bone height gain (mm) test/control**	**Bone density (test/ control)**	**ISQ (test/ control)**
Altintas [34]	CBCT	100 / 100	ND	254,91 / 16.25 (P<0.05)	ND
Borges [35]	CBCT, ISQ	96,4 / 100	7.91 / 8.31 (P>0.05)	194.42 / 207 (P>0.05)	51 / 50 (P>0.05)
Felice [36]	CT, histomorphometry	100 / 100	14.4 / 14,1 (no significance)	ND	ND
Fouad [37]	CBCT, ISQ	100	4.85 / 8.59 (P<0.05)	269,08 / 375.59 (P<0.05)	74 / 78.3 (P<0.05)
Johansson [38]	CBCT, retrieved implants	3 groups (test/ test/control) 1 failure / 100 / 100	ND	ND	ND
Khaled [39]	CT, ISQ	100	5.0 / 7.0 (P=0.002)	420 / 548 (P<0.001)	77 / 78 (P=0.901)
Lie [16]	CBCT, histology	100 / 100	7.78 / 9.99 (no significance)	ND	ND
Ranaan [40]	CBCT, ISQ	94,4 / 95	12.82 / 14.36 (P=0.002)	ND	78.95 / 81.45 (P=0.108)
Scarano [41]	CBCT, histology	ND	ND	ND	ND

Other outcome	Complications (test/control)
New bone around apices implants (test: 0/12, control: 3/12)	No complications observed
Bone around implants (similar results test/ control)	- 2 sinus mucosal perforations <2 mm (1/1) - 2 postoperative wound infections (1/1) - 4 incomplete closing of lateral window (3/1) 1 implant no osseointegration (1/0)
New bone formation in histology (test: 24.2%, control: 36.1% (p=0.002))	- 3 rupture of sinus membrane (2/1) 1 window filled with fibrotic tissue ? Bio-Oss was placed (1/0)
ND	2 membrane perforations (2/0)
- Retrieved implants, bone-to-implant contact (test 1: 93,5%, test 2: 92,0%, control: 93,5%) - Apico-buccal/lingual distances (test 1: 0.6/1.2, test 2: 0.5/0.8, control: 0.6/0.8) - No significant results	- 1 implant no osseointegration (1/0) - 3 Not completely ossified walls (3/0)
ND	3 small membrane perforations (2/1)
- Detailed description of histology: new bone formation, less organized and immature at test side. - Patient satisfaction:100% both sides	- ND
- Two different implants - 1 histological biopsy (test): new bone formation - Bone height after 24 months less than after 6 months	- 9 membrane perforations <2 mm (4/5) - 4 lost implants (2/2)
- Graft volume (mm3) imm postop, 6 mo postop (test: 2801, 1912.1; control: 3101, 2716) - Histology: newly formed bone (test: 27%, control: 34%)	- 3 membrane perforations (2/1)

Figure 2. *Risk of bias analyzed per study.*

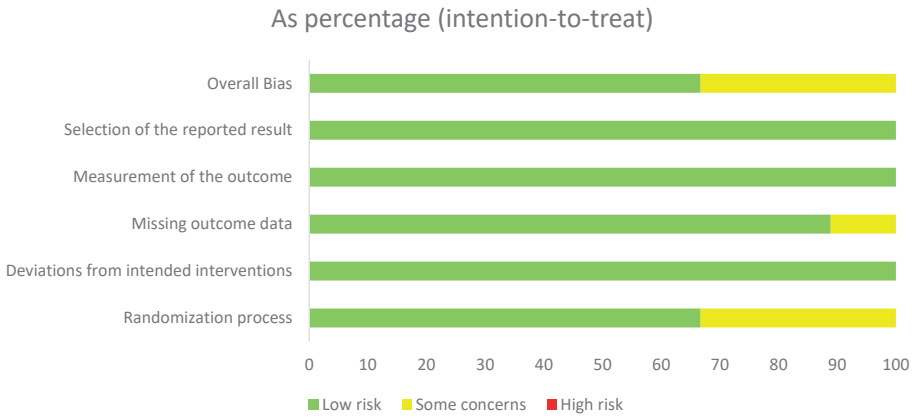

Figure 3. *Risk of bias summary; 33,3% of the studies had some concerns in risk of bias and 66,7% of the studies had low risk.*

The seven articles in table 3 showed high overall implant survival in the test group and control group of respectively 97.92% and 98.73%. There was no evidence of heterogeneity (P=1.00, I^2 =0%). The fixed-effects model was used in the meta-analysis. There was no statistically significant difference between the test and control group, with a risk ratio (RR) of 1.00 (95% confidence interval 0.79-1.25, P=0.94) (Fig. 4).

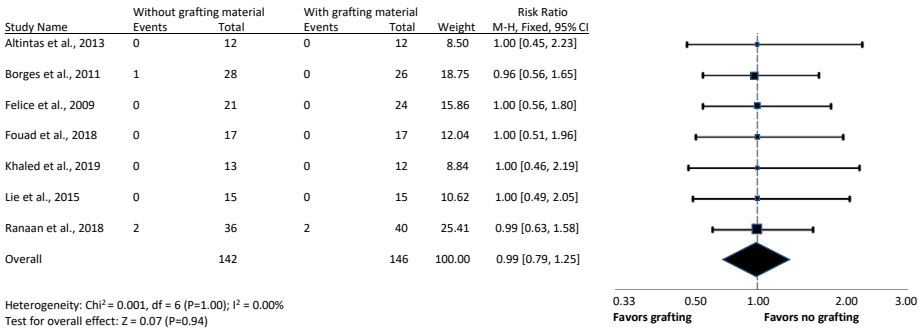

Figure 4. *Forest plot comparing implant survival in graftless and grafting groups.*

Bone gain on radiographic images

Six articles[16, 35-37, 39, 40] described the vertical bone height gain measured on computed tomography (CT) images or cone-beam computed tomography (CbCT) images. Due to evidence of heterogeneity (I^2 = 83.5%, P=0.27) the random-effects model was applied in the meta-analysis. The analysis showed a significant difference (P=<0.01) with less vertical bone height gain in the graftless group with a mean difference of -1.73 mm (95% CI -3.04 to -0.41) (Fig. 5).

Four studies analyzed new bone formation around the implants on CT's, but no significant differences between the two sides were found[34-36, 38].

Scarano et al.[41] described the graft volume immediate and six months postoperative after elevation of the sinus membrane. At both times the graft volume was less on the test side (see table 2).

Bone density

Four studies compared bone density. Meta-analysis was applied using the random-effects model, because of substantial heterogeneity (I^2 = 62.86%, P<0.001). Bone density was significant higher (P=<0.001) on the grafted side with a mean difference of -94.7 HU (95% CI -134.9- -54.5) (Fig. 6).

Study Name	Without grafting material Mean	SD	Sinuses	With grafting material Mean	SD	Sinuses	Weight	Mean Difference IV, Random, 95% CI
Borges et al., 2011	7.91	3.60	15	8.31	2.60	15	14.01	-0.40 [-2.65, 1.85]
Felice et al., 2009	14.40	1.70	10	14.10	2.50	10	15.99	0.30 [-1.57, 2.17]
Fouad et al., 2018	4.85	0.51	10	8.59	0.74	10	22.68	-3.74 [-4.30, -3.18]
Khaled et al., 2019	5.00	1.53	10	7.03	0.79	10	20.47	-2.03 [-3.10, -0.96]
Lie et al., 2015	7.78	3.65	5	9.99	3.82	5	6.03	-2.21 [-6.84, 2.42]
Ranaan et al., 2018	12.82	1.48	16	14.36	1.48	18	20.82	-2.33 [-2.54, -0.54]
Overall			66			68	100.00	-1.73 [-3.04, -0.41]

Heterogeneity: $Tau^2 = 1.91$; $Chi^2 = 6.36$, df = 5 (P=0.27); $I^2 = 83.54\%$
Test for overall effect: Z = 2.57 (P=0.01)

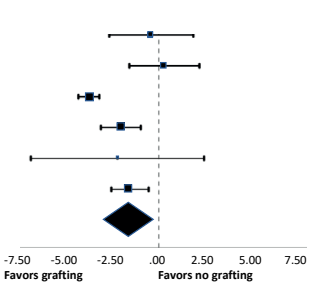

Figure 5. *Forest plot comparing vertical bone height gain in graftless and grafting groups.*

Study Name	Without grafting material Mean	SD	Sinuses	With grafting material Mean	SD	Sinuses	Weight	Mean Difference IV, Random, 95% CI
Atlintas et al., 2013	254.9	246.9	12	16.3	438.7	12	1.92	238.7 [- 46.2, 523.5]
Borges et al., 2011	194.4	84.8	15	207.0	143.6	15	15.67	- 12.6 [- 97.0, 71.8]
Fouad et al., 2018	269.1	16.3	10	375.6	49.4	10	38.10	-106.5 [-138.7,- 74.3]
Khaled et al., 2019	420.0	23.0	10	548.0	25.0	10	44.31	-128.0 [-149.1,-106.9]
Overall			47			47	100.00	- 94.7 [-134.9,- 54.5]

Heterogeneity: $Tau^2 = 853.7$; $Chi^2 = 40250.3$, df = 3 (P<0.001); $I^2 = 62.86\%$
Test for overall effect: Z = 4.61 (P<0.001)

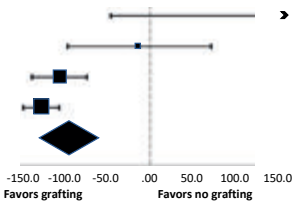

Figure 6. *Forest plot comparing bone density in graftless and grafting groups.*

Implant stability

The implant stability was measured six months after implantation in four studies[35, 37, 39, 40]. Only one article found a significant difference in favor of the grafted side[37]. Due to the substantial heterogeneity ($I^2 = 61.48\%$, P<0.001), the meta-analysis was applied using the random effect model. There was no significant difference found in mean ISQ between the non-grafted and grafted side (-2.12 95% CI -4.40- -0.15, P=0.07) (Fig 7).

Study Name	Without grafting material Mean	SD	Implants	With grafting material Mean	SD	Implants	Weight	Mean Difference IV, Random, 95% CI
Borges et al., 2011	51.00	6.00	27	50.00	8.00	26	16.44	1.00 [-4.06, 6.06]
Fouad et al., 2018	74.00	3.19	17	78.30	5.08	17	28.10	-4.30 [-7.85, -0.75]
Khaled et al., 2019	77.00	5.00	13	78.00	5.00	12	20.66	-1.00 [-5.38, 3.38]
Ranaan et al., 2018	78.95	7.52	32	81.45	5.04	36	34.81	-2.50 [-5.35, -0.35]
Overall			89			91	100.00	-2.12 [-4.40, 0.15]

Heterogeneity: $Tau^2 = 1.49$; $Chi^2 = 8.93$, df = 3 (P=0.60); $I^2 = 61.48\%$
Test for overall effect: Z = 1.83 (P=0.07)

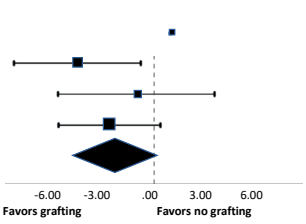

Figure 7*. Forest plot comparing implant stability in graftless and grafting groups.*

Histology

Histology showed 24% vs. 36% of new bone formation in the bone cylinders on the test and the control sides respectively in the study of Felice et al. Scarano et al. found comparable results with new bone formation of 27% and 34% respectively[36, 41]. The implants removed from the study of Johansson et al. showed no significant differences between the test and control groups[38]. Lie et al. described new bone formation and remodeling with presence of osteoblasts and osteoclasts in both groups[16]. However, the test side showed less organized and immature bone quality. Ranaan et al. retrieved one implant for histological analysis to prove new bone formation on the test side[40].

Publication Bias

A funnel plot was drawn of the studies that compared bone height gain (Fig. 8). One study[37] is found to be outside the funnel plot. Another study[16] shows a deviation of the standard error (SE) from the overall result[16, 37]; this asymmetry may indicate publication bias.

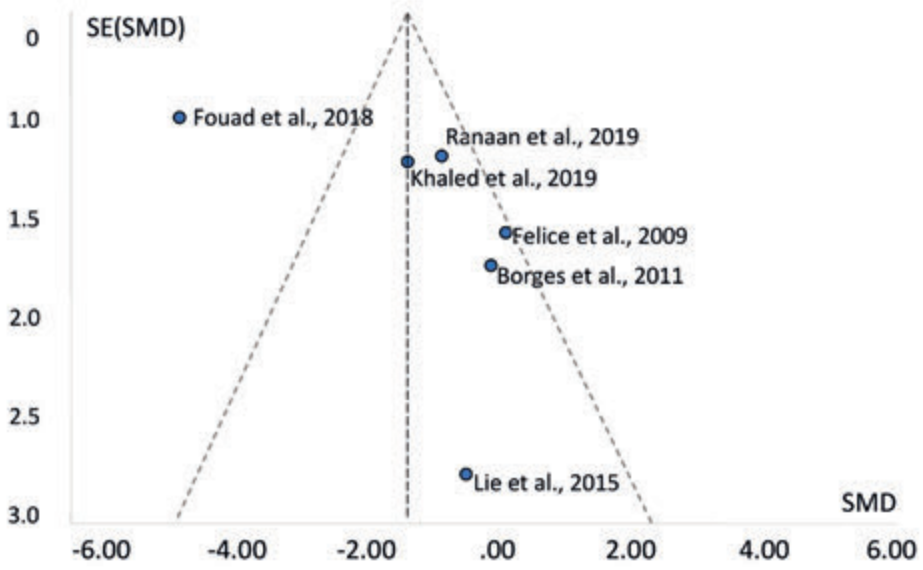

Figure 8. *Funnel plot assessing potential publication bias for studies reporting vertical bone height gain (SE=Standard Error, SMD=Standard Mean Difference).*

DISCUSSION

Osseointegration of implants is essential to provide stability and long-term success. To achieve a reliable osseointegration, the presence of bone is mandatory. Sufficient residual bone or new bone formed by sinus membrane elevation has a positive influence on the implant survival[42, 43].

Tenting of the sinus membrane by simultaneous implant placement without grafting material can only be successful if the remaining alveolar height guarantees primary implant stability[19, 44, 45].

In the posterior maxilla the vertical distance between the floor of the maxillary sinus and the crest of the posterior maxillary alveolar process constitutes the subantral bone height. This bone height is often used to determine whether implants can be placed simultaneously with sinus floor elevation in a one-step procedure or whether a staged approach has to be preferred[46]. According to the literature a minimal remaining alveolar crest height of about 3 mm must be present for sufficient primary implant stability[45]. Primary implant stability, however, can only be reached in combination with an adequate preparation of the implant socket using an undersized drilling technique and implant type, for example.

