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The fluorohydroxyapatite (FHA) FRIOS[®] Algipore[®] is a suitable biomaterial for the reconstruction of severely atrophic human maxillae

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Abstract: Grafting of the maxillary sinus is an established treatment modality to provide sufficient bone for the fixation of dental implants. We stated the hypothesis that the porous fluorohydroxyapatitic (FHA) biomaterial FRIOS[®] Algipore[®] could be used as a suitable biomaterial for sinus grafting in severely atrophic maxillae. To investigate the accuracy of our hypothesis, 69 trephine specimens from 26 patients who received maxillary sinus grafting with FRIOS[®] Algipore[®] were retrieved during the installation of dental implants. The specimens were processed undecalcified and subjected to histomorphological and histomorphometrical examination. After a mean healing time of 7 months, 23.0% (± 8.3) new bone had formed around the implanted particles. Bone formation was also evident within the pores of the particles. Statistical analysis indicated that bone formation originated from the sinus floor. Particles provided scaffolding for the promotion of newly formed bone towards apical sinus portions. Mineral dissolution from the walls of the pores was observed prior to and during bone apposition. Thereafter, portions of the particles were resorbed during bone remodeling and replaced by newly formed bone. The present investigation shows that the biomaterial FRIOS[®] Algipore[®] is a suitable biomaterial for sinus grafting of severely atrophic maxillae.

Osseointegrated dental implants are a widely used method of replacing missing teeth, but often require bone augmentation prior to implant placement. The atrophic posterior maxilla offers a particular challenge when osseointegrated reconstruction is considered (Brånemark 1999). Sinus grafting has become a standard method to provide adequate bone for implant fixation in such cases (Boyne & James 1980; Jensen et al. 1998). However, a variety of grafting materials is employed for sinus grafting. Autogenous bone is the standard against which other methods must be measured (Burchardt 1983). Nevertheless, autografts

are hampered by unpredictable resorption (Wheeler 1997; Jensen et al. 1998), donor site morbidity (Canady et al. 1993; Eufinger & Leppanen 2000) and limited quantities (Springfield 1996). Therefore, biocompatible substitutes have been developed as an alternative for the harvesting of autogenous bone. Suitable biomaterials must generate adequate bone volume even in challenging cases. Bone formation depends, to a large degree, on inducible progenitor cells that can be transformed into competent osteoblasts (Oreffo & Triffitt 1999). Osteoblasts are most abundantly present in vital bone matrix and bone

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marrow that are both significantly reduced in atrophic maxillae. Biomaterials that are used for the reconstruction of bone are nonviable foreign bodies, which only provide scaffolding for the formation of new bone. Appositional bone growth around biomaterials can be considered as a result of a host response. Thus, it would be desirable if biomaterials provide stability until bone formation has been largely completed and thereafter become gradually replaced by vital bone during bone remodeling. By that means, a higher contact percentage between dental implants and vital bone would possibly be present after implant installation. However, no experimental model corresponding with the situation of the severely atrophic maxilla is established. The nature of histologic events is therefore best documented on

clinical samples retrieved after sinus grafting. The purpose of the present investigation was to investigate the suitability of the porous fluorohydroxyapatite (FHA) FRIOS® Algapore® to trigger bone formation in the maxillary sinuses of severely atrophic human maxillae. The process of graft healing, bone remodeling and biomaterial replacement was examined histomorphologically and histomorphometrically.

Material and methods

Biomaterial

The commercially available porous biomaterial FRIOS® Algapore® (Kasperk & Ewers 1986) was obtained from Friadent GmbH, Mannheim, Germany. This granulate is

manufactured from calcifying marine algae (*Corallina officinalis*). Biomaterial processing involves pyrolytical segmentation of the native algae and hydrothermal transformation of the calcium carbonate [CaCO_3] into FHA [$\text{Ca}_5(\text{PO}_4)_3\text{OH}_x\text{F}_{1-x}$]. Three-dimensional visualization of particles by scanning electron microscopy (JSM 6310, JEOL Ltd, Tokyo, Japan) provides valuable information about the structural architecture of particles (Figs 1a–c). The particles contain a pore system (mean diameter of pores 10 μm) that is periodically septated (mean interval 30 μm) and interconnectively microperforated (mean diameter of perforations 1 μm). Every pore is limited by one layer of small FHA crystallites with a size of 25–35 nm. The impression of a bilayer texture of the walls arises by the contact of the layers of adjacent pores. The

