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CASE SERIES

Combined Sinus Grafting and Lateral Augmentation by a Hyaluronic Acid-Facilitated Guided Bone Regeneration Protocol – Case Series Supported by Human Histologic Analysis

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ABSTRACT

Guided Bone Regeneration (GBR) is a well-established procedure for the regeneration of alveolar bone defects. In the case of highly complex defect situations, however, inconsistent treatment results are often achieved. Hyaluronic Acid (HA) fulfills several relevant preliminary success criteria for improved regenerative treatment outcomes in complex defects: HA supports the creation of a toxin-free wound area, HA improves wound space stabilization, accelerates wound healing and supports regenerative processes crucial for bone regeneration. The novelty in the reported cases is the use of porcine derived bone substitute particulate hydrated with a cross-linked hyaluronic acid for simultaneous sinus grafting and lateral/vertical ridge augmentation in combination with a ribose cross-linked collagen membrane. The approval of the feasibility is provided with the clinical and histological observations. Three consecutive cases received the abovementioned material combination for staged sinus floor elevation and additional augmentation procedure by one operator according to a standardized protocol. All three sites constantly demonstrate superior clinical outcomes in terms of radiographically impressive tissue enhancement and implant function. The clinical outcomes are supported by qualitative histological analysis reflecting great similarity between samples regarding the observed process of new bone formation and bone substitute behavior. The specific staining allows for detection of osteoclastic activity and indicates the tendency of the particulate bone substitute to degrade over time once integrated.

INTRODUCTION

The lateral window approach introduced by Tatum 1986 allows for accessing the sinus cavity in atrophic maxillae with significantly reduced subantral amount of alveolar bone [1]. The bone formation within the sinus cavity occurs once the Schneiderian membrane separated from the bone surface is sufficiently retained in a position caudally to the eye socket creating room for blood clot formation [2]. Numerous xenogenic or synthetic bone substitutes, autogenous bone or allografts are considered suitable for grafting the sinus, sufficient cranial fixation of the Schneiderian membrane and support of new bone formation within the cavity [2-5]. With the Guided Bone Regeneration (GBR) an established regenerative procedure is available for the long-term function of osseointegrated dental implants [6-10]. The use of bone substitutes is also considered effective in creating and maintaining space within the defect providing the membrane with the mechanical support

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and stabilizing the blood clot in the wound area. As in the GBR, the use of membrane for cover the lateral window is shown to mechanically stabilize the bone graft within the sinus cavity [11]. Thus, the combination of a slowly resorbing Deproteinized Bovine Bone Mineral (DBBM) with a Native Collagen Membrane (NCM), disclosed good clinical success within small standard defects [7]. In rather complex situations, patient outcomes are inconsistent [12]. The amount of newly formed bone obtained after the external sinus lift required for sufficient implant retention and later function remains a matter of debates. An extended healing period is required, when bone substitute materials are in use alone for grafting [5]. Tarnow, et al. [13] histologically monitored the bone formation within sinus cavities grafted with or without a membrane cover in a case series. Furthermore, the protease enzyme activity may harm the regenerative process, since tissues may not be completely mature in the beginning of healing if a soft tissue complication occurs [14].

The adjunct use of so-called "Biologics" recently has aroused increasing interest in attempt to increase the predictability of augmentation procedures. One meta-analysis figures out that the combination of bovine particulate xenograft with a blood centrifugate applied for sinus grafting results in constantly higher amount of newly generated bone compared to other grafting alternatives (Trimmel, et al. [15]). The current hyaluronic acid derivatives feature regenerative properties that can improve the augmentative outcome and may represent a new biologic option for bone regeneration.

Hyaluronic Acid (HA) is an important natural component of the extracellular matrix and is detected almost ubiquitously in the tissues of a mammalian organisms, e.g. in the skin, joints, eyes and in most other organs and tissues including periodontium [15].

Thanks to its biocompatibility and completely absent immunogenicity, as well as its biodegradability and its involvement in numerous biological processes such as tissue healing, HA has been recognized and extensively investigated as a potent biomaterial for various clinical applications in recent decades [17,18]. Moreover, several studies showed bacteriostatic [19,20] fungostatic [21] anti-inflammatory [22] anti-edematous [23] osteoinductive [20,24-26] and proangiogenetic [27] activities of HA.