Many studies have already proven that bone growth can be induced in the floor of the maxillary sinus by membrane elevation even without augmentation[16-18, 29, 38, 47, 48]. As the bone forming capacity of the sinus membrane remains unclear according to literature bone forming in an artificially created space under the sinus membrane must be based on a physiological process similar to callus forming in secondary bone healing or distraction osteogenesis[49]. This is the most probable theory, as the vast majority of literature dealing with this topic reports reliable new bone formation in animal, as well as in human studies[18, 44]. This would mean that the elevation of the sinus membrane is a prerequisite for the formation of a stable blood clot, which ossifies secondarily. The membrane itself is reduced to the function of a barrier whose own, questionable osteogenic potential may not be necessary at all.

Different techniques for the graftless sinus floor elevation have been applied, the sinus can be approached from the lateral window[4, 20, 22], another reliable option is to approach the sinus transalveolar[21, 50]. Studies that used osteotome techniques were excluded from this systematic review, since this technique comes along with different outcomes. Since the residual bone is carefully moved upwards,

the biology of new bone formation is different from sinus membrane elevation through the lateral window. The space created by tenting in the lateral window approach is bigger than in the transalveolar approach.

Recent systematic reviews have assessed studies about the graftless sinus lift[24-29]. However, there is no review that included prospective randomized controlled trials in humans only that compared de-novo bone formation in non-grafted sinus membrane elevation with sinus floor augmentation with bone substitutes using the lateral window approach.

This systematic review shows a high survival rate for dental implants both after conventional augmentation of the posterior maxillary sinus floor with autogenous bone and bone replacement material and without augmentation material: 97.92% and 98.73% respectively. There was no significant difference (P=0.94) between the groups that were compared. From this we can conclude that sinus membrane elevation without the use of bone grafts leads to a reliable and stable bone situation for implantation. It should be noted that the follow-up of the implant survival was limited to only 6 months. A longer follow-up is needed to assess long-term stability not only with regard to the implants, but also regarding the stability of the newly gained bone.

Most studies show more bone gain at the bone grafted side than the graftless side. Three studies found significant differences[37, 39, 40]. Felice et al.[36] found no significant result in bone height gain with a slightly higher bone gain in the test group (P=0.672).

From the four studies that compared bone density, only one article showed a significant higher bone density measured in Hounsfield Units (HU) at the graftless side[34]. It should be noted that in the publication of Altintas et al. a contradiction in results of bone density between text and table was found. The text mentions a higher bone density on the test side in two places, while in the result tables this is indicated for the augmented test side. The other three studies showed a lower bone density at the graftless side[35, 37, 39].

The meta-analysis of the radiologic results six months after the sinus floor elevation showed that the gain in bone height (-1.73 mm, 95% CI -3.04- -0.41, P=0.01) and density (-94.7, 95% CI -134.9- -54.5, P=<0.001) was significant lower in the non-grafted sinus lift groups than in the bone grafting groups. It should be noted that some studies used multisliced computed tomographies (CTs) and others used conebeam computed tomographies (CbCTs), which leads to bias. A multislice CT shows more

scattering around implants and a CbCT is less accurate, but is an optimal tool for imaging the oral- and maxillofacial area and gives less radiation to the patient. The significant difference can be explained by the fact that time is needed for new bone to origin from a blood clot at the graftless side, compared to bone substitutes that already possess bone-like properties and immediately show opacity on a radiograph. It is histologically proven that the newly formed bone on the non-grafted side is less calcified and shows fewer fibrous cells. Nevertheless, the transplant-free bony drill cores in the study of Lie et al. showed intensive new bone formation[18].

The meta-analysis of implant stability shows no significant differences between the non-grafted and grafted group six months after implant placement (-2.12 95%CI -4.40- 0.15, P=0.07), both groups show ISQ values above 60. If the ISQ is higher than 60, this is considered favorable for a high survival rate of implants[51]. This means that the ISQ values after non-grafted and grafted sinus lifts are sufficient.

From this literature review it can be concluded that the character of the newly formed callus-like bone with lower radiological density and opacity does not allow a prediction of higher implant failure. Despite that the bone gain and bone density is significant lower at the graftless side, this has no effect on the implant survival or implant stability.

Even though this systematic review and meta-analysis only included prospective randomized controlled trials without high risk of bias and only one surgical approach technique to the sinus was accepted, this study has also some limitations. The articles included are not completely homogenous, three studies[16, 36, 41] performed a two staged procedure, whereas six studies described simultaneous implantation[34, 35, 37-40]. The implants were used for the tenting technique of the sinus membrane. In the single-stage procedure with tenting by the implants, new bone formation and osseointegration of the implants take place in the same period as after previous or graftless augmentation, which leads to a significantly shorter overall treatment time. In the two-staged procedure the tenting technique is a pre-implant surgical procedure, the implants are placed six months later. The idea is to first allow bony consolidation to take place so that implants can be placed in sufficient and good quality bone substance. No significant differences between one- or two-staged implantation with regard to implant survival is described in the literature[4, 52]. It would be interesting to study the differences of outcome of the two techniques using elevation of the sinus membrane without augmentation materials. Felice et al.[36] described that insufficient bone had grown in one sinus from their test group six months after a graftless sinus lift procedure. Nevertheless, they decided to implant immediately and simultaneously add bone replacement material, which was followed a satisfying result.

An important factor that influences the possibility of immediate implantation is the severity of the atrophy of the posterior maxilla. If the maxilla is complete edentulous the extension of the maxillary sinus can result in a severe three-dimensional atrophy with an osteoporotic-like bone structure. The cortical layers can be too thin and must be regarded as insufficient for primary stable implant placement. Therefore, after complete tooth loss in the upper jaw and high maxillary atrophy, the space created by the tenting technique can be much larger than in patients with only partial tooth loss. When only a limited number of teeth are missing, a sinus cavity of limited volume bordered by bony walls needs to be filled with new bone. In cases of high atrophy and complete tooth loss, it can be much more difficult to create a stable blood clot as a prerequisite for new bone formation. Lie et al. have presented the only study so far that included complete edentulous patients only. This may affect the results. Other factors that may influence the results are the different space holders used, the different types of bone replacement materials and the mean residual bone height (table 1).

As in all publications on surgical procedures, wound healing complications also have an influence on the results. Table 2 lists these. Particularly with the technique presented here, extensive perforation of the sinus membrane can make it impossible to perform the procedure successfully. The extent to which these had an influence on the meta-analysis cannot be determined, since the focus was on the issue of bone volume gain and implant survival. The complications mentioned in the literature analyzed here are obviously processed in the publications.

Analysis of the funnel plots suggested that two studies may have potential risk of publication bias[16, 37]. The data of these publications should be interpreted with caution.

Only further studies with long-term observation of a larger patient population in prospective standardized trials will show whether the newly formed bone in the floor of the maxillary sinus remains stable over time after a graftless sinus lift. Only in this way will it be possible to make a reliable statement on the long-term osseointegration of implants.

In conclusion: This systematic literature review and meta-analysis shows a high implant survival rate in non-grafted maxillary sinus lifts and conventional sinus lifts using augmentation materials (97.92% and 98.73% respectively). The graftless sinus lift groups show a significantly lower vertical gain in bone height with a mean difference of -1.73 mm ($P=0.01$) and a significantly lower bone density with a mean difference of -94.7 HU ($P<0.001$). The ISQ values do not show a significant difference between the test and control group ($P=0.07$). The values in both groups are considered as a good prediction of high implant survival in both procedures.

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Conflict of interest
The authors declare no potential conflict of interest.

Ethical approval
Not required

Patient Consent
Not required

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CHAPTER 5

Implant survival after graftless sinus floor augmentation in highly atrophic maxillae: A randomized controlled trial in a split mouth study

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ABSTRACT

Purpose

The success rate of dental implants after graftless sinus augmentation versus conventional sinus augmentation surgery in atrophic maxillae in edentulous patients was investigated.

Methods

This randomized study was performed in ten edentulous patients with marked maxillary atrophy. On the graftless side, the sinus membrane was lifted by a resorbable membrane. The control side was augmented with a mixture of autografts and xenografts. Implant placement followed six months postoperatively. Outcomes were implant survival, success of prosthetic rehabilitation and stability of vertical bone gain.

Results

Ten patients were included. Postoperative radiology showed sufficient bone gain on both maxillary sides. Follow-up varied from 57 to 88 months. The conventional side showed significant ($p=0.041$) more bone gain than the experimental side (respectively 9.69 mm and 6.20 mm). A total of 59 implants were placed: 30 after conventional, 29 after graftless augmentation. One implant was lost on the conventional side and four on the experimental side. The implant survival was significantly higher on the conventional side (96.7% vs. 86.2%, $p<0.001$, RR=4.14). Prosthetic restoration was functionally successful in all cases.

Conclusion

Bone gain and implant survival were significantly lower in the non-grafted side versus the grafted side. Prosthetic rehabilitation was possible in all ten patients. The non-grafted technique may have some potential for clinical use, although it showed poorer results.

BACKGROUND

Extreme atrophy of the edentulous maxilla is a common problem that requires augmentation surgery for achieving a sufficient alveolar bone volume allowing for dental implant placement[1-3]. Lateral sinus membrane elevation for the posterior maxilla[4, 5] is a reliable procedure for augmentation of the maxilla with autogenous, xenogenous or other bone replacement material[6-10].

The sinus lift procedure is not straight-forward and is associated with complications that may compromise the stability of the graft and the overall success of the treatment, such as the perforation of the sinus membrane, which occurs in more than 20% of cases[11, 12]. The use of autogenous bone comes along with donor site morbidity[13-15]. The choice of augmentation technique and augmentation material remains controversial and depends mainly on the degree of atrophy of the upper jaw, the experience of the surgeon, the medical condition of the patient and the medical-technical possibilities of the operating room[3, 5, 16, 17]. The practitioner can solve these problems with circumscribed augmentative surgery using bone graft substitutes, computer-assisted cone beam computed tomography (CBCT) based computer-guided implant placement and short dental implants[18, 19]. Simultaneous augmentation and implantation in the posterior maxilla is another possibility and has been discussed widely in literature[20-22]. It is acceptable only if the remaining vertical bone height and width are sufficient for primary implant stability.

Ellegaard et al.[23] introduced a sinus lift technique in the posterior maxilla with sinus membrane elevation and simultaneous implant placement without grafting material. Later, Lundgren and co-workers[24] published extensively on this topic and established it in daily practice. Over the years this technique has been widely used[25-27]. In 2015 we published a variant of this technique, in which we elevated the sinus membrane without augmentation material in severely atrophied edentulous patients in order to place dental implants in a second step. The aim of the study at that time was to investigate spontaneous bone regeneration[28]. The aim of the present study was to evaluate implant survival, success of prosthetic rehabilitation and stability of vertical bone gain on the non-grafted maxillary side compared to conventional sinus floor augmentation with a mixture of autogenous and xenogenous bone.

METHODS

In January 2013 we started our pilot study as a prospective randomized controlled clinical trial in a split mouth study design to compare the efficacy of two different techniques for the augmentation of atrophic posterior maxillae in completely edentulous patients (fig. 1). This human study design is a translational study that has emerged from a number of animal studies in the past. The reason we developed this particular technique is that the research group already had years of experience and evidence of new bone formation after periosteal elevation with mesh space holders in animals [29-32]. This study[28] was approved by the medical ethics committee of the Maastricht University Medical Center: azM/UM: NL41286.068.12 / METC 12-2-066. The study was conducted in full accordance with the principles outlined in the Declaration of Helsinki. All included patients were fully informed about the study design and alternatives and signed the informed consent form.

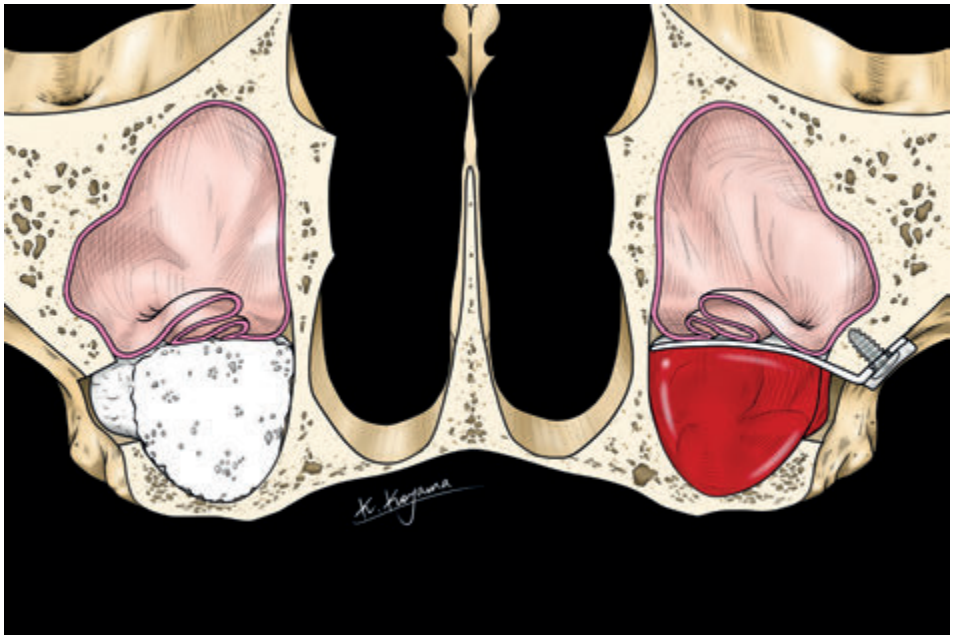

Figure 1. *Split mouth study design to compare two different techniques for augmentation of the atrophic posterior maxilla: one side is augmented with a mixture of autogenous and xenogenous bone, on the contralateral side the sinus membrane is lifted and the space is filled with a blood clot.*

Ten completely edentulous patients from the outpatient clinic of the Department of Cranio- and Maxillofacial Surgery of the Maastricht University Medical Center (MUMC), with bilateral atrophic maxillae and insufficient total prostheses were included in the study. The inclusion criteria were: complete edentulous, age 18-75 years old, residual bone height of 1-8 mm, bone width of at least 5 mm. Patients with contraindications for general anesthesia, a history of radiotherapy in the head/neck region, treatment with bisphosphonates, poor oral hygiene, uncontrolled diabetes, pregnancy, infection and increased tendency to hemorrhages, were excluded from participation of this study.

The maxillary side being treated with the experimental technique was assigned randomly; a randomization was made in SPSS (statistical package for the social sciences, IBM Corp., Armonk, NY, USA) from patient one to ten. Five papers said "experimental side LEFT" and five said "experimental side RIGHT", they were placed in ten sealed opaque envelopes by a medical student, without informing anyone about the content. The envelope was opened by the responsible surgeon (SL) on the day of surgery right before the start of the operation. The patients were blinded regarding which side would be the test or control side.