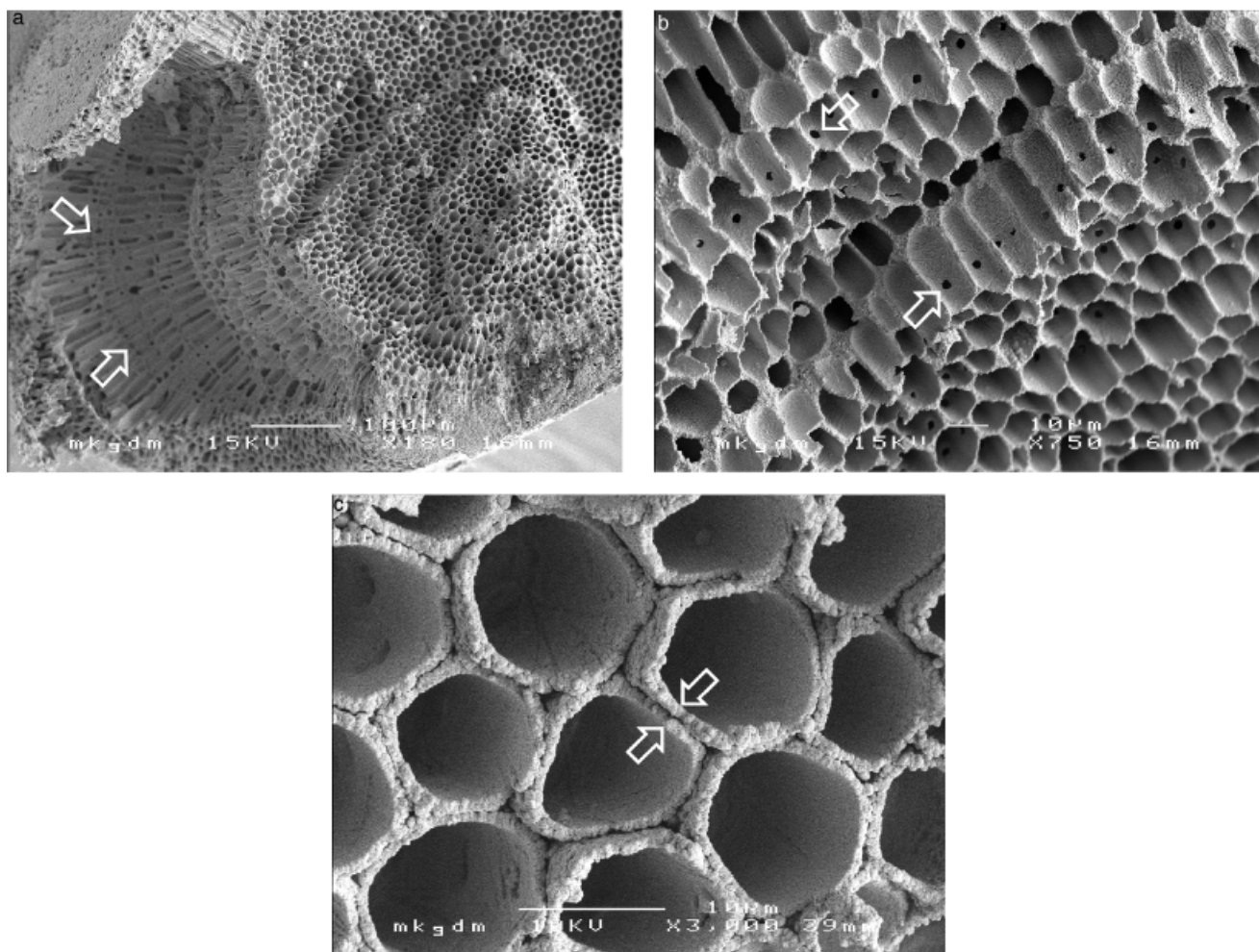


Fig. 1. (a) Scanning electron microscopic examination visualizes the spatial arrangement of the pore system within the biomaterial particles. Arrows show the periodical septation of the pores. (b) Microperforations (arrows) within the fragile walls of the pores connect adjacent pores with each other. (c) Small FHA crystallites are assembled within the walls of the pores. Every pore is limited by one FHA layer. The impression of a bilayer texture of the walls (arrows) arises by the contact of the layers of adjacent pores. (a) Bar = 100 μm . (b,c) Bar = 10 μm .

specific pore volume of the biomaterial averages $0.93 \text{ cm}^3/\text{g}$, while the surface area averages $50 \text{ m}^2/\text{g}$.