Natural HA features the highest regenerative potential but shows a fast degradation profile in vivo. Crosslinked HA is manufactured from natural HA following well-established technologies. With an increasing crosslinking rate, the degradation pattern extends for up to several months or even years. Concomitantly HA becomes increasingly inert by losing its physiological properties. Slightly crosslinked derivatives featuring longer resorption profiles of several weeks are adjunctively used in bone augmentation or periodontal regeneration (HYADENT BG, REGEDENT GmbH, Germany).

Several factors are crucial for successful regeneration of alveolar ridge defects at the local level [28]:

1. Creation of a toxin-free wound area
2. Wound stabilization / undisturbed coagulum formation
3. Uneventful primary wound healing
4. Space maintenance to ensure bone regeneration

Effects in angiogenesis & wound healing

The results of a recently published meta-analysis clearly showed that unexposed areas resulted in a significantly higher bone gain than areas with and after wound dehiscence, both with one-step and with two-step augmentation procedures [29]. Thus, there is a need for techniques and materials to improve wound stability and accelerate the healing.

In animal studies, HA also showed promising results for the healing of connective tissue [30,31] and facilitated re-epithelialization, ensured good elasticity of the connective tissue and increased microvascular density when used surgically in skin wounds. The additional application of HA accelerates the early neoangiogenesis and significantly reduces the healing time [32]. This property has some clinical relevance. The use of HA on human skin wounds and skin ulcers led to faster wound healing compared to controls, both for intraoral [33,34] and extraoral wounds, respectively [35,36].

Wound area protection

Due to strong hygroscopic properties (1 g HA absorbs up to 6 l water) [37] HA binds immediately the blood flooding the wound, which accelerates the coagulum formation and immediately stabilizes the wound area. The abovementioned bacteriostatic effect on pathogens [19,20], means that intraoperative use of HA can reduce bacterial contamination of the surgical wound space and reduce the risk of post-operative infections.

Bone graft stabilization

Particularly during wound closure and during the early healing phase, compressive pressure at the augmented site can lead to a membrane collapse and to a partial displacement of graft material [38,39]. Therefore, the risk of connective tissue ingrowth into the grafted area instead of successful bone regeneration is increased [40,41].

Mixing particulate bone graft with APCs results in a stable bone putty ("sticky bone"). This increases the initial mechanical stability of the bone graft and facilitates the

application procedure. Thanks to pasty consistency, HA also significantly improves the stability of particulate bone substitute material by forming "sticky bone", comparable to that obtained with APCs.

Support of bone regeneration by HA

HA favors cell attachment & proliferation of various relevant cell types (fibroblasts, osteoblasts, etc.) [42,43]. Based on the promising in vitro data for HA towards the stimulation of osteoblasts [17,44,45] several in vivo studies have been carried out to evaluate the regenerative potential of HA on bone regeneration.

Several animal experiments impressively showed that HA significantly accelerated the bone healing process after tooth extraction, particularly during the critical initial phase [26,46]. A clinical study corroborated this result. Additional application of HA into extraction sockets resulted in a significantly higher percentage of newly formed bone than the blood clot did alone [47].

In an external sinus lift study, Synthetic Tricalcium Phosphate (TCP) applied with HA showed significantly more new bone formation, less residual bone graft material and a higher volume stability of the augmented area than the TCP use alone [48].

MATERIALS AND METHODS

The three patients are periodontitis patients regularly visiting the SPT program at the Department of Periodontology, Witten/Herdecke University, Germany. The history of progredient Furcation Involvement (FI) ranging for the maxillary molars from grade 2 to grade 3 and subclass B to C was the rationale behind the tooth loss, occurred either in the past or during the maintenance phase. All edentulous posterior maxillae characterized by significantly diminished height of the bone ridge with residual 1 to 3 mm of bone in subantral dimension. The treatment strategy followed the concept of staged approach using lateral window technique for the Sinus Floor Elevation (SFE) and biomaterials for grafting the sinuses. The choice of grafting materials was identical for the cases reported. All three patients received the TL implants (SP TL Straumann implant, Straumann group, Germany) at the second stage 6 to 8 months after SFE. This strategy allowed for core biopsy retrieval at osteotomy, all participating patients donated the core biopsies for laboratory processing. The Ethic Committee of Witten/Herdecke University approved the tissue retrieval (188/2015) and signed consents were obtained.