Surgical procedure

The operations took place in general anesthesia at the MUMC. All patients were operated by the same surgeon (SL). All patients received 2200mg amoxicillin/clavulanic acid peri-operatively; this was continued for 7 days post-operatively (Augmentin 500/125mg, GSK, Brentford, Middlesex, UK, 3x/day). The sinus floor was approached by the lateral window technique. One side was augmented with an equal mix of autogenous bone (anterior iliac crest) and xenogenous bone (Bio-Oss™, Geistlich, Wolhusen, Switzerland). On the randomized test side the maxillary sinus membrane was lifted and stabilized with a resorbable perforated membrane, no bone substitute materials were added (fig. 2).

The resorbable membrane we used was made of poly(D,L)-lactide (PDLLA) (Resorb X™, KLS Martin, Tuttlingen, Germany). The membrane (40 x 40 x 0.2 mm) was cut to the right size and extra perforations were made. This was followed by heating the membrane in a warm water bath allowing the membrane to be formed to the ideal shape. When the shaped membrane was cooled down, the membrane was rigid and it could create a stable support to keep the sinus membrane elevated. Two resorbable pins (5 mm length) of the Sonic Weld™ system (Sonic Weld™, KLS Martin, Tuttlingen, Germany) were used to fixate the membrane to the lateral wall of the sinus. The distance from the sinus floor to the position of the PDLLA membrane was always determined by the surgeon depending on the anatomical situation and was similar or even higher than

on the conventional side. This distance could not be technically measured correctly, but always had to be at least 10 mm in order to be well prepared for the subsequent implant placement of at least 8 mm length. The space created in the sinus was filled with autogenous venous blood. Finally the wound was closed tightly with resorbable sutures (Vicryl™ Rapid 4x0, Ethicon, Johnson & Johnson, New Brunswick, NJ, USA)[28].

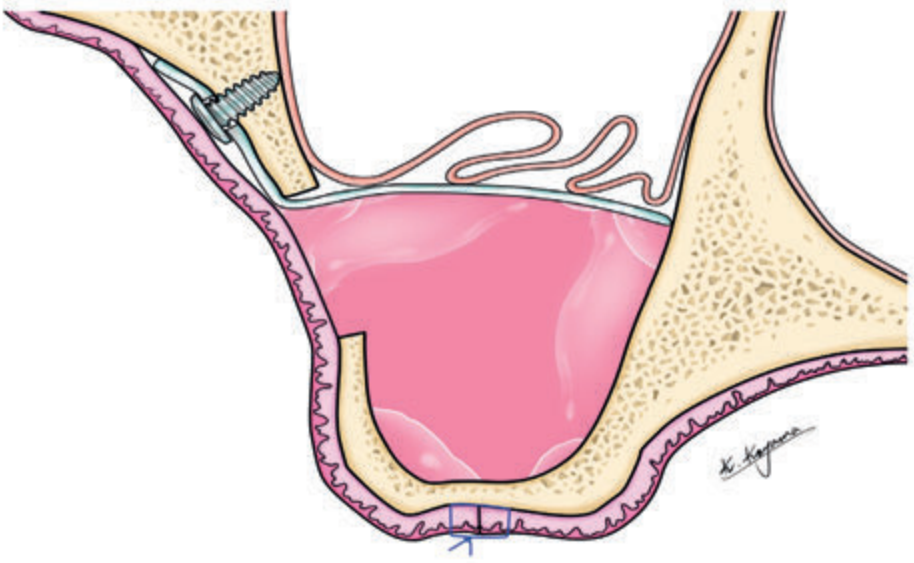

Figure 2. *Schematic drawing of sinus membrane elevation stabilized with a resorbable membrane.*

According to the study protocol six Straumann® Bone Level implants, three per side, were placed six months after the sinus floor augmentation (Straumann AG, Basel, Switzerland). The ideal implant position was planned preoperatively with the aid of the computer and transferred to the operating room using a drilling template (Blue Sky Plan™, Libertyville, IL, USA). Prior to implantation, bone biopsies of 8 mm length were taken exactly in the region of the planned implant placement using a trephine drill. In detail: Instead of using a solid twist drill, we used a trephine drill of 2 mm inner diameter and 3 mm outer diameter for the preparation of the implant bed. Cylindrical bone samples from the center region of the augmented maxilla could be obtained for histological evaluation. The histological outcome has been described in detail in an earlier publication[33]. The implantation sites were closed with tensionless continuous sutures (Vicryl™5x0)

Another six months later the implants were exposed, followed by prosthetic rehabilitation by the prosthodontist (fig. 3). Implant survival and success of prosthetic rehabilitation were documented.

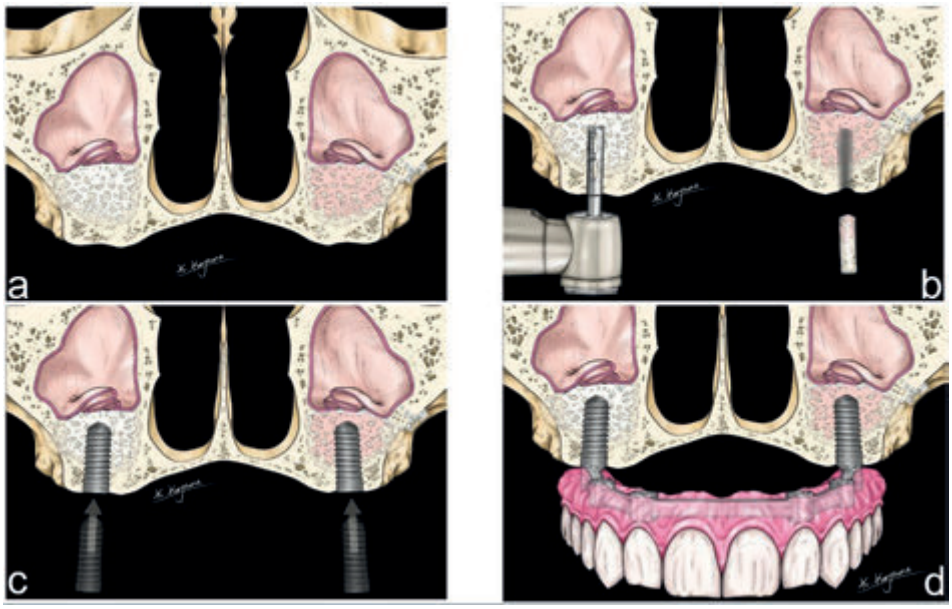

Figure 3. *Schematic drawing of implant placement.* ***(a)*** *After six months sufficient bone gain was apparent.* ***(b)*** *Bone biopsies are taken with a trephine drill.* ***(c)*** *Implants are inserted at the same place where the bone biopsies were taken: three on each side.* ***(d)*** *After six months, the implants are exposed and prosthetic rehabilitation is established.*

Radiological follow-up

Radiological follow-up with CBCT (iCatVision™ model 17-19, Imaging Sciences International, Hatfield, PA, USA) was applied pre-operatively to the maxillary sinus lift procedure, immediately postoperative and four months later.

The residual vertical bone height from the pre-operative CBCT and the vertical bone gain four months after sinus membrane elevation were measured on the radiographic images by two independent researchers (SL and CL) and the average was taken. A protocol for these measurements was made: first the CBCT was uploaded in the 3D planning program (Nemotec™ 3D Scan Dicom, Madrid, Spain), second the CBCT was positioned in a way that the palate was oriented horizontally in the coronal and sagittal planes and the maxilla was placed in the midline in the transversal plane. The third step was to define the panoramic plane of the maxilla, in this plane the bone heights were measured (fig. 4).

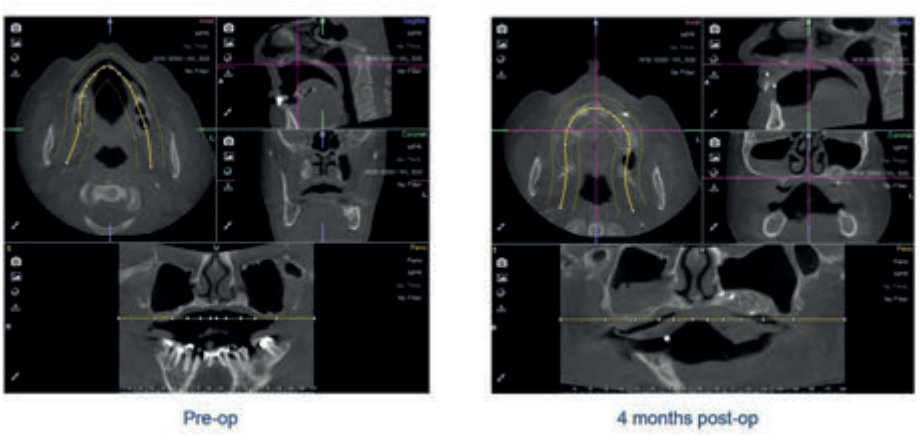

Figure 4. *Planes of the preoperative and 4-months postoperative CBCTs in the right orientation: transversal, sagittal and frontal. The lower parts show the defined panoramic plane in which the measurements of bone height were made.*

In the augmented posterior region of the maxilla, two locations were marked on each side where vertical height measurements were taken. As described previously, the CBCT, four months post augmentation, was used to produce a drilling guide. The sites where the two posterior implants were placed, pre-planned with the implant 3D-planning software, were exactly the sites where bone height was measured. First the bone height in the four-month postoperative CBCT scan was documented, and afterwards the bone height at exactly this point in the preoperative scan was identified (fig. 5).

All trephine biopsies have showed us new bone formation in macro- and microscopy[33] on both sides, with less bone density on the experimental side. This explains a lower radiographic opacity on the experimental side. Therefore we made the sensible decision to consider any radio-opacity from gray to white as bone.

Implant survival

Six months after implant placement, the implants were exposed. Implant survival was assessed radiologically at the day of exposure. One year after functional loading of the upper prosthesis another radiological check was performed and implant survival was registered again. The clinical follow-up after implant placement varied from 57 to 88 months. The criteria of Albrektsson et al. (1986)[34] were used to evaluate the success of the implants:

- No signs of radiographic peri-implant translucency
- Vertical bone resorption less than 0.2 mm per year after the first year under loading
- The clinical appearance must be free of pain, infections, neuropathies

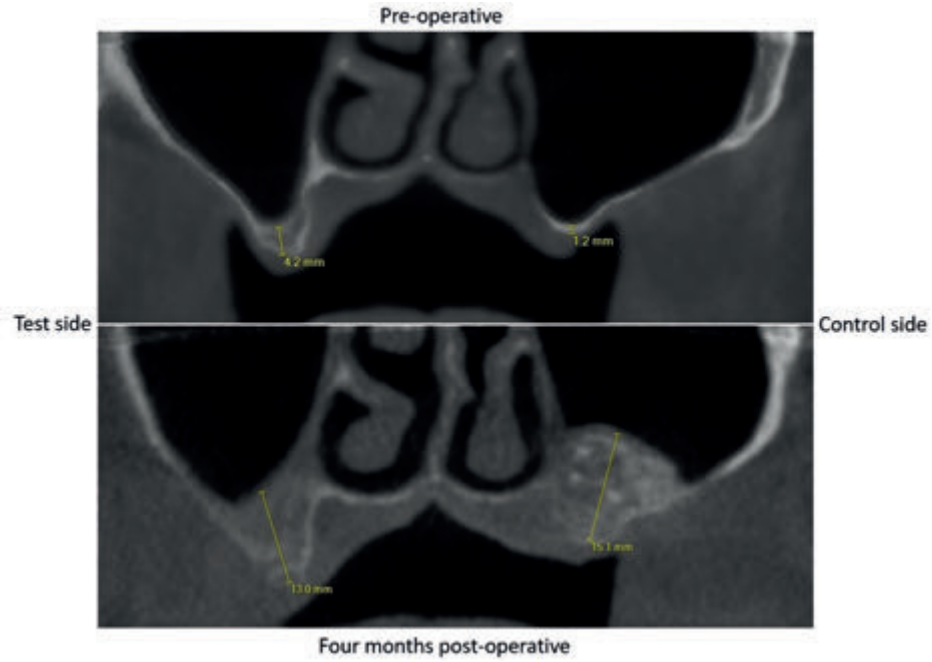

Figure 5. *Vertical bone height measurements on two corresponding locations pre-operatively and four months after augmentation.*

Success of prosthetic rehabilitation

Prosthetic constructions were described as fully functional if they did not show any vertical positional change, had a perfect fit and did not show any occlusal disturbances.

Statistical analysis

Descriptive statistics were performed using SPSS™ (statistical package for the social sciences version 25, IBM Corp., Armonk, NY, USA). Mean and standard deviations (SD) were given. The mean difference and p-value was determined by a one-sample t-test.

RESULTS

A total of ten patients, four males and six females, were treated according to the study protocol. The age ranged from 50 to 70 years with an average of 60.5 years (SD 7.7). A bilateral sinus membrane elevation had been performed in all patients in a split-mouth design. Six months after maxillary sinus augmentation, only one patient showed too little vertical bone gain on the graftless side in the preoperatively planned implant site. On this side only two implants could be placed. A total of 29 implants were inserted, 14 in the test group and 15 in the control group. During the sinus lift procedure two small membrane lacerations of about 1 mm occurred at the test side and two sinus membrane perforations (1 and 2 mm in length) occurred at the control side. These lacerations did not need any treatment. In one patient, the incision site for bone harvesting became infected one week postoperatively. The patient was treated with antibiotics (Augmentin 500/125mg, GSK, Brentford, Middlesex, UK) for 7 days. The wound healed within three weeks. No other postoperative complications occurred. No patients dropped out of the follow-up. The follow-up period ranged from 4 years and 9 months to 7 years and 4 months.

Radiology

Six months after augmentation all patients showed sufficient new bone formation, which allowed for dental implant placement. The non-augmented and the augmented sides were compared and both showed sufficient new bone formation. However, the non-augmented side showed less opacity suggesting less bone density or less presence of mature bone (see figs. 4 and 5).

The two assessors (SL and CL) followed the protocol to measure bone height gain separately, so that the results would be as accurate and reliable as possible. An inter-observer variability analysis was performed which showed a rate of 0.98, from which we can trust that the numbers in the results are reliable. The gain in vertical bone height is documented in table 1.

The average residual bone of the test side was 4.66 mm (SD 2.87 mm) and of the conventional side 4.53 mm (SD 2.22 mm). The paired samples t-test showed no significant difference between the test and control sides (P = 0.866).

In the test group vertical bone gain ranged from 0.04 mm to 18.28 mm with an overall mean of 6.20 mm (SD=4.92 mm). The control group showed a range in vertical bone gain from 2.24 mm to 17.97 mm with an overall mean of 9.69 mm

(SD=4.62 mm). The one-sample t-test showed a mean difference between the test and control side of -3.49 mm (95% CI -6.82 - -0.16). The vertical bone gain height on the experimental side was significantly lower than on the contralateral control side (P=0.041).