Surgical procedure

Twenty-six patients suffering from severely atrophic posterior maxillae with a residual bone $< 3 \text{ mm}$ were reconstructed by grafting both maxillary sinuses. Patients were of both sexes (15 female, 11 male) with a mean age of 52 years (range 38–76 years). Surgery was carried out in general anesthesia by one surgeon (R.E.). A crestal incision was performed and a full-thickness mucoperiosteal flap was elevated to expose the facial wall of the maxillary sinus. A longitudinal osteotomy was prepared for laterobasal approach to the maxillary sinus using a conventional dental handpiece. Accumulating bone debris was saved with a suction trap. Sinus membrane elevators were used to dissect the Schneiderian membrane from the alveolar recessus. Minor ruptures of the Schneiderian membrane were closed by resorbable micro-sutures or placement of collagen tapes (Vlassis & Fugazzotto 1999). Blood was added to the mixture of FRIOS® Algipore® and bone debris (ratio biomaterial/bone 10/1) until clotting occurred. After placement of the graft into both alveolar recessus, the lateral wall osteotomy site was obturated with a titanium shield (Frios Bone Shield®, Friadent, Mannheim, Germany) to ensure graft containment and prevent soft tissue invagination. The mucoperiosteal flap was then repositioned and sutured with nonresorbable gut. Grafted sinuses were allowed to heal for a mean time of 7 months. At the time of dental implant installation, trephine specimens were retrieved from corresponding implant sites using a water-cooled 3 mm wide trephine drill. Informed consensus was obtained from all patients.

Sample preparation

The samples were placed in 200 ml disposable pipet tips for apico-coronal orientation and immediately fixed in 4.5% neutral buffered formaline overnight. The samples were then dehydrated in a graded series of ethanol and embedded in methacrylate. After hardening of the resin, undecalcified specimens were obtained utilizing a modified Donath technique

(Donath 1988; Erben 1997). Ground bone slices (average thickness $10 \mu\text{m}$) were stained with 1% thionine (Derkx & Birkenhaeger-Frenkel 1995) and subjected to histological evaluation by transmission light microscopy (Eclipse 800, Nikon Corp., Tokyo, Japan).

Histological examination

Histological interests were focused on new bone formation, bone remodeling, and biomaterial replacement. After morphological examination, area values for bone and biomaterial were obtained. A semiautomatic image analyzing software (Lucia 32G, version 4.10, Laboratory Imaging Ltd, Prague, Czech Republic) was employed by one operator (A.S.). Two regions of interest (ROI) representing apical and coronal portions of the trephine specimens were defined and traced separately. Neither automatic nor manual quantification provided a practicable solution for tracing bone portions within the pores of the particles. Therefore, these amounts were included into the biomaterial area.

Statistical analysis

Histomorphometrical data were analyzed by a computer software package (SAS statistical software system, version 8.1, SAS Institute Inc., Cary, NC, USA). Mixed model analysis was performed with the fixed factors patient sex, patient age, healing time, sampling site (premolar/molar) and specimen portion (apical/coronal) to determine the impact of these factors on the amount of new bone formation and biomaterial resorption. The structure of covariance was modeled by a random effect. For patient age, the range of 38–76 years was broken into two groups (38–51 years, 13 patients, 36 samples; 52–76 years, 13 patients, 33 samples), according to the median value of 52 years. For healing time, the range of 102–371 days was broken into two groups (102–207 days, 13 patients, 33 samples; 209–371 days, 13 patients, 36 samples), according to the median value of 208 days (7 months). For sampling site, specimens were classified as premolar (30) and molar (39) samples. For apico-coronal quantum differences within the same specimen, values obtained from apical and coronal ROIs were referred to. All values

are reported as means $\pm$ standard deviations. For all analyses, a P -value < 0.05 was considered to indicate statistical significance.