All transmucosally placed implants integrated without complications and were loaded by screw retained zirconia crowns. Meanwhile all implants in the reported cases are functioning for ≥ 12 months without any signs for biological or technical complications.

The bone substitute was a deproteinized porcine bone mineral (DPBM, SMARTGRAFT, REGEDENT, GERMANY) mixed with xHyA, the cross-linked hyaluronic acid (HYADENT BG, REGEDENT, GERMANY). Applied as "sticky bone" it served for sinus grafting and additionally for lateral and/or vertical augmentation. For achieving appropriate barrier function, a Ribose cross-linked collagen membrane (OSSIX® PLUS, REGEDENT, GERMANY) covered on top of the grafted area to seclude the newly created volume from non-ossifying cells of the soft tissue.

The osteotomies followed the full-thickness flap reflection exposing the newly formed crest of the alveolar ridge and macroscopic considering the amount of mineralized tissue as suitable for implant placement. The retrieved samples were fixated with formalin and processed in paraffin after decalcification. Serial sections were generally stained with H.E., trichrome staining; furthermore, the osteoclast activity was evaluated by TRAP reaction and PAS staining disclosed the process of ossification.

Three triplicates of radiographs document the baseline level of the residual subantral bone in comparison to the level achieved by GBR/sinus lifting and to the new crestal bone level displayed at loaded implants for all three cases (Figure 1).

The formalin fixated tissue samples were forwarded to the lab facility at University of Bonn, Germany. The decalcifying and paraffin embedding followed the sequential dehydration and serial sections were obtained for each sample. A recognized oral biologist released the qualitative microscopic analysis (W.G.).

The microscopic observations revealed newly appositionally formed trabecular bone at the residues of bone substitute in all specimens without exception. The trichrome staining disclosed osteoid formation and the TRAP reaction clearly highlighted the activity of osteoclasts in intimate contact with the residual particulate graft material. All microscopic images are apparently free of inflammatory infiltrate or unspecific multinuclear giant cells.

CASE DESCRIPTION

The illustrated case depicts the universal utility of the HA in supporting hard tissue formation. The challenge in this case was the severe loss in crestal bone height after extraction of the two molars, which caused reduction in subantral bone but also a vertical ridge deficiency (Figure 2). Part of the treatment plan was to perform vertical augmentation parallel to lateral window sinus grafting and lateral augmentation using one and the same material combination (Figures 3,4). The sticky bone was prepared on the tray by hydrating the DPBM particulate with xHyA (SMARTGRAFT and HYADENT BG, REGEDENT, GERMANY). Once grafting in both areas completed, the ribose cross-linked collagen membrane was trimmed and positioned

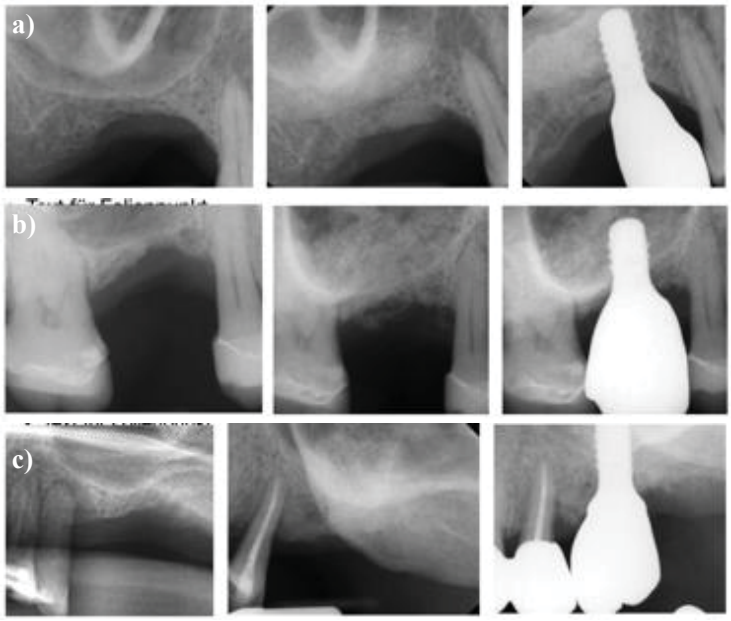

Figure 1 Triplicates of periapical x-rays at baseline, 6 months after SFE & 12 months after loading.