Table 1. *Radiologically assessed vertical bone height gain four months after sinus membrane elevation/augmentation.*

10 patients, CBCT		**Bone height**					
		Experimental side (mm)			Conventional side (mm)		
		Before	After	***Gain***	Before	After	***Gain***
1.	Ant	3.73	8.92	***5.19***	4.57	16.00	***11.43***
	Post	7.28	7.35	***0.07***	7.54	18.64	***11.10***
2.	Ant	1.26	16.64	***15.38***	8.11	13.11	***5.00***
	Post	2.77	21.05	***18.28***	0.83	13.68	***12.85***
3.	Ant	1.69	10.18	***8.49***	3.12	13.63	***10.51***
	Post	1.40	8.93	***7.53***	8.23	11.16	***2.93***
4.	Ant	5.55	8.50	***2.95***	0.88	11.73	***10.85***
	Post	5.26	8.12	***2.86***	4.57	8.86	***4.29***
5.	Ant	6.78	12.75	***5.97***	2.79	14.44	***11.65***
	Post	4.60	8.21	***3.61***	6.61	12.20	***5.59***
6.	Ant	6.60	10.25	***3.65***	6.08	13.54	***7.46***
	Post	6.86	11.02	***4.16***	5.01	12.62	***7.61***
7.	Ant	3.35	12.38	***9.03***	5.36	8.02	***2.66***
	Post	7.23	11.52	***4.29***	6.96	9.20	***2.24***
8.	Ant	0.99	10.23	***9.24***	3.25	15.99	***12.74***
	Post	6.84	7.65	***0.81***	2.59	20.56	***17.97***
9.	Ant	11.69	11.73	***0.04***	4.23	16.79	***12.56***
	Post	6.44	9.35	***2.91***	4.01	20.08	***16.07***
10.	Ant	1.97	12.42	***10.45***	3.69	14.03	***10.34***
	Post	0.98	10.48	***9.50***	2.12	14.26	***12.14***
Mean (sd)	Ant	4.36 (3.35)		***7.20 (4.29)***	4.21 (1.99)		***9.88 (3.76)***
	Post	4.97 (2.44)		***5.19 (5.52)***	4.85 (2.49)		***9.49 (5.55)***
	Overall	4.66 (2.87)		***6.20 (4.92)***	4.53 (2.22)		***9.69 (4.62)***

Implant survival and prosthetic survival

Implants of appropriate width and length (Bone Level Implants, Straumann®, Basel, Switzerland) were placed in the maxilla (table 2).

Table 2. Characteristics of the inserted Bone Level Implants.

Implant sizes (diameter x length in mm)	Test side			Control side		
	Anterior	Mid	Posterior	Anterior	Mid	Posterior
1	3.3 x 8	3.3 x 8	3.3 x 8	3.3 x 10	4.1 x 12	4.1 x 12
2	3.3 x 10	4.1 x 10	4.1 x 12	3.3 x 10	3.3 x 12	4.1 x 12
3	3.3 x 12	4.1 x 10	3.3 x 10	3.3 x 10	4.1 x 12	4.1 x 12
4	3.3 x 8	3.3 x 8	3.3 x 8	3.3 x 10	3.3 x 10	3.3 x 8
5	4.1 x 10	4.1 x 12	3.3 x 8	4.1 x 10	4.1 x 12	4.1 x 10
6	4.1 x 10	3.3 x 10	3.3 x 10	4.1 x 10	4.1 x 10	3.3 x 10
7	3.3 x 10	4.1 x 10	4.1 x 10	4.1 x 10	4.1 x 10	4.1 x 10
8	4.1 x 10	4.1 x 10	3.3 x 8	3.3 x 10	4.1 x 10	4.1 x 10
9	3.3 x 12	3.3 x 12	4.1 x 10	4.1 x 10	4.1 x 12	4.1 x 10
10	4.1 x 10	4.1 x 12	-	4.1 x 10	4.1 x 12	4.1 x 10

Implant failure was seen in three patients. During the second stage surgery and uncovering of the fixtures in each of two patients one implant on the test side was lost. A third implant was lost in another patient on the control side. In this particular patient another implant on the test side was lost three months after functional loading. Again, another patient who had lost an implant during exposure on the test site lost another implant on the test site eight months after functional loading. During the last follow-up (varying from 57-88 months), no more implants were lost (table 3).

In summary a total of five implants were lost during follow-up: four at the test side and one at the control side. The overall implant survival was 86.2% on the test and 96.7% on the control side ($P<0.001$). The risk ratio of losing an implant on the test side is 4.14 (95%CI 1.88-6.39).

Table 3. Implant failure.

10 patients	Test side	Control side
Total implants placed	29	30
Implant failure during exposure	2 (middle, posterior)	1 (anterior)
Total implant failure one year after functional loading	4 (3 middle, 1 posterior)	1
Total implant failure at last follow-up	4	1
Overall implant survival (%)	86.2	96.7

If anteriorly placed implants are excluded, implant survival is 78.9% on the test side and 100% on the control side (P=0.125). The remaining implants fulfilled the criteria of implant success as defined by Albrektsson in 1986[34].

Table 4 shows the data on the existing residual bone before implant placement at the exact sites where the implants were later lost. The table shows that the four lost implants on the test side had less residual bone than the average. Three locations even deviated by more than one standard deviation.

Table 4. *Residual bone height before sinus floor augmentation on the sites where implants were later lost.*

Implant loss	Side	Location	Residual bone (mm)
Patient 1	Conventional	Anterior	6.41
	Experimental	Middle	1.26
Patient 2	Experimental	Middle	1.69
	Experimental	Posterior	1.40
Patient 3	Experimental	Middle	3.35

All patients received a prosthetic restoration (figs. 6 and 7) on a bar-retained superstructure. Despite the loss of implants, all prosthetic restorations were functional until the end of follow-up according to the definition presented above.

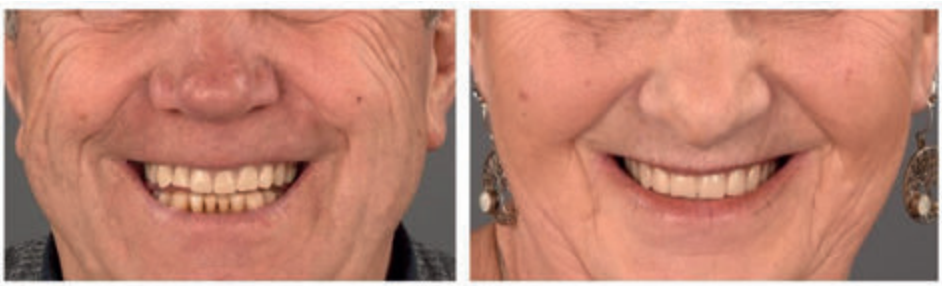

Figure 6. *Esthetic smile results of the upper denture.*

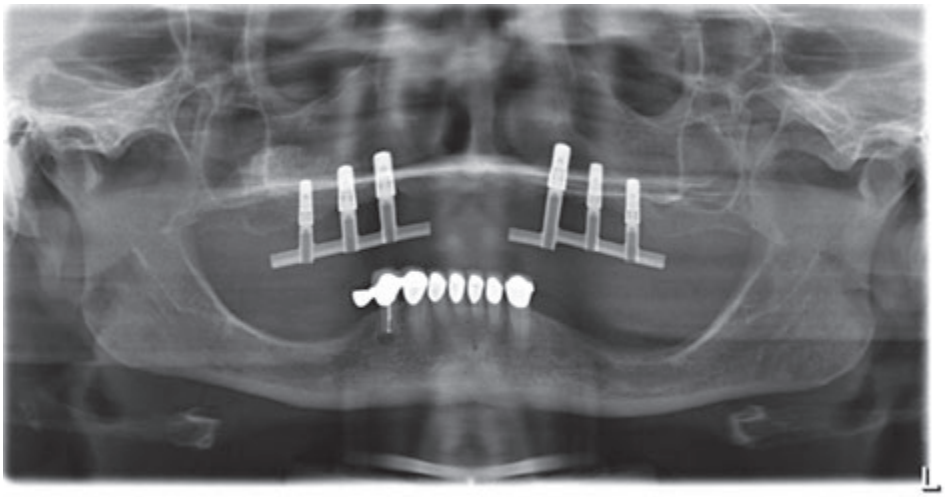

Figure 7. *Panoramic x-ray of a bar-retained superstructure on six implants in the augmented maxilla (test: left side, control: right side).*

DISCUSSION

At the end of this study, we wondered whether graftless sinus floor augmentation, as we investigated it, could be a real alternative to the many existing techniques described in the literature to create a stable bone supply in the atrophic posterior maxilla pre-implantologically. Our group recently published a systematic review[27] that concluded that both non-grafted maxillary sinus lifts and conventional sinus lifts with augmentation materials have a high implant survival rate (97.92% and 98.73%, respectively). Aghaloo et al. have addressed this question in 2007 and again in 2016[35, 36]. The article from 2016 is a systematic review article that deals with scientific contributions from 1980 to 2014 and describes the five most important augmentation procedures. All five techniques – guided bone regeneration, interpositional grafting, maxillary sinus augmentation, inlay and onlay grafting or combinations of the above can be successfully applied in pre-prosthetic augmentation surgery of the maxilla. The technique of sinus floor grafting without graft material has not been studied, as this technique was quite new. However, there is a consensus in the relevant literature that if the residual height of the alveolar process in the posterior maxilla is less than 6 mm, augmentation measures are usually recommended[2].

Established and successful grafting procedures for augmentation on the posterior edentulous atrophic maxilla exist, which offer long-term implant survival of 85 to 100%[37-39]. Nkenke et al. in 2004 and Kessler et al. in 2005 conducted studies on large patient series in which autogenous bone was harvested from the anterior or posterior iliac crest in pre-prosthetic indications[13, 40]. If large bone volumes are required for three-dimensional maxillary augmentation with lateral maxillary widening, these techniques can still have their justification. In 2014, Nkenke and Neukam published an article dealing only with comparative clinical trials on the harvest of autogenous bone grafts[41]. Six intraoral or distant donor sites were identified. From the patients' perspective, intraoral bone harvesting at the ramus was preferred. Interestingly, the comparison of chin bone harvesting with iliac crest bone harvesting led to a preference for pelvic bone harvesting, although this requires treatment under general anesthesia. This choice was justified by the high morbidity of chin bone harvesting. Pain, loss of superficial skin sensitivity and wound healing disorders led to a high morbidity rate after chin bone harvesting. This is astonishing, since the literature often suggests that intraoral bone harvesting causes less problems than harvesting at the iliac crest. There is sufficient literature on this issue that we cannot go into detail here. Nevertheless, the unavoidable morbidity of autogenous bone harvesting was the main motivation to submit our study to the Ethics Committee in the first place, which considered the argument of non-existent morbidity in our study protocol as decisive for approval. However, it should not be forgotten that only

autogenous bone grafts provide all biological advantages desired at a defect side, such as: scaffold for osteoconduction, growth factors for osteoinduction and progenitor cells for osteogenesis, which altogether seems to be decisive with regard to bone volume stability and the structure of augmented bone sites[42]. With autogenous bone as bone source for augmentation exceptionally high implant survival of up to 100% after cumulative 3-year analysis after placement of implants in the maxilla regardless of source, chin or iliac crest bone were reported in literature[43].

The use of bone replacement materials is the classical alternative to autogenous bone. An almost unmanageable amount of alternative bone product is offered. Bone substitutes can be used just as successfully as autogenous bone. Al-Nawas and Schiegnitz published a systematic review and meta-analysis on bone substitutes as augmentation materials in maxillary sinus floor augmentation. The mean implant survival rate was 98.6% for implants placed in sinuses augmented with bone substitute materials. In the comparison groups, sinus floor augmentations with a mixture of autogenous bone and bone replacement material and autogenous bone were used exclusively. In the former group the mean implant survival was 88.6%, in the latter 97.4%. All procedures appear to allow long-term implant survival[44]. Similar results were published by many other authors[1, 45, 46].

Even the question whether sinus lifting is necessary at all is difficult to answer, if short implants of less than 8 mm can successfully be loaded in maxillary bone with a residual height of 4 to 6 mm[47]. However, their long-term prognosis is still unknown. This statement must be critically evaluated and can only be seen in the interaction of augmentation, implantation and prosthetic rehabilitation. In most patients there is atrophy of the maxilla as well as atrophy of the edentulous mandible. If the intermaxillary space becomes too large as a result, short implants may fail if the ratio of the length of the implant and the height of the prosthetic structure is also unfavorable to the implant length. In a recently published study Al-Nawas and Schiegnitz address the question whether narrow-diameter implants (mini implants) in the atrophic jaw are successful. They warn against mini implants in the masticatory posterior region[48]. The same could also apply to short implants with unfavorably high prosthetic abutments. In addition, dental implant manufacturers often only guarantee the success of their products if the implant-prosthetic construction aspect ratio is 1:1[49].

In this context, Summers' technique, which allows the insertion of longer implants, should not go unmentioned[50]. One advantage of the crestal sinus lift, a "minimally invasive" technique, is that it is less traumatic for the patient than the external sinus lift. The narrow and complex surgical access via the burr hole of the crestal sinus lift

requires a high degree of skill on the part of the surgeon. An equally important factor of the crestal sinus lift according to Summers is the augmentation height of about 4 to 5 mm that is possible[51].

Ellegaard et al.[23] and later Lundgren[24] were the first to describe successful implantation after sinus membrane elevation without the use of any bone grafts or applying the crestal sinus lift. A coagulum is formed after creating a bone wound by removing the sinus membrane from the floor of the sinus, the lateral and medial sinus walls. The osteogenetic capacity of the surrounding bony walls on at least three sides of the sinus leads to the formation of bone forming callus from the coagulum. The smaller this space is, the more stable is the coagulum formed in this space. When the space is bigger, like in completely edentulous maxillae, this may lead to a less stable callus. When no bone grafts are used in a sinus membrane elevation, this space does not contain a scaffold[33].

This study is the first study about the implant-survival after graftless maxillary sinus membrane elevation that included patients that were all completely edentulous. The use of a resorbable membrane from material like PDLLA has the advantage that no material had to be removed in a second surgery and the crucial region of interest would stay untouched when the implants were placed. The insertion of the implants was challenging because the usual feeling of insertion resistance was missing. As indicated above in the preimplantation radiographic analysis, bone maturation was not yet complete at implant placement or was completed without sufficient calcification. Next to this we do not exactly know what the resorbable material would do and what influence it has on bone growth. It is known that it is not always fully absorbed after sinus membrane elevation. This was closely studied in a publications of Cricchio et al.[52, 53]. To discover what the PDLLA membrane did in our human study, we should have retrieved histological evidence including the sinus membrane. Since this would bring too much damage to the patient, this would not be approved by the medical ethics committee.

A limitation of the technique used in this study is that the open window to the sinus cannot prevent the growth of granulation tissue into the defect. On the other hand, the periosteum directly covers the opening to the maxillary sinus. There is a possibility that the bone forming capabilities of the periosteum play a beneficial role in stimulating bone growth.