Results

Histological results

No inflammatory round cell infiltrates were observed. *De novo* synthesis of bone matrix was evident in all trephine specimens. Appositional bone growth was seen in most of the particles that were cross-linked by a framework of trabecular formations of bone (Fig. 2a). Also observed was the growth of newly formed bone into the pores of many particles (Fig. 2b). Uncovered portions of particles were in contact with intervening fibrovascular soft tissue. A few particles without bone contact were completely encapsulated by soft tissue. Bone formation was closely linked to angiogenesis. Marrow spaces contained moderate numbers of marrow stromal cells, adipocytes and a vascular network that aligned bone trabeculae. Some vascular ingrowth into the particles was also seen. In active appositional sites, seams of osteoblasts formed a barrier between marrow spaces and deposits of osteoid. Such appositional sites with ongoing bone formation were predominantly present in apical portions of the specimens. Collagen fibrils were located within recently synthesized matrix. Calcification fronts were clearly detectable. Within the mixture of biomaterial, nonviable bone debris and viable new bone, areas of resorption were observed. At areas of resorption, multinucleated giant cells that functionally resembled osteoclasts were traced in resorption lacunae along bone trabeculae. Marked portions of particles which showed appositional bone growth and intraporous bone were resorbed during bone remodeling and replaced by newly formed bone (Fig. 2b,c). Some multinucleated giant cells also surrounded uncovered particle portions. Bone remodeling respected lamellar boundaries, and incipient lamellar reinforcement was visible in many of the cancellous bone trabeculae. Also seen was disintegration of the walls of the pores (Fig. 2d) prior to and during appositional bone growth where multinucleated giant cells were adjacent to biomaterial particles. Small biomaterial