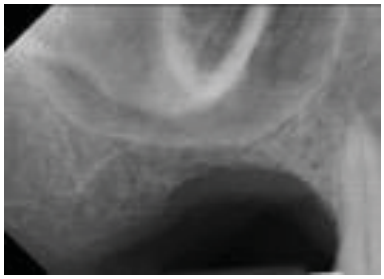

Figure 2 X-Ray at baseline: Residual subantral bone ≤ 2 mm.

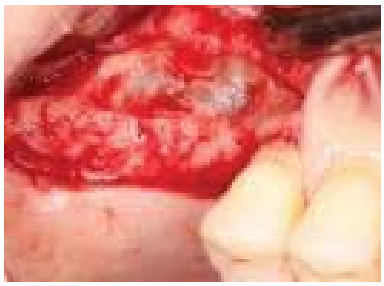

Figure 3 Situation after flap elevation and preparation of the lateral window.

for cover the total area across the ridge (OSSIX® PLUS, REGEDENT, GERMANY, Figure 5). The membrane edges overlapped the defect extension for 2-3 mm thus achieving the stabilization effect without any additional fixation. Following the CAF principle, the tensionless suture closely adapted the flap tissue margins and achieved complete closure of the site (Figure 6). The healing was uneventful, the sutures were removed after 7 days (Figures 7,8), and the implant placement was scheduled 7 months later.

RESULTS

The control x-ray obtained before implant placement displays two vertically augmented areas (Figure 9 arrows), one beneath and one crestal to the residual subantral native bone (Figure 9). The newly formed alveolar crest (Figure 10) exposed by a midcrestal incision impressed with the new dimension in width and displayed residual portion of the CLCM material well attached to the underlying mineralized

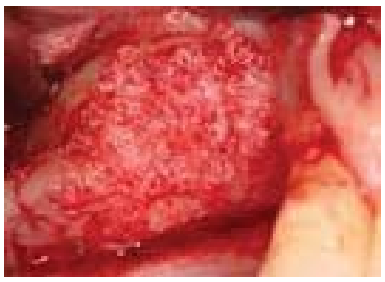

Figure 4 Situation after filling the sinus cavity and lateral augmentation.

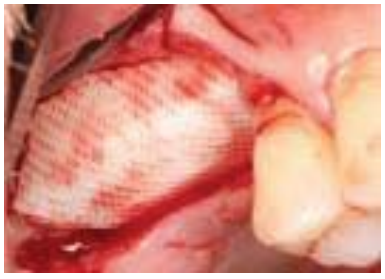

Figure 5 Situation after additional vertical augmentation and membrane placement.

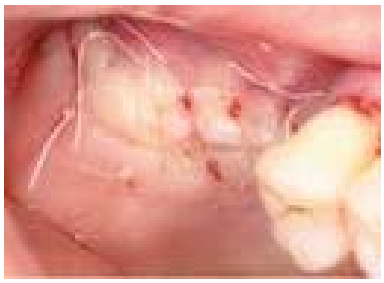

Figure 6 Tension-free wound closure by coronally repositioned flap tissue.

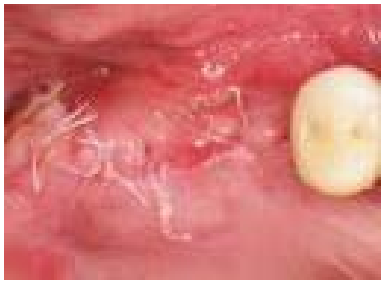

Figure 7 Suture removal 7 days post-OP.

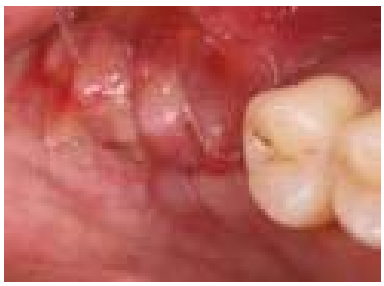

Figure 8 Uneventful primary soft tissue closure displayed after suture removal.