We trusted the functional biological process that functional loading will result in bone apposition and that the PDLLA membrane would not interfere at implant level. Nevertheless, we can conclude from these clinical results that the implants are

osseointegrated. Only long-term (>10 years) follow-up might show, if the functional loading due to the placement of dental implants in conjunction with appropriate prosthetic rehabilitation will render a stable callus in a non-grafted atrophic maxillary sinus. Further studies have to prove, if earlier or maybe later implant placement will render better results with regard to implant survival. The staged procedure we chose was based on the empirically gained experience of conventional implantology.

This study has some limitations: The sample size is small, there was no option to take bone biopsies with inclusion of the sinus membrane or retrieve implants for histological prove of implant osseointegration. In addition, we know that the posterior maxilla is often more atrophied than the anterior. If we exclude the anteriorly placed implants we see a survival rate of 100% on the conventionally treated side versus 78.9% on the side treated without bone graft (not significant).

We can also discuss whether the higher implant loss on the test side could be caused by the very small amount of residual bone shown in table 4. In a next study, it might be interesting to exclude patients with less than 4 mm of residual bone. In this way, we could investigate whether the experimental technique leads to better implant survival.

Furthermore, a uniform definition of the term "loss of function" after prosthetic restoration does not exist and whether there will be one in the near future remains questionable. Often it remains unconsidered or undefined on the basis of which criteria the end of the functional phase of a dental restoration is reached. Mostly retrospective case series with at least 100 patients and an observation period of at least 3 years allowed a study-related estimation of the survival of prosthetically restored implants (implants as surrogate parameters), but the different endpoints as well as the study design (case series) or different forms of prosthetic rehabilitation do not allow pooling of the results[54-57]. The 5-year implant success rates varied between 69.5% and 98.4% (the corresponding 10-year success rates between 79.4% and 94.3%), depending on the prosthesis used[58]. The long time periods make it clear that the event "loss of function" usually occurs only after a very long time, if one has a normal clinical use period in mind. Such a long time can often hardly be waited for results in randomized trials. So far the results of implant survival in this study show acceptable results since all prosthetic restorations were still functioning.

CONCLUSIONS

We conducted an experiment with completely edentulous humans with atrophic maxillae by comparing conventional augmentation procedures with a sinus membrane lifting technique without using any bone grafts. The results showed new bone formation on both test sides. However, the non-grafted side showed significant less bone gain than the grafted side, with an overall mean of respectively 6.20 mm (SD 4.92) and 9.69 mm (SD 4.62).

Implant survival was 86.2% in the non-grafted side vs. 96.7% in the grafted side ($p<0.001$). Prosthetic rehabilitation was possible in all ten patients with reasonable patient satisfaction. At the last follow-up all prostheses were functional.

Within the limitations of this study we can conclude that the non-grafted technique might have some potential for clinical use, although it showed a higher implant failure. This technique in the complete edentulous maxilla is a challenging procedure. It can be applied to avoid the use of any bone grafts and reduce morbidity in patients where this is favorable. Further research with more statistical power will be necessary to support the hypothesis of this study.

List of abbreviations:
CBCT: cone beam computed tomography
MUMC: Maastricht University Medical Center
PDLLA: resorbable membrane we used was made of poly(D,L)-lactide
SD: standard deviation

Declarations:
Ethics approval and consent to participate
This study was approved by the medical ethics committee of the Maastricht University Medical Center: azM/UM: NL41286.068.12 / METC 12-2-066. The study was conducted in full accordance with the principles outlined in the Declaration of Helsinki. All included patients were fully informed about the study design and alternatives and signed the informed consent form.

Consent for publication
Written informed consent has been obtained from the patients for publication.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare no conflict of interest.

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Authors' contributions
Conception and design of the study by: SL, HAM, PK
Acquistion of data: SL, CL, RC, PK
Analysis of data: SL, CL, RC, HAM, PK
Drafting of article and critical revision: SL, CL, RC, HAM, PK
Final Approval: SL, CL, RC, HAM, PK
All authors read and approved the final manuscript.

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CHAPTER 6

Quality of masticatory function in edentulous patients wearing implant overdentures after graftless maxillary sinus membrane elevation

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ABSTRACT

Background

Graftless sinus lift shows good results in terms of bone gain, radiology and implant survival. Clinically, the graftless sinus lift can be recommended as an alternative to conventional procedures using augmentation materials.

Objectives

The objective of this study was to evaluate the masticatory performance, the masticatory ability and patient satisfaction and their correlation after graftless sinus floor augmentation.

Methods

The study group consisted of patients who had received a graftless sinus lift in a split mouth design and was compared to two control groups: patients with implant-supported overdentures in the maxilla without sinus lifts and individuals with a natural dentition.To assess objective masticatory performance, the mixing ability test was performed. Three questionnaires were used to assess masticatory ability, quality of life and patient satisfaction.

Results

Each group consisted of ten patients. Both the graftless sinus lift group and the edentulous control group had a worse masticatory performance compared to the natural dentition group. The questionnaires showed better masticatory ability in the natural dentition group, but only between the edentulous control group and the natural dentition group a significant difference was found. No significant results were found regarding the correlation between the objective and subjective outcomes.

Conclusions

Masticatory performance, masticatory ability and patient satisfaction do not differ significantly between graftless maxillary sinus augmentation and conventional augmentation procedures.

BACKGROUND

Oral health and functioning are important factors of overall well-being[1]. Limited masticatory function and poor oral intake in completely edentulous patients have a major impact on aspects such as functional ability in daily life, self-image and social interactions[2-5]. Optimal dental prosthetic rehabilitation improves quality of life (QoL) in edentulous patients by improving chewing function, but also by having a positive effect on aesthetics[6-8]. The masticatory function of edentulous patients is highly dependent on the correct retention of the prosthesis[9, 10]. Intraosseous implant supported overdentures provide more retention than conventional overdentures[11], which makes them more advantageous in terms of patient satisfaction and oral health related QoL.

A prerequisite for implant placement is the presence of adequate bone mass in width and height. The absence of teeth in the maxilla or mandible can lead to atrophy, resulting in insufficient bone volume for implant placement. Atrophy in the maxilla results from a 'double-edged sword', i.e. dynamic bony adaptation occurs centripetally, both from the alveolar ridge after tooth loss and from the side of the maxillary sinus by pneumatization[12, 13].

Augmentation of the maxillary sinus floor provides adequate and stable bone to both anchor the implants and withstand the masticatory forces[14-16]. Autogenous, xenogeneic, allogenic or alloplastic bone grafting material can be used to augment the maxilla, but in some cases it is preferable not to use any bone graft.

Simple elevation of the mucosal lining of the sinus floor without graft material may be sufficient to induce de-novo bone formation in the floor of the maxillary sinus[17-21]. Studies report good results in new bone formation and a high rate of implant survival after sinus membrane elevation without the use of bone graft material[21]. However, not much is reported on the prosthetic rehabilitation and patient satisfaction after graftless sinus floor augmentation, which is the most important factor for the patient. Because we concluded in our recent study[19] that prosthetic rehabilitation was good after we performed the graftless sinus lift, we wanted to prove this with this current study.

Therefore, the aim of this study was to gain insight into the effects of graftless sinus membrane elevation prior to intraosseous implant placement on masticatory performance and consequently on oral health related quality of life (OHR-QoL) (masticatory ability) in this patient group, compared to patients with implant based overdentures in the upper jaw without a history of bone augmentation and compared to individuals with a complete natural dentition. In addition we wanted to know if there would be a correlation between these objective and subjective outcomes.

METHODS

In this cross-sectional study, patients at Maastricht University Medical Center+ (MUMC+) were enrolled from the study group between June and August 2020 and from two different control groups between April and July 2021. The first group, maxillary sinus elevation (MSE), consisted of complete edentulous patients with implant-supported overdentures. These patients had undergone bilateral maxillary sinus augmentation due to severely atrophic posterior maxillae at an earlier stage. The experiment was performed in a split-mouth design in which patients received sinus membrane elevation with a mixture of autologous and xenogeneic bone on one side and sinus membrane elevation without bone graft on the other side.

A detailed description of patient recruitment and surgical procedure can be found in previously published articles[19, 22]. The second group, edentulous controls (EC), included completely edentulous patients with overdentures on a superstructure on four to six implants in the maxilla without a history of sinus floor augmentation. The third group, natural dentition controls (NDC), included individuals, aged 50 to 70 years, with a complete natural dentition with no more than one tooth missing per quadrant and not wearing a denture. Patients with an American Society of Anaesthesiology (ASA) physical status classification of III or higher or with a history of pathologic changes in oral structures were excluded.

This study was approved by the medical ethics committee of the MUMC: METC 2021-2528. The study was conducted in full accordance with the principles outlined in the Declaration of Helsinki. All included patients were fully informed about the study design and signed the informed consent form.

Measurement procedure

Masticatory performance was assessed objectively in all three test groups using a mixing ability test (MAT) and masticatory ability was measured by the Quality of Masticatory Function Questionnaire (QMFQ). The QMFQ contains five questions related to edentulous patients, these five questions were naturally not answered by the group with natural dentition. In addition, the OHR-QoL was assessed using a questionnaire specifically for edentulous patients; the Oral Health Impact Profile for Edentulous People (OHIP-EDENT). A visual analogue scale (VAS) was used to measure the outcome on patient satisfaction. Of course, the latter two questionnaires were not administered to the natural dentition group. Given the design of the split-mouth study each question offered the additional option of indicating a difference between the left and right side of the mouth.

The QMFQ and OHIP-EDENT were conducted through oral interviews rather than self-assessment. This insured the integrity and completeness of the responses[23]. All oral interviews were conducted by the same research assistant (HK). To avoid bias in the results, this person was not familiar with the patients. Both the interviewer and the patients were blinded to the randomization of the split-mouth procedure. Due to its nature, the VAS was self-administered by the patients. However, the interviewer did remain in the room to answer any questions.

Masticatory performance

An objective measure of chewing function was determined using the mixing ability test (MAT). This test involves chewing on a 20 mm diameter wax tablet with two 3 mm thick layers, one red and one blue. The tablet is then flattened between sheets of film to a thickness of 2.0 mm and photographed on both sides with a high-quality scanner (Epson V750, Long Beach, CA). The degree of intermixing between the two layers is determined by correlating the color intensities with the chewing function. This results in a so-called mixing ability index (MAI) between 5 and 30, with a lower value representing a better degree of mixing and thus a better masticatory function[24]. Previous studies have shown high reliability of the MAT in different patient populations, with intraclass correlation coefficient (ICC) values ranging between 0.7 and 0.907[25-27]. In this study, patients were instructed to chew 20 times on the tablet. No further instructions were given. Subsequently, each patient answered additional questions about the side of the mouth that was used most during the test.

Masticatory ability

The QMFQ was used as a method for subjective assessment of masticatory function. Originally written in French, this questionnaire was developed in Canada and consists of 29 questions divided into six domains: Chewing ability, prosthesis, habits, meats, vegetables and fruit[28]. Responses are recorded on a 5-point Likert scale, with questions related to chewing ability (1 = always problems / major difficulties, 5 = never problems / no difficulties)[29, 30]. The translated versions have a Cronbach's α-value of 0.87 and 0.91, respectively, indicating a good internal consistency. The discriminant and construct validity analysis showed satisfactory results.

In this study, the English version was translated into Dutch. The translation into Dutch was performed by two independent experts in the field; both are oral- and maxillofacial surgeons at MUMC+. After discussion and clarification of any differences between the two translations, the final Dutch translation was independently back-translated by two non-experts. This translation showed no significant differences in semantics. We considered that this translation was of sufficient quality for use in the study.

Oral Health related Quality of Life

The Oral Health Impact Profile (OHIP) is a questionnaire developed by Slade and Spencer (1994)[31] to be used in the assessment OHR-QoL. The OHIP-EDENT is a modified version of this questionnaire developed specifically for edentulous patients[32]. Regarding its measurement properties, the developers found comparable scores to the original 49-question version. In addition, independent studies examining the internal consistency and reliability have also found acceptable values[33]. It consists of 19 questions designed to assess physical, psychological, and social impact of edentulism[34]. Responses are recorded on a 5-point Likert scale (1 = never, 5 = very often). The Dutch version was used[33].

Patient Satisfaction

The VAS was used to measure the present patient satisfaction with the prosthesis. Originally developed to quantify pain[35, 36], the use of a VAS provides more reliable results compared with a Likert Scale and avoids ordinal scales[37, 38]. Each patient was presented with 5 questions accompanied by a picture of a horizontal bar numbered from 0 mm to 100 mm with 0 representing the worst imaginable health status and 100 representing the best imaginable health status. The following questions were asked: 1) "Are you satisfied with the prosthesis in the upper jaw?", 2) "Are you satisfied with the aesthetic appearance of the prosthesis?", 3) "Do you worry that the prosthesis will fall out?", 4) "Are you satisfied with speech?", and 5) "Are you satisfied with your ability to chew and eat?".

Statistical analysis

Normally distributed continuous data were reported using means and standard deviations (SDs); this was applied to MAT and VAS results. For ordinal and non-normally distributed continuous data medians and interquartile ranges (IQR) were used; these were applied for the QMFQ and the OHIP-EDENT questionnaires. Normality of continuous data was assessed using the Shapiro-Wilk test. Differences in nominal data between the three groups were assessed using the chi-square statistic. Differences in continuous data were compared using ANOVA for three groups and the independent t-test for comparing two groups. Ordinal and non-normally distributed continuous data were compared by the Mann-Withney U test. In the case of missing questionnaire items imputation was performed by substituting the average value of the relevant question for all subjects.

Correlations between MAT and questionnaire scores were examined with Spearman's rho test. Before performing this test, monotonicity was assessed using simple scatter plots. All statistical analyses were performed using IBM SPSS Statistics, version 26.0.0.0. (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY).

RESULTS

Demographics

For each group, 10 subjects were included in the study. The MSE group, EC group and the NDC group randomly included 4 males and 6 females and therefore did not differ from each other. The time between implantation and MAT ranged from 39 and 79 months in the first group (mean: 58.1, SD: 14.7) and from 11 and 173 months in the second group (mean: 65.9, SD: 52.7). Patient demographics are shown in Table 1.

Table 1. *Demographic and clinical characteristics of the included subjects. *: p<0.05; †: Chi-square test; ‡: ANOVA; #: Independent t-test.*

Patient characteristics	**Split mouth study design; grafted/ graftless n=10**	**Implant supported dentures n=10**	**Natural dentition n=10**	***p*-value**
Gender (n)				
Male	4	4	4	-†
Female	6	6	6	-†
Age (Mean ± SD)	65.2 (8.2)	67.8 (7.6)	60.1 (4.4)	0.058*‡
Follow-up time (Mean ± SD)	58.1 (14.7)	65.9 (52.7)	-	0.658#

Five patients in the MSE group reported more intensive use of one side of the jaw during MAT, three of them preferred the control side while the other two preferred the graftless side. None of the patients indicated a preference for a side based on a difference in masticatory function.