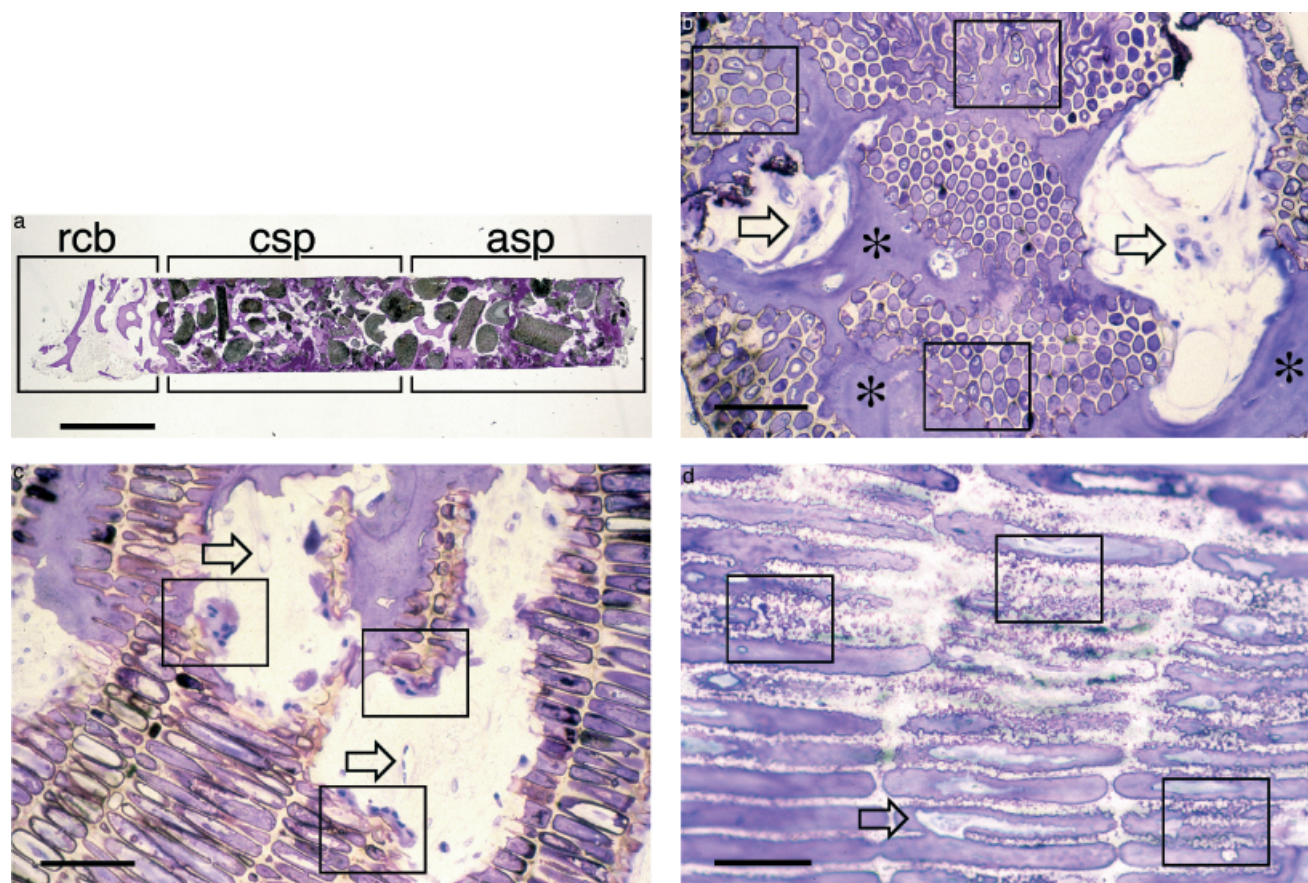


Fig. 2. Histological examination of trephine specimens obtained 7 months after maxillary sinus grafting with the FHA biomaterial FRIOS[®] Aligpore[®]. Specimens are undecalcified and stained with thionine. (a) Low-power view showing an entire specimen. Biomaterial particles are crosslinked by a framework of trabecular formations of newly formed bone. Statistical analysis (see Fig. 4) showed that coronal specimen portions (csp) contained higher amounts of newly formed bone than apical specimen portions (asp). This finding indicated that bone formation originated from the residual crestal bone (rcb) of the sinus floor and that particles provided scaffolding for the promotion of newly formed bone towards apical sinus portions. (b) Cross-section of a biomaterial particle. Several portions of the particle have been resorbed by multinucleated giant cells (arrows) and almost completely replaced by newly formed bone (asterisks). New bone has also grown into the pores of a biomaterial particle. Note the presence of osteocytes inside the pores (frames) what have been obstructed by new bone. (c) Osteoclastic activity with ongoing resorption of intraporous bone along with the walls of a biomaterial particle by multinucleated giant cells (frames). Remnants of the periodical septations of the pores are visible in the upper middle part of the figure. Also present are vascular formations (arrows). (d) High-power view showing disintegration of the walls of the pores (frames) in the absence of osteoclastic activity. This was seen prior to and during appositional bone growth where multinucleated giant cells were adjacent to biomaterial particles. Synopsis with Fig. 1c showing that the walls of the pores are composed of small FHA crystallites suggests that this observation may be most probably due to dissolution of FHA crystallites from the walls of the pores by hydrolases from surrounding multinucleated giant cells. Also visible is intraporous bone and an osteocyte passing into a microperforation (arrow). (a) Bar = 2 mm. (b,c) Bar = 50 μ m. (d) Bar = 20 μ m.

fragments were identified within the marrow spaces. Histomorphometrical results are summarized in Fig. 3.

Statistical results

For bone and biomaterial values, no significant correlations with patient sex, patient age, healing time, and sampling site were calculated ($P > 0.05$). Calculation for bone values showed that coronal ROIs contained significantly higher amounts of newly formed bone than apical ROIs ($P = 0.0012$; Fig. 4). For biomaterial values, no significant differences between coronal and apical ROIs were calculated ($P = 0.1418$).

Discussion

The present investigation showed that the FHA biomaterial FRIOS[®] Aligpore[®] triggered formation of new bone in the grafted sinuses of severely atrophic human maxillae. The average amount of bone that had formed after a mean healing time of 7 months was 23.0%. This is in agreement with other authors using a combination of porous hydroxyapatite and autogenous bone for sinus grafting who have found equivalent bone formation after healing times of 6–7 months (Wheeler et al. 1996; Yildirim et al. 2000, 2001). The increase in cancellous bone mass was supported by the biomaterial particles that provided scaffold-

ing for bone promotion. Histological examination revealed that a physiologic framework of cancellous bone had formed around the biomaterial particles. We have previously demonstrated the biocompatibility of FRIOS[®] Aligpore[®] (Schopper et al. 1999; Watzinger et al. 1999).