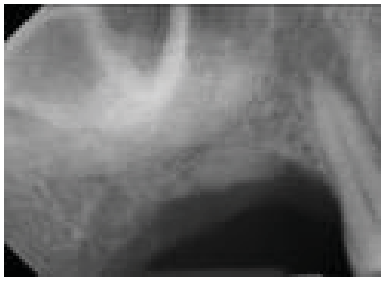

Figure 9 Periapical X-Ray 8 months post-OP discloses defect resolution of the sinus are and a significant vertical bone gain.

tissue layer (Figure 11). The core biopsy (Figure 12) retrieved by a hollow cylinder bur revealed clinically suitable grade of mineralization for placement of an WNI TL implant (WNI, SP TL, 10 mm; Straumann Group, Germany) which was inserted supplied with the gingiva former for transmucosal integration (Figure 13). The amount of keratinized mucosa was sufficient to keep up with the rule of a 2 mm zone of keratinized tissue around the implant neck circumferentially. The implant integrated within 8 weeks and a screw retained full zirconia crown was inserted.

The core biopsy broke apart into two pieces at removing it from the trephine, apparently separating the supracrestal from the subcrestal core portion (Figures 14-17). Both

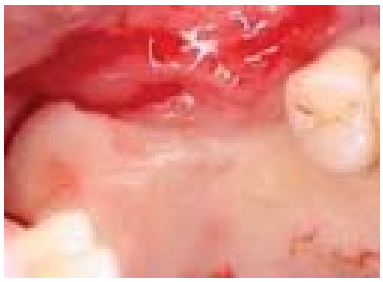

Figure 10 Clinical impression 7 months post-OP.

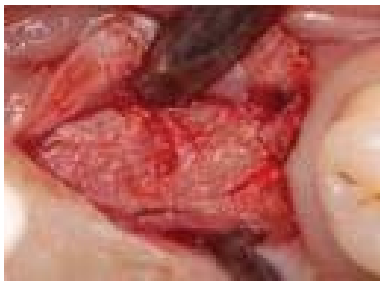

Figure 11 Optimally restored alveolar ridge.

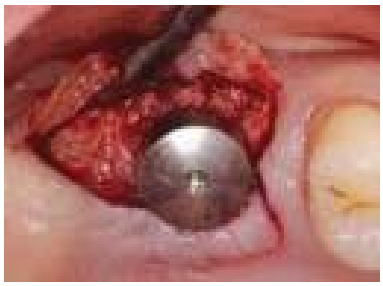

Figure 12 Situation after implant placement and gingiva former installation.

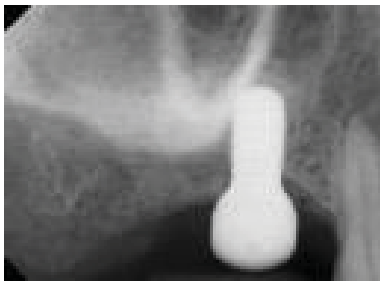

Figure 13 X-Ray after implant placement.

Figure 14 Retrieved bone core for histological examination.

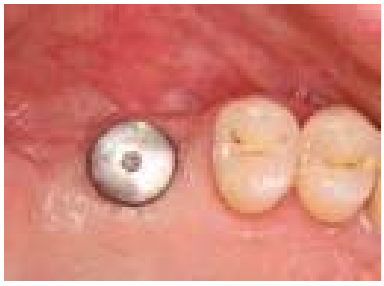

Figure 15 Situation 8 weeks after implantation.

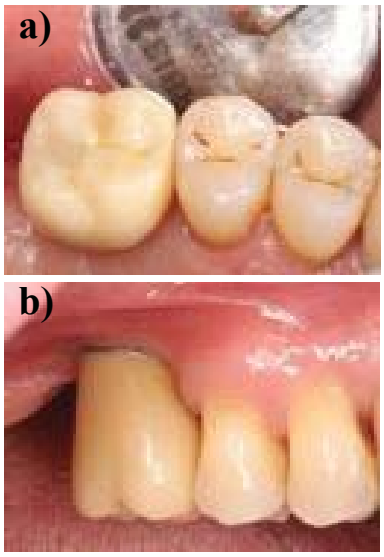

Figure 16 Final reconstruction with screw-retained zirconia crown inserted.

portions, however, displayed newly formed woven bone intimately embedding the residues of particulate graft material (Figure 18). The appositional bone formation revealed by the PAS staining of osteoid activity appeared ubiquitously in all regions of the specimen (Figure 19). Although disrupted into two parts, both display residual subantral bone retained almost in the middle of the core. Besides, the fragments of native bone detected on one side in total length of the core represent the mesial border of the augmented zone. The subsequent degradation of the particulate residues is indicated by the positive TRAP reaction, which specifically highlights the osteoclast activity at the DPBM remnants (Figure 20).

