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 de-novo bone formation 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.

1. Introduction

Bone healing can be influenced decisively by mechanical forces. The functional stressing in fracture healing has widely been examined and can constitute a trophic stimulus for the tissues to heal (Pauwels, 1948; Kessler et al., 2002; Kessler et al., 2005a). On the contrary, in certain circumstances, a permanent mechanical stressing, such as 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 (Laer, 2010).

The form and size of the maxillary sinus vary 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.

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With regard to augmentative pre-implantological procedures in the maxilla, the sinus floor augmentation occupies a prominent position (Boyne and James, 1980; Timmenga et al., 2003). It is by far the most commonly used technique (Thorwarth et al., 2005b). 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 (Kessler et al., 2005b; Sakkas et al., 2018). 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 (Jensen et al., 1998; Thorwarth et al., 2005a; Lutz et al., 2015). Ongoing research in this area centers on the design of matrices mimicking active biological qualities of natural materials such as bone (Gruber et al., 2009). 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 (Ramazanoglu et al., 2013). 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 (Srouji et al., 2010; Nasr et al., 2016).

2. Material and methods

The study design for testing in humans has been described in extenso earlier (Lie et al., 2015). 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 2.9 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 (Schlegel and Donath, 1998; Schlegel et al., 2006a; Schlegel et al., 2006b; Schmitt et al., 2013; Lie et al.,

2015). Then the bone samples were cut on the median longitudinal axis and ground into thin sections of 120 μm (Exakt Apparatebau GmbH, Norderstedt, Germany). 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.).

3. 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 and 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 (Fig. 6a and b). A strong bony "keramoosseous" 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) (Barth, 1895) is the only sporadically visible absorption lacunae.

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
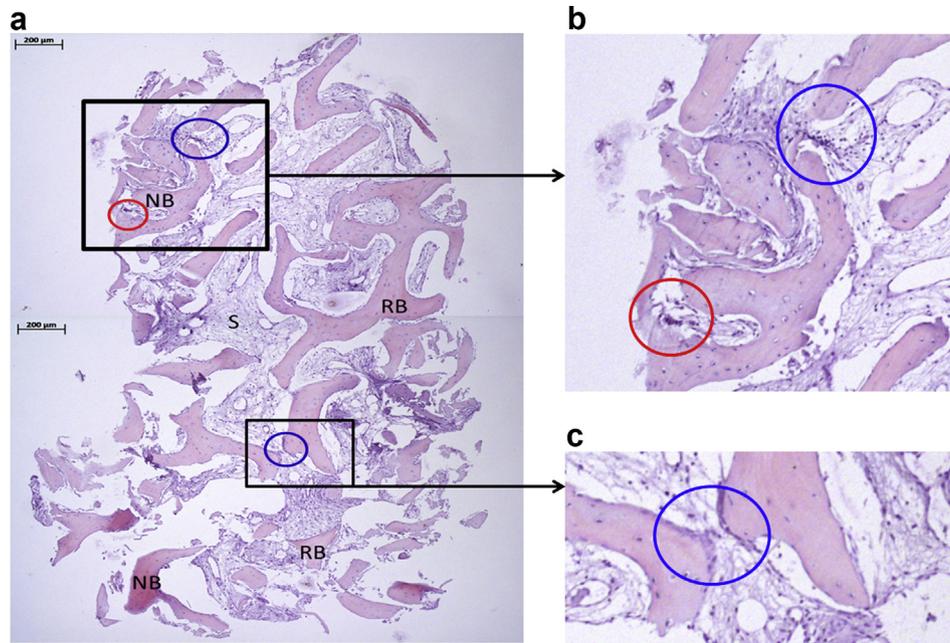
Fig. 1. a) 120 μm thin section and a width of about 3 mm. The bone regenerate is vital, bone trabeculae cover the whole specimen organized in a diffuse pattern. The inter-trabecular space is mostly filled with undifferentiated primary bone marrow consisting of stromal tissues rich in vasculature and 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.
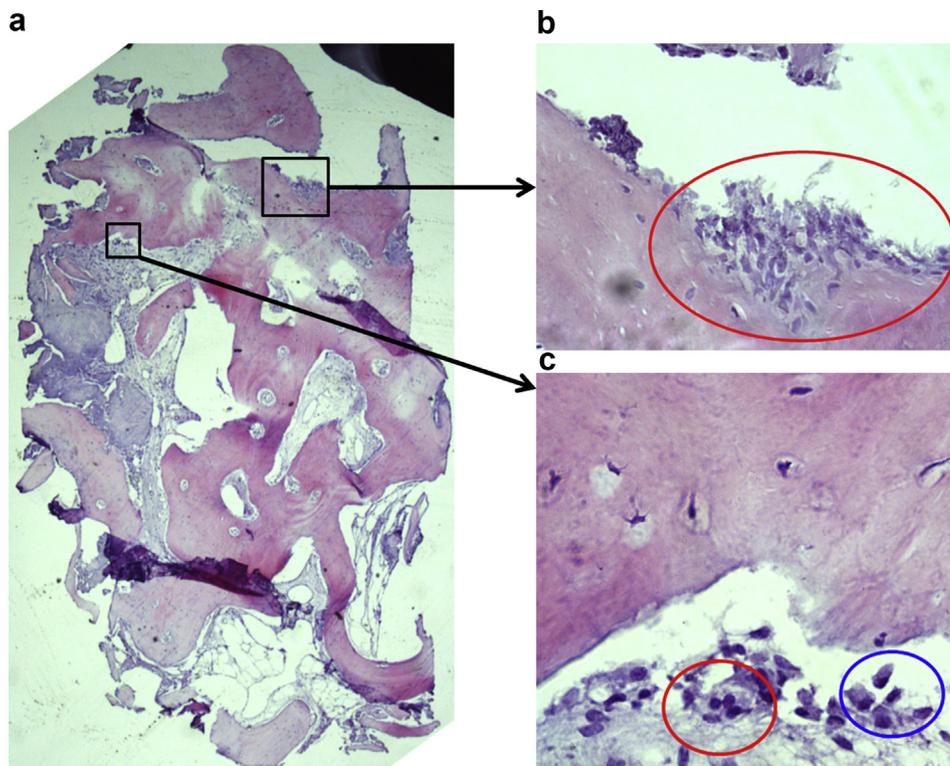