The structural architecture of biomaterials is crucial for bone morphogenesis (Mankani et al. 2001). To our knowledge, bone growth into biomaterials has previously not been described for pore sizes smaller than 40 μ m (Klawitter et al. 1976), although a recent *in vitro* study has suggested enhanced proliferation of human bone cells grown on three-dimensional interconnected pore sizes of 0.5 and

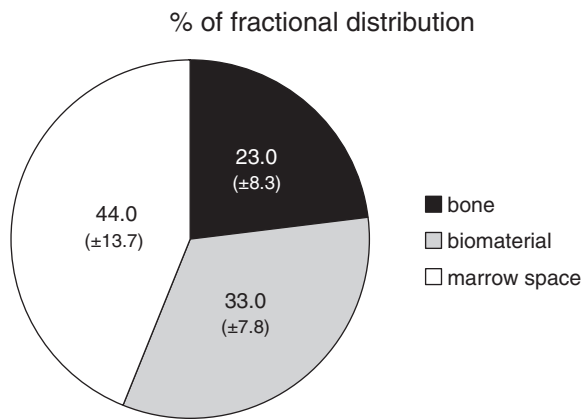


Fig. 3. Summary of biopsy data of 69 specimens. Bone area of the different trephine specimens ranged from 10.2 to 53.2% and comprised a mean value of 23.0% (± 8.3). Biomaterial area ranged from 11.7 to 72.6% with a mean value of 33.0% (± 7.8). Marrow space ranged from 16.6 to 84.3% with a mean value of 44.0% (± 13.7). Data are means $\pm$ standard deviations.

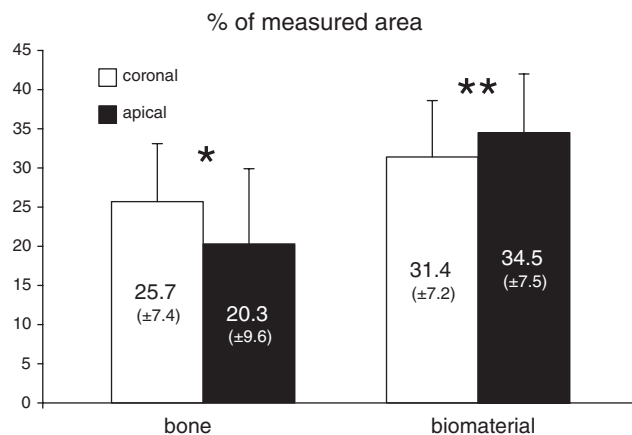


Fig. 4. Comparison of bone and biomaterial values within coronal and apical regions of interest (ROI) by means of mixed model analysis. Coronal ROIs contained significantly higher amounts of newly formed bone than apical ROIs ($*P = 0.0012$, see Fig. 2a), whereas no significant difference was present for biomaterial values ($**P = 0.1418$). Data are means $\pm$ standard deviations of 69 specimens.

16 μ m pores when compared with pore sizes of 50 μ m (Akin et al. 2001). The histological observations of this study showed that mineralized bone matrix along with viable bone cells were present in many of the FHA particles. This may indicate that biomaterials with interconnected pore sizes of about 10 μ m are capable of allowing for the ingrowth of bone *in vivo*.

Sinus grafts are actually placed extracorporally into a created subantral pocket (Watzek et al. 1999). The origin of the osteoblasts that were stimulated to promote bone formation is not known. Stromal fibroblasts of the bone marrow have been considered as osteoprogenitor cells (Krebsbach et al. 1999; Dahir et al. 2000). Ingrowing capillaries may also provide osseoprogenitor cells. In this study, bone formation was closely linked to angiogen-

esis. Newly formed bone was always aligned by a vascular network, and vascular ingrowth into biomaterial particles was also observed. Several authors suggest pericytes to be oligopotential and to differentiate into competent osteoblasts (Diaz-Flores et al. 1991; Brighton et al. 1992; Hirschi & D'Amore 1996; Doherty et al. 1998), while others propose osteoblasts to be derived from vascular endothelial cells (Decker et al. 1995). However, local bone (Keith 1928; Aubin & Liu 1996; Triffitt et al. 1998) and the periosteum (Breitbart et al. 1998; Reynders et al. 1999) may also contribute to bone growth. A statistical analysis showed that there were significantly higher amounts of newly formed bone in coronal than in apical specimen portions. This finding may indicate that bone formation originated from the residual crestal bone of

the sinus floor. Biomaterial particles may then provide scaffolding for the promotion of newly formed bone and growing capillaries towards apical sinus portions.