The second displayed core biopsy was obtained from another case 7 months after a sinus grafting procedure, which strictly followed the same treatment protocol and

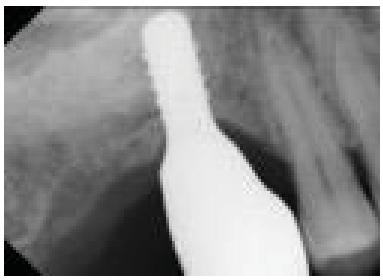

Figure 17 X-Ray after loading the implant 7 months post-OP.

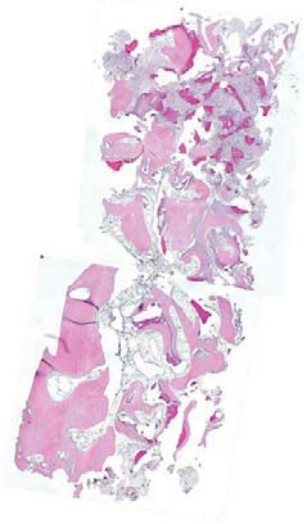

Figure 18 Reconstructed H.E. stained image from both biopsy parts with the native bone on the left and new bone formation in the lower, supracrestal portion and the upper, portion from the grafted sinus area.

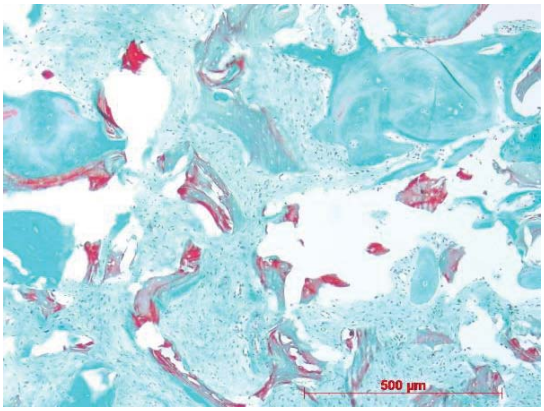

Figure 19 Tri-chrome stained fragment shows the osteoid activity at several regions of the specimen.

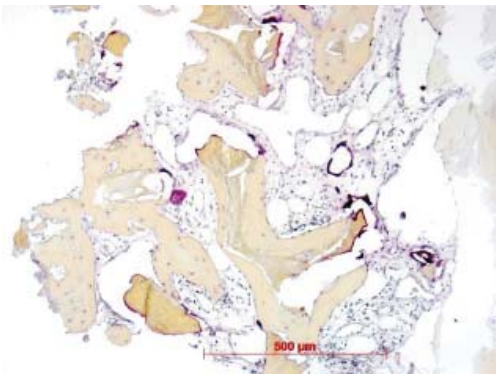

Figure 20 TRAP reaction shows some active osteoclasts at the residues of the bone graft.

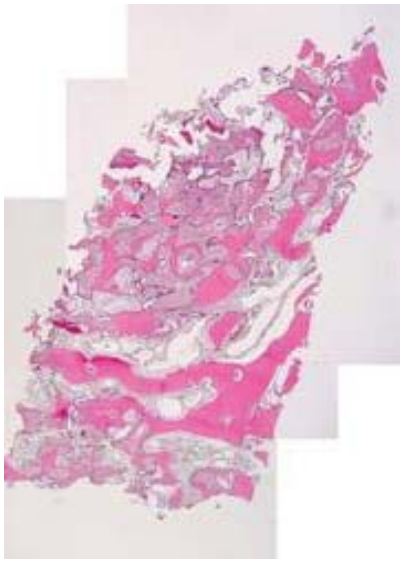

Figure 21 Reconstruction of the microscopic image from another core biopsy retrieved at implant placement 7 months post SFE/lateral augmentation.

used exactly same biomaterials (Figure 21). The histological findings in this case are closely repeating already reported observations. Surprisingly, besides the similar structures these specimens reveal the presence of residual xHyA encapsulated by appositionally grown bone and appear randomly distributed over the total area of the sample (Figure 22 - "H"). The TRAP reaction does not identify any osteoclasts spatially related to the xHyA-filled areas. The TRAP reaction reveals, however, numerous osteoclasts at the residual particles of the bone substitute.