Fig. 2. a) Active bone remodeling is defined by the presence of osteoblastic and osteoclastic activity. b) The red circle shows osteoclastic activity. c) In the blue encircled field osteoblastic activity is documented, in the red encircled field osteoclastic activity.

the 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.
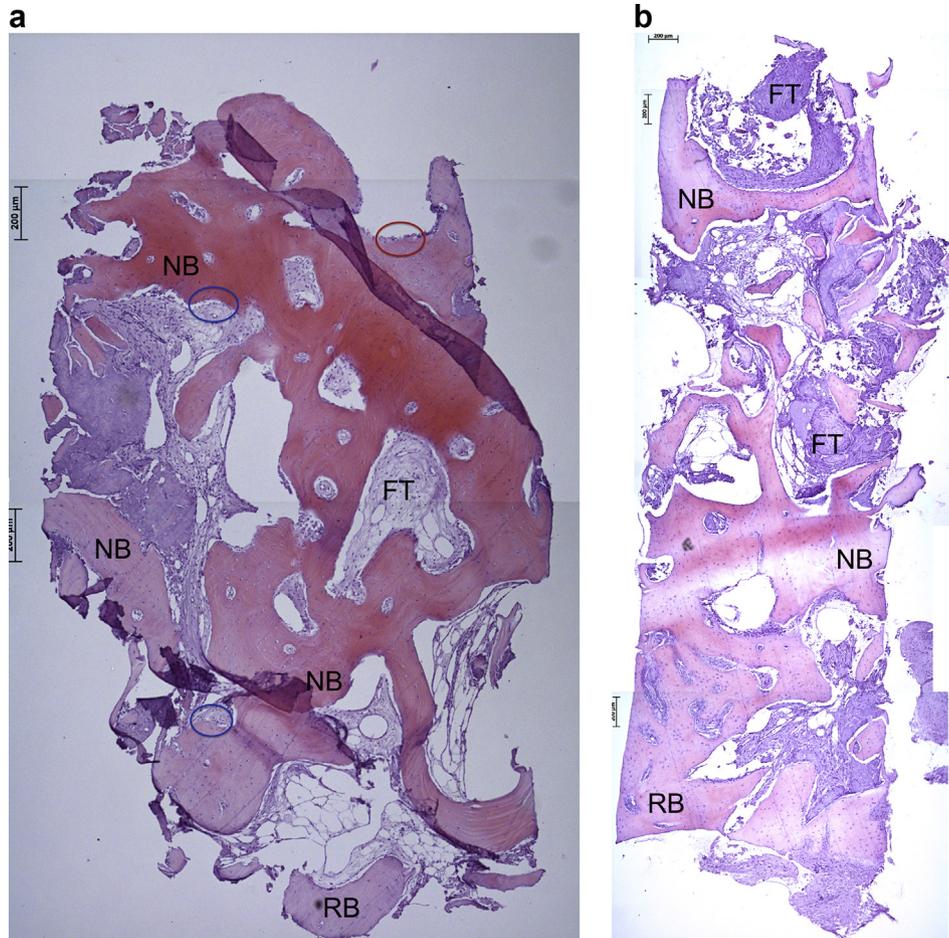
Fig. 3. a) and b) The inter-trabecular space is mostly filled with undifferentiated primary bone marrow. Histologically fibroblasts and fibrocytes are dominant in this granulation tissue. NB = new bone, RB = residual bone, FT = fibrous tissue, blue circle = osteoblast activity, red circle = osteoclast activity.
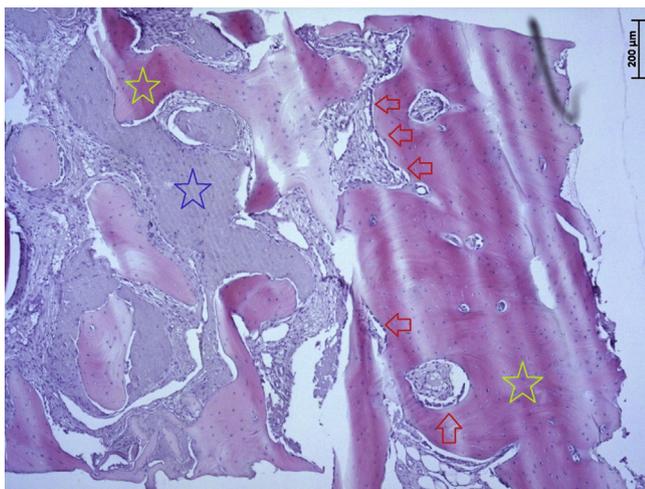

Fig. 4. This histological image shows evidence of persistent neo-ossification and a well-vascularized, cell-rich presence of trabeculae and bone marrow. There are both old trabeculae (blue star) as newly formed (yellow star), but still less calcified and less fiber-rich cells. Osteoid trabecular structures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

Fig. 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.

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.
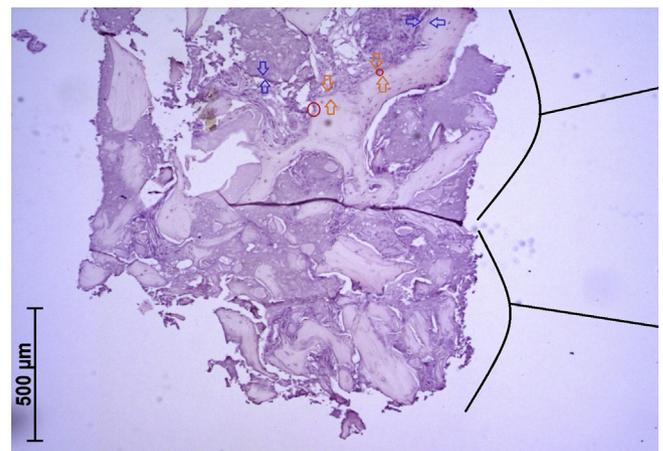
4. Discussion