Histology showed that apical portions of the grafted sinuses were still in the appositional phase of the graft repair and that consolidation of the graft was incomplete after 7 months. This finding suggests that an amount of newly formed bone higher than 23.0% may be expected for longer healing times. Bone formation was not quantitatively correlated with age or sex of patients. It is likely that the multistep regenerative cascade of graft healing is based on a more complex regulation than physiological bone metabolism.

Our morphological observations showed that bone remodeling was evident. After bone growth into the particles had occurred, marked portions of the implanted biomaterial particles were resorbed by the multinucleated giant cells that were involved in bone remodeling. Resorption was followed by a complete or almost complete repair of the resorption lacunae by new bone deposition. Resorbed biomaterial particles were gradually replaced by new bone. The volume of the graft was therefore maintained. The mechanism of osteoclast activation is still not understood. Structural proteins such as collagen or stimulatory signals produced by local cells may be potential activators (Mundy 1999). The presence of mineralized bone matrix within the particles may support biomaterial resorption. Statistical analysis indicated no correlation of biomaterial replacement with healing time after 7 months. The amount of biomaterial resorption failed to reach a significant level by that time.

Besides active osteoclastic resorption of biomaterial particles, the present investigation also showed disintegration of the walls of the pores where no active osteoclastic resorption was observed. This was commonly seen prior to and during appositional bone growth at particle portions where multinucleated giant cells were adjacent to, and may be most probably related with dissolution of FHA crystallites from the walls of pores. The volume of particles was maintained, whereas the overall particle mass was reduced prior to appositional bone growth. Disintegration of the biomaterial particles may be the result of a host response, and hydrolases from surrounding

multinucleated giant cells may be involved in mineral dissolution (Donath et al. 1987). A profound effect on mineral dissolution by pH has been shown *in vitro*, with low acidity considerably increasing mineral dissolution (Kim et al. 2001). The chemical nature and the small size of the FHA crystallites may have favored this. Previous investigations have shown that the deposition of biological apatite and subsequent formation of bone on hydroxyapatite implants depends on the partial dissolution of the implant surface and the reprecipitation of carbonated apatite from the biological milieu (Porter et al. 2002). Accumulated apatitic crystallites from the walls of pores may have stimulated bone formation.

The present investigation demonstrated that the use of the FHA biomaterial FRIOS® Aligipore® can trigger appositional bone formation in the maxillary sinuses of severely atrophic human maxillae even without additional bone harvesting. Our results also showed that a pore size of 10 µm is capable of accepting bone growth into the FHA particles of FRIOS® Aligipore® and that particles thereafter become gradually replaced by newly formed bone during bone remodeling.

Résumé

Épaissir le plancher sinusal est un traitement chirurgical établi qui permet de disposer d'une quantité d'os suffisante pour fixer des implants dentaires. Le FRIOS® Aligipore® (biomatériau poreux fluorohydroxyapatite) pourrait être utilisé pour ce genre d'opération dans les maxillaires sévèrement atrophiques. Afin de vérifier cette hypothèse 69 carottes obtenues par forage chez 26 patients qui avaient subi un épaississement du plancher sinusal avec le FRIOS® Aligipore® ont été récupérées durant l'insertion des implants dentaires. Les spécimens ont été analysés sans décalcification et soumis à un examen tant histomorphologique que histomorphométrique. Après un temps de guérison moyen de sept mois, 23±8% de nouvel os s'était formé autour des particules implantées. La formation osseuse était également évidente à l'intérieur des pores des

particules. L'analyse statistique indiquait que la formation osseuse provenait du plancher sinusal. Les particules formaient un coffrage pour la promotion de cette néoformation osseuse vers les portions apicales du sinus. Une dissolution minérale depuis les parois des pores a été observée avant et durant l'apposition osseuse. Ensuite des portions de particules ont été résorbées durant le remodelage osseux et remplacées par du nouvel os. L'investigation présente montre que le biomatériau FRIOS® Aligipore® est approprié pour l'épaississement du plancher sinusal dans les maxillaires sévèrement atrophiques.