DISCUSSION

This short case series presents the clinical and histological outcome of sinus floor elevation concomitantly combined either with a lateral or vertical augmentation. While several biomaterials are considered suitable for grafting the sinus cavity [49], the use of particulate bone substitute especially for vertical augmentation of edentulous alveolar ridge

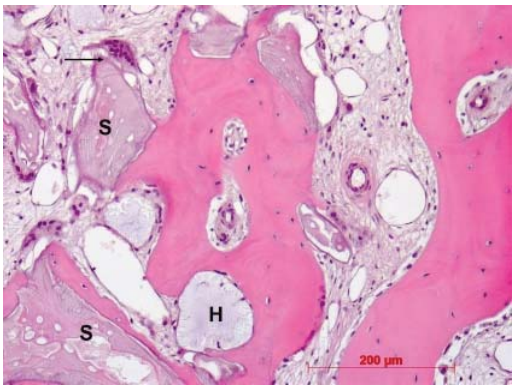

Figure 22 Newly formed spongeous bone, Smartgraft residues (S), xHyA residues (H), sinusoids (stars), H.E.-staining, x10.

without reinforced membrane is critical due to lack of graft stability [50].

To overcome this limitation, we used "sticky bone" which was prepared by hydrating DPBM with xHyA. Thus, implementing bidirectional function, the improved stability of the graft itself and facilitated adhesion at the treated site was achieved. Recent publications confirm the stimulating effect of xHyA molecules on cells of mesenchymal origin promoting osteoblast differentiation and accelerating the matrix formation for mineralization process [45]. Moreover, xHyA exerts numerous positive factors on the soft tissues [32-35]. Therefore, the combination of xHyA as an active biologic applied together with a DPBM represents a novel approach in reconstructive treatment of bone defects. The human histological analysis supports the positive clinical experience by disclosing new appositional bone formation as at the residual bone substitute as at residual xHyA areas which appear vacuole-like embedded in the new tissues. The specific TRAP reaction identifies the osteoclastic activities at the residues of the bone substitute indicating the degradability of the porcine derived particulate. A recent clinical study performs volumetric and qualitative analyses of grafted sinus cavities using the CBCT based approach [51]. The bone substitute used in this study was a bone-albumin impregnated allograft. The authors compare the outcome from the µCT analysis of the core biopsies retrieved at implant placement to the CBCT data. According to the data from an animal study [52] the radiographically based analysis alone should be treated with caution once xenograft particulate material is the substitute of choice.

Besides the sophisticated bone graft combination, one more factor accounts for the treatment success of our modified GBR protocol in lateral and vertical augmentation. The use of a slow-resorbing ribose crosslinked collagen membrane instead of a fast-resorbing conventional native collagen membrane may additionally promote the integration of the substitute into newly formed bone. A recent animal study confirms the impact of membrane longevity towards new bone formation in lateral augmentation of chronic bone

defects. The ribose cross-linked collagen membrane served as a sufficient barrier between the augmented site and the soft tissue, characterized by promoting significantly more new bone formation and less residual graft particles compared to a native collagen membrane, even without additional fixation at surgery [52]. A higher number of treated patients is required to substantiate these observations.

CONCLUSION

Within the limits of this short case series, we conclude that the adjunct use of Hyaluronic Acid (xHyA) in GBR and sinus grafting protocols support the creation of a pathogen-free wound area, improves wound space stabilization, accelerates wound healing and supports regenerative processes for bone regeneration. This potentially results in an accelerated process for new bone/tissue formation accompanied by a higher turnover-rate of substitute material. Therefore, the proposed biomaterial combination presents apparently symbiotic qualities and fulfills several pre-success criteria crucial for facilitating superior regenerative outcome particularly in complex defects.

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AUTHOR'S CONTRIBUTION

A.F. case handling, writing the manuscript; W.G. handling of the samples, qualitative microscopy, proofreading the manuscript

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