The MAI scores in each group followed a normal distribution. The mean scores were 18.2 (SD=3.0) for the MSE group, 17.1 (SD=3.3) for the EC group and 14.9 (SD=1.2) for the NDC group. There was a significant difference between the test groups (P=0.031).

The post hoc test revealed no significant differences between the MSE and EC groups (P=0.664) and no significant differences between the NDC and EC groups (P=0.161). However, the test revealed a significant difference between MSE and NDC (P=0.027).

The descriptive analysis of the total scores of each questionnaire is shown in tables 2 to 4 below. The Mann-Whitney-U-test for the results of the QMFQ (excluding the questions regarding edentulous patients) showed that there was a significant difference between the EC and NDC groups (P = 0.004). The MSE group was

not significantly different from the EC and NDC groups (P = 0.190 and P = 0.105, respectively). The Mann Whitney U test for the QMFQ total score (including the five questions specific to edentulous patients) showed no significant result between the MSE and EC group (P=0.280).

Similarly, no significant difference was found between MSE and EC groups for the OHIP-EDENT after applying the Mann-Whitney U test (table 3).

For the questionnaires, patients had the opportunity to indicate differences between the left and right sides: Two patients reported that they were less satisfied overall with one side than with the other. In one patient this concerned the graftless side and in the other the control side.

Finally, using the Shapiro-Wilk test it was determined that the VAS scores were normally distributed. An independent sample t-test was used to compare the means between the MSE and EC groups. These were not significantly different from each other (P=0.601; Table 4).

Again, patients could indicate differences between left and right after completing the VAS scores, but no comments were noted.

Spearman's rho test did not demonstrate strong correlations between the objective scores of the MAT and the subjective scores of the questionnaires (Table 5).

Table 2. Descriptive analysis of the QMFQ scores.

QMFQ	Total score			Score minus prosthesis questions		
Group (n=30)	Min	Max	Median (IQR)	Min	Max	Median (IQR)
Maxillary sinus elevation (n=10)	67	125	114.5 (24)	59	110	101 (22)
Edentulous controls (n=10)	86	121	106.5 (10)	74	106	92 (18)
Natural dentition controls (n=10)			-	78	110	108 (9)

Table 3. Scores OHIP-EDENT with no significant difference.

OHIP-EDENT (n=20)	Min	Max	Median (IQR)
MSE (n=10)	20	71	26.5 (21)
EC (n=10)	21	60	34 (18)
Mann-Whitney U	P = 0.315		

Table 4. Descriptive analysis of the VAS-scores shows a normal distribution P>0.05.

VAS (n=20)	Min	Max	Mean (SD)	Shapiro-Wilk P-value
MSE (n=10)	238	500	398 (76)	0.471
EC (n=10)	187	480	379 (84)	0.210

Table 5. Spearman's rho correlation coefficients between MAT and questionnaire scores for each group. No significance was found.

Spearman's rho (n=30)	QMFQ	OHIP-EDENT	VAS
MSE (n=10)	-0.552 (p=0.098)	0.350 (p=0.322)	-0.436 (p=0.208)
EC (n=10)	-0.176 (p=0.626)	0.365 (p=0.300)	-0.061 (p=0.868)
NDC (n=10)	-0.608 (p=0.062)	-	-

DISCUSSION

The results of this study show that the MSE group had comparable results in masticatory performance to the EC group. The results showed significantly lower masticatory performance compared to the NDC group. A previous study using the MAT showed mean MAI scores of 15.8 (2.0), 18.5 (3.1) and 21.2 (3.6) in groups with natural dentition, maxillary denture and implant-supported mandibular overdenture and full denture, respectively[24]. The results of the current study are consistent with these data.

The MSE group showed no significant differences in the QMFQ scores compared to the EC group (P=0.109). The NDC group has a high score, questions concerning the prosthesis were naturally excluded in this group. The MSE group showed a median score of 114.5 (91.6%) which suggests a good chewing ability.

Our results indicate that the assessment of masticatory function has been shown to be subject to a large subjective component, with individual patient data not necessarily correlating consistently with objective measurements.

With regards to the split-mouth design, it is difficult to draw conclusions regarding the masticatory function of the graftless side compared to the conventional side. Five patients of the MSE group reported more intensive use of one side during MAT, three of them showed a preference for the control side while the other two preferred the graftless side. Given the small sample size, no conclusions could be drawn from this. None of the patients indicated a preference for a side based on a difference in masticatory function. With regard to the VAS, two patients reported that they were less satisfied overall with one side than with the other. One of them preferred the graftless side and the other the control side. Again, no conclusions could be drawn from this.

Similar to the QMFQ results, it is difficult to contextualize the OHR-QoL questionnaire results. A median score of 26.5 for the OHIP-EDENT and 398 for the VAS in our study group indicate a high quality of life and acceptable satisfaction in patients that underwent a graftless sinus lift.

This study showed no significant results regarding the correlation between the masticatory performance and chewing ability. Only the NDC group showed a strong, but non-significant negative correlation between the MAI and the QMFQ scores, from which it can be concluded that the lower the MAI, the better the QMFQ scores.

This study has some major limitations that need to be discussed. The major limitation of this study is the small sample size and the fact that the study group was treated in a split mouth design. Nevertheless we wanted to study this group and compare results to two different control groups. Because of the split mouth design it is impossible to separate the two techniques and evaluate them independently. If the graftless technique is used more frequently in the future, patient satisfaction should be evaluated in patients who have been fully treated with the graftless maxillary sinus lift to obtain reliable results.

From the clinician's perspective, these results are important as the patient evaluates the overall result of a long pretreatment procedure. Similar results in functional tests and good, albeit subjective, results in quality of life put the responsibility for deciding which technique can best help the patient back in the hands of the physician, who can more independently decide which procedure to ultimately choose based on the data published by our study group.

CONCLUSION

The aim of the present study was to investigate the masticatory function, oral health-related quality of life and patient satisfaction in a small group of patients who had received a graftless maxillary sinus floor augmentation and compare them with patients with implant-supported overdentures without a history of maxillary sinus augmentation and with individuals with natural dentition. In particular, we wanted to investigate whether the positive histologic findings and relatively good implant survival of this 'graftless' group[18, 19] were associated with similarly good functional outcomes.

Based on this study, there is no reason to believe that masticatory function or oral health-related quality of life differ significantly between graftless maxillary sinus augmentation and the conventional method with augmentation material. The decision as to which procedure to prefer is subject to further criteria, which are more in the general medical, the anatomical and surgical-technical areas and correspond to the patient's wishes.

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CHAPTER 7

GENERAL DISCUSSION

GENERAL DISCUSSION

The aim of this research was to evaluate the presence, quality and quantity of new bone formation for implant placement in the atrophied maxilla without the use of bone graft substitutes.

Augmentation surgery of the maxillary sinus in the posterior maxilla plays a special role in pre-implant field of oral- and maxillofacial surgery. The local conditions of the posterior maxilla are not only determined by tooth loss, atrophy of the alveolar process, but also by a possible expansion of the maxillary sinus recess.

The adjacent structures must remain separated for functional and infection prophylactic reasons. All interventions on the walls of the paranasal sinuses must ensure their ventilation and inflammation must be avoided. Any intervention on the Schneiderian membrane can inevitably lead to tears in the mucosa. These can heal without consequences if treated correctly. However, the insertion of foreign material, including autogenous bone, can trigger inflammatory reactions that jeopardize not only the success of the augmentation but also the integrity of the maxillary sinus.

The therapy of sinusitis is one of the oldest surgical therapies and actually a core topic in otolaryngology. The long and standardized use of surgical therapies in maxillary sinusitis, which can be both ventilatory and dentogenic in nature, have accumulated an enormous wealth of experience from which we wanted to benefit in our research. Another phenomenon we took advantage of was the experience with distraction treatments, which we adapted to the elevation of the periosteum in several experiments on large animals. The success of these preliminary studies, the vast clinical experience, and the critical use of augmentation materials at a site that may not need augmentation at all led to the scientific question that underlies this investigation.

Titanium remains the preferred material for the fabrication of dental implants. It is characterized by its good physical and chemical properties and its biocompatibility. At the same time, however, due to their bioinert surface properties, titanium dental implants have a limited ability to stimulate bone growth in the peri-implant bone on their own and to favorably influence osteoblast adhesion on the implant surface. Therefore, numerous chemical and physical methods have been developed to modify the surface structure in order to improve the bioactivity, i.e. the ability of the implant surface to interact with the underlying tissue. Micro- and nano-level surface structures, roughness, wettability and the hydrophilicity of the surface are of crucial importance

for the bioactivation of dental implants. For this purpose, ablative processes such as acid etching, sandblasting, sandblasting/acid etching (SLA), laser ablation, numerous physical and chemical coating processes, UV irradiation and other functionalization procedures by coating with proteins, peptides, drugs, etc. are used.

Many studies, especially in vitro, indicate the influence of micro- and nanoscale surfaces of titanium implants on humoral or immunological host response. For example, contact of blood with nanotube designed surfaces leads to upregulation of mRNAs that order and accelerate osteoblast apposition and osseointegration[1]. Blood coagulation as well as the inflammatory response in the surrounding tissues are favorably influenced by nanostructured surfaces, which positively affects new bone formation and osseointegration of implants[2]. At the cellular level, the surface structures lead to a so-called "polarization" of macrophages, which are the first humoral cells to come into contact with the implant surface. Macrophages with M2 markers have a positive effect on osteoblast behavior and stimulate cell proliferation, cell adhesion, phosphatase activity and extracellular mineralization[3]. For example, sandblasting of the implant surface leads to such stimulation of M2 macrophages. These structural effects of the dental implants used were taken into account in the choice of implant type. To what extent the excellent blood supply to the newly formed bone positively influenced the above-mentioned processes cannot be determined. What is certain is that the primarily lower stability of the implants in the not yet fully calcified bone initially led to the expectation of lower osseointegration. Despite increased implant loss rates on the test side, the biological processes just described on the implant surface probably contributed to the overall success.

Appreciation of the results obtained

- The hypothesis underlying the clinical trial was confirmed. Spontaneous bone growth can be induced in an artificially created space in the maxillary sinus floor even without augmentation material.
- Augmentation material, regardless of its type, is therefore not an absolute indication for a successful sinus lift procedure.
- Histological examination provided evidence of new bone formation.
- The bone regenerate was stable and active enough to integrate dental implants in the long term – osseointegration of dental implants.
- At the end of the study period, all prosthetic restorations were functional.
- The procedure presented here can reduce costs, risks and morbidity for patients.

Future Perspectives

Sinus floor elevation is a procedure that is performed regularly and will continue to be performed in the future. Inventing the best bone grafting material and surgical technique to make the procedure as effective as possible, without comorbidity, and with as low cost as possible will continue to play a role in pre-implant surgery. Sinus floor augmentation will continue to be an issue. After conducting this study and writing this dissertation, several questions remain:

- The question of the bone regeneration potential of the maxillary sinus mucosa could not be assessed.
- The influence on bone regeneration of the resorbable PDLLA membrane remained unanswered.
- An ideal time for the placement of dental implants remains to be defined.
- The long-term stability of the bony regenerate should only be assessed after a longer follow-up period of years. True long-term results are still lacking.

Unique feature of this study

To our knowledge, this is the first and only study on spontaneous bone regeneration in completely edentulous patients with a high degree of posterior maxillary atrophy.

CONCLUSION

Elevating the sinus membrane without the use of any bone grafts results in histologic evidence of new bone formation. This results in new bone for implant placement.

New bone formation after this experimental technique results in poorer quality and quantity of bone compared to new bone formation after using a mixture of autogenous and xenogenous bone. Nevertheless this newly formed bone is still reliable to implant placement and leads to prosthetic rehabilitation.

Masticatory function and oral health-related quality of life are acceptable after the graftless technique and do not differ from the conventional technique.

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CHAPTER 8

SUMMARY

In English and Dutch

SUMMARY

This thesis is a result of several previous conducted studies and led to this current translational study. Surgical techniques continue to evolve, and in today's health care environment, patient satisfaction is considered just as important as the success of the surgery itself. The goal is to provide effective surgeries with optimal results, but with as little co-morbidity and costs as possible.

Sinus lift surgery in the atrophic posterior maxilla to insert implants at a later stage is a regularly performed procedure. The gold standard to date remains the use of autogenous bone, but autogenous bone harvesting is always associated with donor-site morbidity. Many alternative bone substitutes have been developed, but there are still reasons against the use of bone substitutes, e.g. fear of inflammatory reactions or one's own conviction. Studies have shown that new bone growth occurs after the periosteum is elevated, a technique known as tenting. The sinus membrane cannot be considered completely pure periosteum, but new bone growth was observed even after sinus elevation without bone grafts. In the following chapters, a technique in which the sinus membrane is elevated is described, this technique and its results are discussed. Patient satisfaction is also surveyed.

Chapter 1 is the introduction to this thesis and describes the principles of implantology and the basic knowledge of bone metabolism and bone remodeling. It explains the atrophy of the maxilla, especially the posterior maxilla, and how to manage this problem during implant placement. The overall objective of this dissertation was to quantitatively, qualitatively and functionally assess the independent, spontaneous osseous regenerative forces in the wall and floor region of the maxillary sinus without augmentation material. Dental implants should demonstrate the functional loading capacity and stability of the bone regenerate in the maxillary sinus.

In 2012/2013 we started this study, which was approved by the Medical Ethics Committee of Maastricht University and the Maastricht University Medical Center.

In **Chapter 2** we shared our first experience with the sinus floor elevation via the lateral window approach in fully edentulous patients with highly atrophic maxillae, without the use of any bone grafts. The experimental technique consisted of creating a space between the sinus membrane and the sinus floor, the sinus membrane was held upwards with a degradable PDLLA-membrane fixed on the lateral sinus wall. We conducted a prospective clinical randomized study in which this new technique was compared to the conventional sinus floor augmentation with the use of a mixture of autogenous

and xenogeneic bone. Due to the split-mouth model, the test and control sides could be directly compared. To be sure that this experimental technique is effective and safe, we decided to study the first five patients after surgery in order to include the next five patients in the study. The implants were placed six months after the sinus lift, and bone biopsies were taken at the implant sites beforehand. New bone formation was detected both radiologically on cone beam CTs and histologically on the test and control sites. Thirty implants were placed after taking thirty bone biopsies. Vital new bone was demonstrated on the experimental side. The implant survival rate to date was 100%. Patient satisfaction was high and no prosthetic complications occurred. The successful initial results were convincing enough to continue the study and include five more patients.

After including all ten patients for this split mouth-study, we aimed to prove the hypothesis that an artificially created space under the sinus membrane in the floor of the maxillary sinus will lead to spontaneous callus formation and a stable osseous consolidation without the use of augmentation material. Six months after sinus elevation cylindrical bone biopsies were taken prior to implant placement. The histologic findings are described in detail in **Chapter 3**. New bone formation with active osteoblastic and osteoclastic activity was evident in all bone samples. Even on the non-grafted side callus-like bone formation was detected.