Zusammenfassung

Um ein genügend grosses Knochenangebot für die Implantation zu erhalten, hat sich das Auffüllen der Kieferhöhle als mögliche Behandlung bewährt. Wir stellten die Hypothese auf, dass ein Biomaterial aus porösem Fluorhydroxyapatit (FHA) in der Darreichungsform von FRIOS® Aligipore® für den Aufbau von massiv atrophischen Oberkiefern geeignet ist. Um unsere Hypothese zu überprüfen, sammelte man von 26 Patienten, bei welchen für die Sinusbodenelevation FRIOS® Aligipore® eingesetzt worden war, insgesamt 69 Bohrkern, die beim Vorbohren für die Zahnimplantate als Nebenprodukt entstanden. Die Präparate wurden in nichtentkalkter Form aufbereitet, um sie nachher histomorphologisch und histomorphometrisch untersuchen zu können. Nach einer durchschnittlichen Heilphase von 7 Monaten hat sich um 23,0% (+8,3) der implantierten Partikel neuer Knochen gebildet. Die Knochenbildung war auch in den Poren der Partikel deutlich erkennbar. Statistische Analysen lassen vermuten, dass die Knochenbildung vom Sinusboden her startete. Die Partikel nahmen dabei die Funktion eines Gerüsts ein, welchem entlang sich der Knochen weiter Richtung apical bildete. Der Abbau von Mineralanteilen aus den Wänden der Poren heraus beobachtete man vor und während der Knochenapposition. Später wurden Partikelanteile auch während der Knochenremodellierung resorbiert und mit neu gebildetem Knochen ersetzt. Diese Untersuchung zeigt, dass das Biomaterial FRIOS® Aligipore® bei massiv atrophischen Oberkiefern ein geeignetes Biomaterial für den Aufbau des Sinus maxillaris ist.

Resumen

El injerto del seno maxilar es una modalidad establecida de tratamiento para suministrar suficiente hueso para la fijación de implantes dentales.

Hemos establecido la hipótesis que el biomaterial de fluoroapatita porosa (FHA) FRIOS® Aligipore® podría ser usado como un biomaterial adecuado para injertos del seno en maxilares severamente atroficos. Para examinar la exactitud de nuestra hipótesis, se recuperaron 69 especímenes trepanados durante la colocación de implantes dentales en 26 pacientes que se sometieron a injertos de seno maxilar con FRIOS® Aligipore®. Los especímenes se procesaron sin descalcificar y se sometieron a examen histomorfológico e histomorfométrico. Tras un periodo de cicatrización de 7 meses, se había formado un 23,9% (±8,3) de hueso nuevo alrededor de las partículas implantadas. También fue evidente la formación de hueso entre los poros de las partículas. El análisis estadístico indicó que la formación de hueso se originó del suelo del seno. Las partículas proporcionaron el andamiaje para la promoción de nuevo hueso formado hacia las porciones apicales del seno. La disolución mineral de las paredes de los poros se observó antes y durante la aposición de hueso. Por lo tanto, porciones de las partículas fueron reabsorbidas durante el proceso de remodelado óseo y sustituidas por hueso neoformado. La presente investigación muestra que el biomaterial FRIOS® Aligipore® es un biomaterial adecuado para injerto de seno de maxilares severamente atroficos.

要旨

上顎洞移植は、歯インプラントの固定のために十分な骨を付与するための、確立された治療法である。我々は、多孔性のフルオロハイドロキシアパタイト (FHA) からなる生体材料 FRIOS® Aligipore® は極度に萎縮した上顎において上顎洞移植に適した生体材料であるという仮説を立てた。この仮説の正確さを調べるために、FRIOS® Aligipore®による上顎洞移植を受けた26名の患者において、インプラント埋入手術中に、トレフアンによって69の生検標本を採取した。標本は非脱灰で処理をし、組織形態学及び組織学的形態計測の検査を行った。平均7ヶ月の治癒期間後に23.0% (±8.3) の新生骨が、移植した粒子の周囲に形成されていた。新生骨は、粒子の孔の中にも形成されていた。統計分析によると、骨形成は上顎洞底から始まっていた。新生骨の形成は、材料の粒子が足場を提供することによって、上顎の根尖方向に向かって促進された。骨添加の生じる前とその最中に、粒子の孔壁面からミネラルの溶出が観察された。すなわち骨のリモデリング中に粒子の一部が吸収され、新生骨に置換された。本研究は、FRIOS® Aligipore®は、極度に萎縮した上顎において上顎洞移植に適した生体材料であることを示している。

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