Several studies have already proven new bone formation after maxillary sinus lift procedures followed by leaving a space filled with blood. In most studies direct implant placement helped to
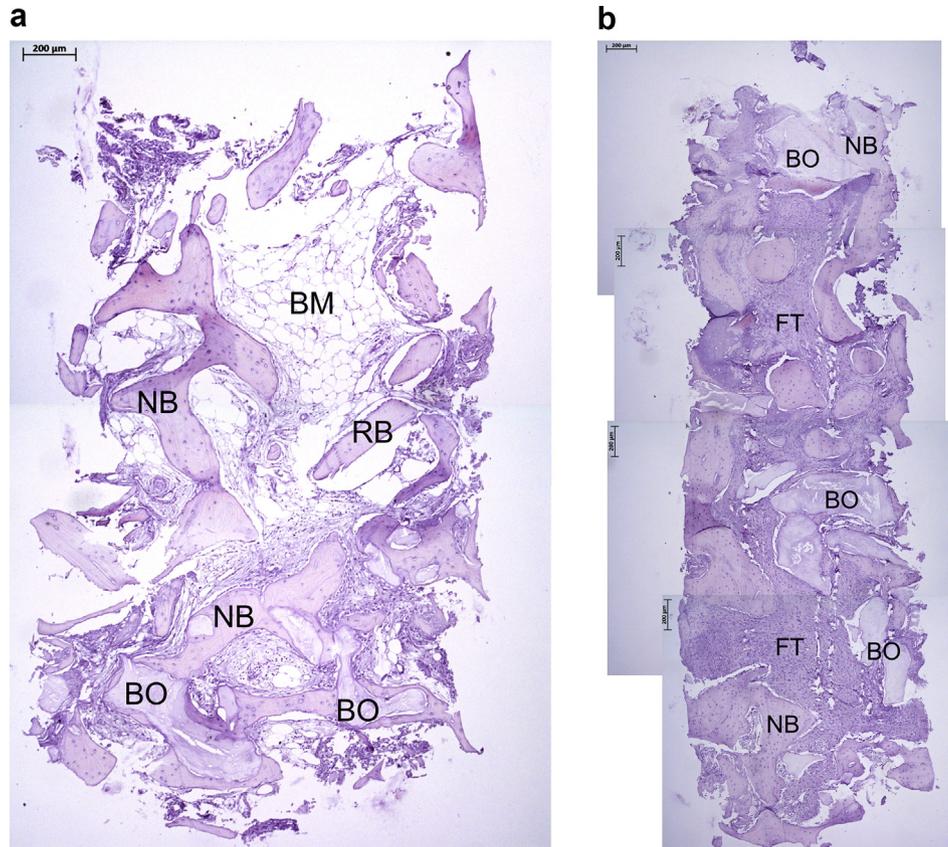
Fig. 6. a) The bone biopsies of the conventional side show a combination of Bio-Oss® embedded in bone marrow and newly formed bone. b) The respective augmentation compartments BO: FT: NB are at ratio of 30: 40: 30 percent. BO = Bio-Oss®, NB = new bone, RB = residual bone, BM = bone marrow, FT = fibrous tissue.

create a submembraneous space in the sinus with the implant as a spaceholder (Lundgren et al., 2004; Jungner et al., 2015; Elton Gonçalves Zenóbi, 2018). 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 for 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 1930s (Krompecher, 1937). 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 standstill 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 (Degidi et al., 2006; Galindo-Moreno et al., 2010). 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—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 (Tarnow et al., 2000). 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 (Montgomery, 1964; Soparkar et al., 1994; Sesenna et al., 2010). 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 (Eto and House, 1995). 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 with 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.

Regarding 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 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 (Murray, 1983). 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 (Shirley et al., 2005). 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 (Kessler et al., 2002). 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 (Scala et al., 2012). Rong et al. state in their publication (Rong et al., 2015) 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 (Palma et al., 2006; Cricchio et al., 2009). 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 (Srouji et al., 2010; Graziano et al., 2012). 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. Our 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 (Gruber et al., 2008).

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.

5. 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 (Krompecher, 1937). 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 be exhausted. The limiting factor of bone formation in the artificially created functional "dead space" will be defined by the "distance problem" of spontaneous bone generation.

In pre-prosthetic implant placement, short implants are common. The use of these short implants has been increased in recent

years (Pommer et al., 2016). These so called "shorties" could be an ideal option in atrophic maxillae with a limited amount of newly generated bone. To gain an optimum amount of bone volume in spontaneous bone generation it is of utmost importance to plan the insertion of implants at the right moment. If the right moment for inserting implants is missed, 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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