In **Chapter 4**, we reviewed the existing clinical evidence on the efficacy of the graftless maxillary sinus membrane elevation. After critical selection by two independent investigators, nine studies were included, and only randomized controlled trials were eligible. Risk of bias was assessed using the Revised Cochrane risk-of-bias tool for randomized trials. Meta-analysis was conducted for seven studies. Results showed a high overall implant survival rate in both the graftless and bone grafted sinus lift groups (97.92% and 98.73%, respectively). The graftless sinus lift group showed significantly lower vertical bone height gain with a mean difference of -1.73 mm ($P=0.01$) and a significant lower bone density with a mean difference of -94.7 HU ($P<0.001$). The implant stability quotient values showed no significant differences between the test and control group ($P=0.07$).

In 2020, it was more than seven years after the implantation of the first included patient and nearly five years after the implantation of the last included patient. **Chapter 5** evaluates implant survival after the aforementioned follow-up period of 57-88 months on both the test and control sides. In addition, vertical bone gain after sinus membrane elevation and success of prosthetic rehabilitation were assessed in these ten patients. The results showed an implant survival of 96.7% (1 implant

lost out of 30 implants placed) on the conventional side versus an implant survival of 86.2% (4 implants lost out of 29 implants placed) on the graftless side at final follow-up. Implant survival was significantly higher on the conventional side, with a risk ratio of 4.14; that is, the graft-free side had a 4.14-fold higher risk of implant loss than the conventional side. The conventional side showed significantly higher bone gain (p=0.041) than the experimental side (9.69 mm and 6.20 mm, respectively). Prosthetic rehabilitation was possible in all ten patients.

This suggests that in our study approach, the nontransplant technique may have some potential for clinical use, although it showed worse results.

Finally, in **Chapter 6**, we conducted a study to evaluate the conclusions drawn from the previous studies in terms of the patient's satisfaction. The aim of this study was to assess the masticatory function and oral health-related quality of life in the study group and to assess the correlation between the objective and subjective results. Since the histological results were good, bone gain was proven and the implant survival was acceptable, we wanted to know whether the patients in our maxillary sinus elevation study group were satisfied with the function of their prosthesis. For this study we formed two control groups to compare with the study group: The first group consisted of ten healthy patients who had an implant-supported overdenture in the maxilla without a history of bone augmentation. The second group consisted of ten individuals who had their own natural dentition and had not lost more than one tooth in each quadrant (third molars excluded).

To assess masticatory performance in an objective way, a mixing ability test was performed in which patients had to chew on a wax tablet; a higher chewing index represents poorer masticatory performance. The subjective masticatory ability was assessed using the Quality of Masticatory Function Questionnaire (QMFQ). The oral health related quality of life was assessed by the questionnaire Oral Health Impact Profile for Edentulous individuals (OHIP-EDENT). Final, patient satisfaction was assessed by using questions about the prosthesis; responses were presented on a visual analogue scale (VAS).

The results showed a higher masticatory index in both the study group and the edentulous control group without augmentation compared to the group with natural dentition. The study group was significantly different from the natural dentition group, other results showed no significance.

The questionnaires showed better masticatory ability in the natural dentition group, but only a significant difference was found between the edentulous control group and the natural dentition group in terms of QMFQ. The VAS scores showed no significant results between the study and edentulous control groups. No significant results concerning correlation between the objective masticatory performance and subjective masticatory ability were found.

Based on this study, there is no reason to assume that masticatory function, oral health-related quality of life, and patient satisfaction differ significantly between graftless maxillary sinus augmentation and the conventional augmented method. The limitations of this study, small sample size and split mouth design, should be considered.

Chapter 7 discusses the conclusions and future perspectives of this thesis.

From this monographic dissertation we can conclude that elevation of the sinus membrane without the use of augmentation material leads to histological evidence of spontaneous new bone formation. This leads to a sufficient bony base for placement of dental implants at a later stage.

The demonstrated new bone formation in this experiment leads to a qualitatively and quantitatively different result compared to the new bone formation after using a mixture of autogenous and xenogeneic bone. Nevertheless, with regard to subsequent implantation, new bone formation after graftless sinus membrane elevation can be described as an acceptable alternative if the use of bone substitute materials must be avoided. Prosthetic rehabilitation based on implants could be achieved as an independent target in every case.

Masticatory function and oral health-related quality of life are acceptable after the graft-free technique and do not differ from conventional techniques.

SAMENVATTING

Dit proefschrift is een resultaat van verschillende eerder uitgevoerde studies en heeft geleid tot deze huidige translationele studie. Chirurgische technieken blijven zich ontwikkelen en tegenwoordig wordt de patiënttevredenheid in onze gezondheidszorg even belangrijk geacht als het succes van de operatie zelf. Het doel is om effectieve ingrepen aan te bieden met optimale resultaten, maar met zo weinig mogelijk co-morbiditeit en kosten.

De sinuslift operatie in de atrofische bovenkaak om in een later stadium implantaten te kunnen plaatsen is een regelmatig uitgevoerde operatie. Het gebruik van autoloog bot is tot op heden nog steeds de gouden standaard, maar het nemen van autoloog bot gaat altijd gepaard met co-morbiditeit ter plaatse van de donor locatie. Er zijn veel alternatieve botsubstituten ontwikkeld, maar er zijn nog steeds redenen waarom men liever geen botsubstitutie gebruikt, zoals angst voor ontstekingsreacties of de eigen overtuigingen. Studies hebben aangetoond dat nieuwe botformatie optreedt nadat het periost is opgetild, een techniek die bekend staat als tenting. Het sinusmembraan kan niet volledig als zuiver periost worden beschouwd, maar nieuwe botformatie wordt ook gezien na een sinuslift zonder bottransplantaten. In de volgende hoofdstukken wordt een techniek beschreven waarbij het sinusmembraan wordt opgehoogd, deze techniek en de resultaten ervan worden besproken. Ook wordt de tevredenheid van de patiënten gepeild.

Hoofdstuk 1 is de inleiding van dit proefschrift en beschrijft de beginselen van de implantologie en de basiskennis van botmetabolisme en botopbouw. Er wordt uitleg gegeven over de atrofie van de bovenkaak, met name de posterieure bovenkaak, en hoe dit probleem kan worden opgelost tijdens het plaatsen van implantaten. De algemene doelstelling van dit proefschrift was het kwantitatief, kwalitatief en functioneel beoordelen van de onafhankelijke, spontane ossale regeneratieve krachten in de botwanden van de sinus maxillaris zonder het gebruik augmentatiemateriaal. Tandheelkundige implantaten moeten de functionele belastbaarheid en stabiliteit van het botregeneraat in de sinus maxillaris aantonen.

In 2012/2013 zijn we gestart met deze studie, goedgekeurd door de Medisch Ethische Commissie van de Universiteit Maastricht en het Maastricht Universitair Medisch Centrum.

In **Hoofdstuk 2** deelden wij onze eerste ervaring met de sinusbodemelevatie via de laterale 'window' benadering in volledig edentate patiënten met sterk atrofische maxillae, zonder gebruik van bottransplantaten. De experimentele techniek bestond uit het creëren van een ruimte tussen het sinusmembraan en de sinusbodem, het sinusmembraan werd omhoog gehouden met een afbreekbaar PDLLA-membraan op de laterale wand. Wij voerden een prospectieve klinisch gerandomiseerde studie uit waarin deze nieuwe techniek werd vergeleken met de conventionele sinusbodem augmentatie met gebruik van een mengsel van autoloog en xenogeen bot. Door het split mouth model konden de test- en controlezijden direct met elkaar vergeleken worden. Om er zeker van te zijn dat deze experimentele techniek doeltreffend en veilig zou zijn, besloten wij de eerste vijf patiënten na de operatie te bestuderen, zodat de volgende vijf patiënten in de studie konden worden opgenomen. De implantaten werden zes maanden na de sinuslift geplaatst, voorafgaand werden botbiopten genomen op de implantaat locaties.

Nieuwe botvorming werd zowel radiologisch op conebeam CT's als histologisch op de test- en controleplaatsen gedetecteerd. Dertig implantaten werden geplaatst na het nemen van dertig botbiopten. Aan de experimentele zijde werd vitaal nieuw bot aangetoond. Het overlevingspercentage van de implantaten bedroeg tot op heden 100%. De tevredenheid van de patiënt was groot en er traden geen prothetische complicaties op. De succesvolle eerste resultaten waren overtuigend genoeg om de studie voort te zetten en nog vijf patiënten bij te includeren.

Na alle tien patiënten te hebben geïncludeerd voor deze split mouth studie, wilden we de hypothese bewijzen dat een kunstmatig gecreëerde ruimte onder het sinusmembraan in de sinusbodem van de maxilla zal leiden tot spontane callusvorming en een stabiele ossale consolidatie zonder het gebruik van augmentatiemateriaal. Zes maanden na de sinusbodemelevatie werden cilindrische botbiopten genomen voorafgaand aan de implantatie. De histologische bevindingen worden gedetailleerd beschreven in **Hoofdstuk 3**. Alle botbiopten toonden nieuwe botvorming met actieve osteoblastische en osteoclastische activiteit. Zelfs aan de transplantaatloze zijde werd een callus afgeleide botvorming waargenomen.

In **Hoofdstuk 4** hebben we het bestaande klinische bewijs over de werkzaamheid van de transplantaatloze sinusmembraan ophoging beoordeeld middels een review. Na een kritische selectie van twee onafhankelijke onderzoekers werden negen studies geïncludeerd, alleen gerandomiseerde gecontroleerde trials waren geschikt. Een risico op vertekening werd beoordeeld met behulp van de Revised Cochrane risk-of-bias tool voor gerandomiseerde trials. Voor zeven studies werd een meta-analyse

uitgevoerd. De resultaten toonden een hoge totale implantaatoverleving in zowel de transplantaatloze als de met bot geaugmenteerde sinuslift groepen (respectievelijk 97,92% en 98,73%). De transplantaatloze sinusliftgroep vertoonde een significant lagere verticale bothoogtewinst met een gemiddeld verschil van -1,73 mm (P=0,01) en een significant lagere botdichtheid met een gemiddeld verschil van -94,7 HU (P<0,001). De Implant Stability Quotient waarden toonden geen significante verschillen tussen de test- en controlegroep (P=0,07).

In 2020 was het meer dan zeven jaar na het plaatsen van implantaten bij de eerste geïncludeerde patiënt en bijna vijf jaar na de implantaat plaatsing bij de laatste geïncludeerde patiënt. **Hoofdstuk 5** vergelijkt de implantaatoverleving na de vermelde follow-up periode van 57-88 maanden tussen de test- en de controlezijde. Daarnaast werden bij deze tien patiënten de verticale botgroei na de sinusmembraanelevatie en het succes van de prothetische rehabilitatie beoordeeld. De resultaten toonden een implantaatoverleving van 96,7% (1 implantaat verloren op 30 geplaatste implantaten) aan de conventionele zijde tegenover een implantaatoverleving van 86,2% (4 implantaten verloren op 29 geplaatste implantaten) aan de transplantaatloze zijde bij de laatste follow-up. De implantaatoverleving was significant hoger aan de conventionele zijde, met een Risico Ratio van 4,14; dit betekent dat de transplantaatloze zijde een 4,14 keer hoger risico op implantaatverlies heeft dan de conventionele zijde. De conventionele zijde toonde significant (p=0,041) meer botaanwinst dan de experimentele zijde (respectievelijk 9,69 mm en 6,20 mm). Prothetische rehabilitatie was mogelijk bij alle tien patiënten.

We kunnen concluderen dat de techniek zonder gebruik van bottransplantaat enig potentieel heeft voor klinisch gebruik, hoewel het slechtere resultaten liet zien.

Tenslotte hebben wij in **Hoofdstuk 6** een studie uitgevoerd om de conclusies uit de voorgaande studies te evalueren voor wat betreft de tevredenheid van de patiënt. Het doel van deze studie was om de kauwfunctie en de mondgezondheid gerelateerde kwaliteit van leven in de onderzoeksgroep te beoordelen en de correlatie tussen de objectieve en subjectieve resultaten te beoordelen. Aangezien de histologische resultaten goed waren, de bottoename bewezen was en de implantaatoverleving aanvaardbaar was, wilden wij weten of de patiënten uit onze onderzoeksgroep tevreden waren met de functie van hun prothese. Voor deze studie vormden wij twee controlegroepen om te vergelijken met de studiegroep: De eerste groep bestond uit tien gezonde patiënten die een implantaat gedragen overkappingsprothese in de bovenkaak hadden zonder een voorgeschiedenis van botaugmentatie. De tweede groep bestond uit tien personen die hun eigen natuurlijke dentitie hadden en niet meer dan één tand in elk kwadrant hadden verloren (derde molaren uitgesloten).

Om de kauwfunctie te beoordelen werd een kauwvaardigheidstest uitgevoerd waarbij de patiënten op een wastablet moesten kauwen; een hogere kauwindex staat voor een slechtere kauwprestatie. Het kauwvermogen werd beoordeeld met twee verschillende vragenlijsten: de 'Quality of Masticatory Function Questionnaire' (QMFQ) en de 'Oral Health Impact profile for Edentulous People' (OHIP-EDENT). De tevredenheid van de patiënt werd beoordeeld met vragen over de prothese, waarbij het antwoord werd gevisualiseerd op een 'visual analogue scale' (VAS).

De resultaten toonden een hogere kauw index in zowel de studiegroep als de edentate controlegroep vergeleken met de natuurlijke dentitiegroep. De studiegroep verschilde significant van de natuurlijke dentitiegroep, andere resultaten toonden geen significantie.

Vragenlijsten toonden een beter kauwvermogen in de natuurlijke dentitiegroep, maar er werd alleen een significant verschil gevonden tussen de edentate controlegroep en de natuurlijke dentitiegroep wat betreft de QMFQ. De VAS-scores lieten geen significante resultaten zien tussen de studiegroep en edentate controlegroep.

De objectieve en subjectieve resultaten correleerden niet met elkaar.

Op basis van deze studie zijn er geen redenen om aan te nemen dat de kauwfunctie, de kwaliteit van leven met betrekking tot de mondgezondheid en de tevredenheid van de patiënt significant verschillen tussen een transplantaatloze sinusbodemelevatie van de bovenkaak en de conventionele methode met transplantaten. De beperkingen van deze studie, de kleine steekproefgrootte en het split mouth design, moeten in acht genomen worden.

Hoofdstuk 7 bespreekt de conclusies en toekomstperspectieven van dit proefschrift.

Uit dit proefschrift kunnen we concluderen dat elevatie van het sinusmembraan zonder het gebruik van augmentatiemateriaal leidt tot histologisch bewijs van spontane nieuwe botvorming. Dit leidt tot een voldoende benige basis voor het plaatsen van tandheelkundige implantaten in een later stadium.

De aangetoonde nieuwe botvorming aan de experimentele zijde leidt tot een kwalitatief en kwantitatief slechter resultaat in vergelijking met de nieuwe botvorming na gebruik van een mengsel van autoloog en xenogeen bot. Desalniettemin is de transplantaatloze sinusbodemelevatie met het oog op latere implantaat plaatsing, een aanvaardbaar alternatief indien het gebruik van botvervangende materialen moet worden vermeden. Dit resulteert vervolgens in een succesvolle prothetische rehabilitatie.

De kauwfunctie en de kwaliteit van leven met betrekking tot de mondgezondheid zijn acceptabel na de transplantaatloze techniek en verschillen niet van conventionele technieken.

CHAPTER 9

IMPACT PARAGRAPH

IMPACT PARAGRAPH

This work must be seen in the overall context of a changing field. Dentistry, which in the Netherlands includes oral and maxillofacial (OMF) surgery, is in a critical phase due to several factors. In addition to the demographic and structural conditions for the OMF-surgeons, which need to be described separately, health care and science policy trends are apparent that require the utmost focus, attention and also intervention from those responsible.

Within the last three decades, a significant development of dentistry can be observed. This development cannot be reduced to purely technological progress, but is characterized by a reorientation of dentistry in a biological and oral medical context. A major plus of dentistry is the demonstrable improvement of oral health in the Netherlands, but also worldwide in developed countries. This is the merit of prophylaxis efforts at all levels. From this alone derives the postulate that dentistry should always focus on prevention as the primary goal, although there is still considerable potential for optimization in this area as well, since a large part of the daily work in the dental practice still consists of simply repairing avoidable primary and secondary defects. In this context, financing issues also play a role in delineating ethical issues of possible overtreatment from treatments that can be assigned to esthetics and cosmetics. Optimal oral function, as well as esthetics, become increasingly important nowadays. Surgical techniques and various materials are developed to meet the high expectations of patients.

A cornerstone of good oral surgery is quality of work. Guidelines are good tools to excel in dental-medical decision making, not least as a final authority in litigation. However, guidelines are also bulky and experience shows that they are not always read in their entirety. This work is also intended to contribute to proving, in the chosen form of a scientific paper, the need for a stringent and critical review of the quality of structure, process and outcome in pre-prosthetic surgery.

Dental implantology has undoubtedly brought tremendous success in masticatory functional restoration of the dentition. It has been used worldwide for more than 60 years and has paved the way for implant surgery in other medical specialties. Coupled with this tremendous clinical impact is the use of titanium as the starting point for many implants in general reconstructive surgery. The first applications were characterized by clinical situations in which masticatory function was completely lost: edentulous patients. Dental implantology has already led to a change in pre-prosthetic surgery in the 80s and 90s of the last century which can be called revolutionary, especially

lowering of the floor of the mouth and vestibuloplasty with skin grafts from dermis into the oral cavity played a major role. These procedures were not without risk and occasionally resulted in dangerous swelling with respiratory impairment. Thankfully, the discipline of OMF surgery has accepted the possibility of achieving better results with the help of dental implants themselves. Today, the above-mentioned procedures have almost completely disappeared from the maxillofacial surgeon's arsenal, in favor of the risks for the patient.

However, another phenomenon occurred that has pushed implantology and the associated pre-prosthetic surgery into a special position to this day. Usually, implantological treatments in maxillofacial surgery are not included in the billing tables of the insurance landscapes worldwide, or only under certain conditions. As a result, dental implantology occupies an almost elite position in the medical treatment spectrum. The corresponding impact on the pricing and positioning of the associated products is subject to an enormous economic market power, which is absolutely crucial. This makes studies such as the present one, which on the one hand demonstrates the added value of implant-supported dental restorations, and on the other hand also shows a way of using the self-healing potentials of suitable anatomical regions to create proper conditions for the insertion of dental implants without additional augmentation materials, all the more important.

When it comes to augmentation materials, there is still a consensus that autogenous bone determines the gold standard. Harvesting autogenous tissue is always associated with increased morbidity, and this is also the case in pre-prosthetic surgery in our field. Criticism of autogenous bone harvesting has gone so far that some colleagues consider the harvesting of the iliac crest bone to be an encroachment.

In addition to the offering to replace missing bone by grafting autogenous bone, a large market for bone substitutes has developed, with a market power at least as great as that of the more than 100 companies offering dental implants in the Netherlands. The advertising of these providers suggests solutions for all situations of pre-prosthetic surgery, but the reality shows the limitations of many products. Some could even be labeled as unnecessary or dangerous if the origin of the product or the chemical preparation for safe use in humans has not been clarified beyond doubt.

The implications of the results of this dissertation is that we are aware that there are alternatives to the use of bone graft substitutes that can lead to acceptable outcomes. This results in less co-morbidity, lower risk of post-operative infection, lower cost and

shorter surgical time. Research has yet to identify the best technique and bone graft substitute to meet the desire for the best combination of best results with little or no co-morbidity and minimal cost.

APPENDIX

List of publications
Acknowledgements / Dankwoord
Curriculum Vitae
Music

LIST OF PUBLICATIONS

2021 Lie SAN, Leung CAW, Claessen RMMA, Merten HA, Kessler PAWH. Implant survival after graftless sinus floor augmentation in highly atrophic maxillae: a randomized controlled trial in a split mouth study. Int J Implant Dent. 2021 Oct 18;7(1):107. doi: 10.1186/s40729-021-00387-y

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10.02.2022	Intermolar Distraction Osteogenesis, 41. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St. Anton, Austria.
07.02.2022	Sinus Floor Augmentation, With and Without Augmentation Material, 41. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St. Anton, Austria.
06.11.2020	BOOA-lezing: "Bone height gain and implant survival after the graftless sinus floor augmentation in highly atrophic maxillae" -NVMKA najaarsvergadering, Helmond.
07.02.2020	Kieferorthopädische Chirurgie – Neue Entwicklungen und Trends: Hands-on Übungen, 39. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St. Anton, Austria.
06.02.2020	Neue Entwicklungen in der Kieferorthopädischen Chirurgie – IMDO, 39. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St. Anton, Austria.
03.02.2020	Sinuslift Procedure: Graft versus Graftless Augmentation, 39. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St. Anton, Austria.
20.11.2019	3D planning en osteotomieën, refereeravond voor tandartsen – Sittard
27.09.2019	Klasse II behandelingen, functionele apparatuur versus IMDO en orthognathische chirurgie, najaarsvergadering, Nederlandse vereniging van Orthodontisten - Kasteel st. Gerlach, Valkenburg aan de Geul
16.06.2018	Comparison of two Virtual Planning Programs in Daily Routine, The 14th International Bernd Spiessl-Symposium. Innovation meets Art 2018. – Basel, Switzerland
25.05.2018	Sinusbodemelevatie zonder botsubstitutie, NVMKA voorjaars-vergadering. – Maastricht
05.09.2017	De hypodonte patiënt, Dentsply - Kasteel St. Gerlach, Valkenburg aan de Geul
07.02.2017	3D-Planungssoftware in der Orthognathen Chirurgie, oral presentation, Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St Anton am Arlberg, Austria.
02.2016	- Der Einsatz von Patient Specific Implants (PSI) – Wunsch und Wirklichkeit - PSI in Orthognathic Surgery (workshop) Oral presentation.

	Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St Anton am Arlberg, Austria
27-30.10.2015	ICOMS 2015; First clinical experience in elevation of the maxillary sinus membrane for de-novo bone formation. Oral presentation - Melbourne, Australia
07.02.2015	First clinical experience in sinus floor elevation without augmentation. A histological evaluation. Oral presentation. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden – St Anton am Arlberg, Austria
21.03.2015	Sinusbodemelevatie zonder botsubstitutie. Oral Presentation. Voorjaarsvergadering. Koninklijke Belgische Vereniging voor Stomatologie en Maxillo-Faciale Heelkunde - Brussel, België
07.11.2014	Augmentatie 3.0, Sinusbodemelevatie Zonder Botsubstitutie, NVMKA najaarsvergardering - Bussum, Nederland
06.04.2014	First clinical experience in sinus floor elevation without augmentation. Oral Presentation. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St Anton am Arlberg, Austria
09.05.2013	Dynamic Periosteal Elevation. First results in clinical application. Oral Presentation. Division of Oral and Maxillofacial Surgery, Department of Oral Medicine and Surgery, Tohoku University School of Dentistry - Sendai, Japan
04.02.2013	Dynamic Periosteal Elevation. First results in clinical application. Oral Presentation. Internationales Symposium für Mund-, Kiefer- und Gesichtschirurgen, Oralchirurgen, Zahnärzte und Kieferorthopäden - St Anton am Arlberg. Austria

OTHER

- BOOA Research Grant 2012, "Augmentation of the maxillary sinus floor; periosteal elevation versus autogenous bone and xenogenic material" Grand Hotel Huis ter Duin te Noordwijk aan Zee, Najaarsvergadering NVMKA

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A

Liefste **Harry Hudson**, mijn lieve man, elke dag ben ik dankbaar voor wat je me geeft en voor de persoon die jij bent. Zonder jou had ik de balans tussen werk en privé niet zo goed kunnen onderhouden. Je steunt mij in alles, je staat altijd achter mij en je bent er altijd voor me. Het is ook heel handig om een native English speaker naast mij te hebben, dankjewel voor je hulp met Engels. Ik vind jou geweldig, knap, grappig, leuk en lief. Je bent een 'amazing daddy' voor de kids. Ik hou ontzettend veel van jou.

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CURRICULUM VITAE

Suen An Nynke Lie was born on 28 September 1983 in Heerlen, the Netherlands. She is married and has two children. She graduated from Gymnasium at Bernardinus College in Heerlen in 2002. In 2003 she started medical training at the Faculty of Health, Medicine and Life Sciences at Maastricht University.

After an internship at the Department of Cranio-Maxillofacial Surgery (Head: Prof. Dr. Dr. P.A.W.H. Kessler), Maastricht University Medical Center+ (MUMC+), from July to September 2007, she decided to be trained as an Oral and Maxillofacial (OMF) Surgeon. She spent the final year of her medical study at the same department. Her medical training was successfully completed in June 2009. In the same year she started dentistry at the Radboud University, Nijmegen.

After graduation she started her residency in OMF-surgery at the Department of Cranio-Maxillofacial Surgery, MUMC+, from 2011 to 2015. This included one year at the Elkerliek Hospital in Helmond under supervision of Dr. GJ. Dicker in 2013-2014. Since 2015 she works as a staff member in the above mentioned department in the MUMC+ with clinical focus on pre-implant and implant surgery, orthognathic surgery, 3D planning and navigated surgery in traumatology. During the beginning of her staff membership, she gained additional experience during several visitorships: at the Sint Jan Hospital in Bruges, Belgium, Department of OMF-surgery, under supervision of Prof. Dr. Dr. G. Swennen in 2015; at the University of Zurich, Department of OMF-Surgery, under supervision of Prof. Dr. Dr. H. Essig in 2015; and at the Facial Reconstruction Clinic in Santa Barbara, California, USA, under supervision of Dr. W. Arnett in 2016.

Since 2020 she is the vice director of the training program of the OMF-department at the MUMC+.

Next to her profession, she plays the bass guitar in a band and loves music, snowboarding, cooking, baking, motorcycle riding and spending spare time with her family.

CURRICULUM VITAE

Suen An Nynke Lie is geboren op 28 september 1983 in Heerlen, Nederland. Ze is getrouwd en heeft twee kinderen. In 2002 is zij afgestudeerd aan het Gymnasium van het Bernardinus College te Heerlen. In 2003 begon zij haar opleiding geneeskunde aan de Faculty of Health, Medicine and Life Sciences van de Universiteit Maastricht.

Na een keuze-coschap op de afdeling Mondziekten, Kaak- en Aangezichtschirurgie (MKA) (Hoofd: Prof. Dr. Dr. P.A.W.H. Kessler), Maastricht Universitair Medisch Centrum+ (MUMC+), van juli tot september 2007, besloot zij zich te laten opleiden tot Mond-, Kaak- en Aangezichtschirurg (MKA-chirurg). De gezondheidsstage en wetenschapsstage in het laatste jaar van geneeskunde vond plaats op dezelfde afdeling. Haar artsenopleiding rondde zij in juni 2009 succesvol af. In hetzelfde jaar startte ze met tandheelkunde aan de Radboud Universiteit in Nijmegen.

Na haar afstuderen startte zij van 2011 tot 2015 haar opleiding tot MKA-chirurg op de afdeling Mondziekten, Kaak- en Aangezichtschirurgie, MUMC+. De perifere stage vond plaats in het Elkerliek ziekenhuis in Helmond onder leiding van Dr. GJ. Dicker in 2013-2014. Sinds 2015 is zij werkzaam als staflid op bovengenoemde afdeling in het MUMC+ met klinische focus op pre-implantologie en implantologie, orthognathische chirurgie, 3D planning en navigatie chirurgie in de traumatologie. Tijdens het begin van haar staflidmaatschap deed zij extra ervaring op tijdens diverse bezoekstages: in het Sint Jan Ziekenhuis bij afdeling MKA-chirurgie in Brugge, België, onder supervisie van Prof. Dr. Dr. G. Swennen in 2015, aan de Universiteit van Zürich, afdeling MKA-chirurgie, onder supervisie van Prof. Dr. Dr. H. Essig in 2015 en in de Facial Reconstruction Clinic in Santa Barbara, Californië, VS, onder supervisie van Dr. W. Arnett in 2016.

Sinds 2020 is zij plaatsvervangend opleider bij de afdeling MKA-chirurgie in het MUMC+.

Naast haar werk speelt zij als basgitarist in een band en houdt zij van muziek, snowboarden, koken, bakken, motor rijden en vrije tijd doorbrengen met haar gezin.

MUSIC

Music belongs to my acknowledgements. For me, music is one of the most important things in life. While I was writing this thesis I spent a lot of time listening to several bands. Even if I hear certain music randomly from my Spotify list, it reminds me of specific chapters that I was writing. Music brings creativity, concentration, relaxation and joy.

On the cover of each chapter you can find a QR-code. To listen to the music, scan the QR-code which will give you the option to choose a music platform enabling you to hear the song. If you don't have Spotify Premium or another paid music platform, choose YouTube. Some of these bands helped me in the process of writing, some fit well with the content of the chapter and others give a good feeling while reading the article. I asked Prof. Kessler to pick the song for Chapter 3 and he chose a song from one of his favorite bands.

Chapter 1	*Places*	Owel
Chapter 2	*Sheep Amongst Wolves*	Phoenix Ashes
Chapter 3	*Thunderstruck*	AC/DC
Chapter 4	*Smoke*	PVRIS
Chapter 5	*Anchor*	Start a Revolution
Chapter 6	*Nothing Else Matters – Live*	Metallica & Symphony
Chapter 7	*Dark Water*	Agent Fresco
Chapter 8	*Black Honey*	Thrice
Chapter 9	*Lost – Live, acoustic*	Phoenix Ashes
Appendix	*Here to Mars*	Coheed and Cambria

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