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Research Article

Application of Recombinant Human Bone Morphogenetic Protein-2 (RhBMP-2) in the Reconstruction of Edentulous Posterior Maxilla: Clinical Protocol, Histological Analysis, and Long-Term Implant Success and Survival Rates

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Abstract

Background: This study evaluated the efficacy of recombinant human bone morphogenetic protein-2 (rhBMP-2) in inducing de novo bone formation during the augmentation of the severely resorbed posterior maxilla for dental implant placement.

Methods: Composite grafts consisting of rhBMP-2/absorbable collagen sponge (ACS) mixed with deproteinized bovine bone mineral (DBBM) Bio-Oss in a 1:1 ratio were used to reconstruct severely resorbed posterior maxillae in 13 patients (five men, eight women; age range: 50 to 66 years). Three patients were treated with sinus floor augmentation alone, and 10 patients with a combination of sinus floor augmentation and guided bone regeneration. A total of 71 dental implants were used in this study. The residual bone height below the maxillary sinus ranged from 0.5 to 3.0 mm. Clinical, radiological, and histomorphometric analyses were performed to assess the outcomes of bone augmentation.

Results: The healing period was uneventful in all patients. The mean alveolar ridge height increased by 14 mm (range, 10–18 mm) and the mean alveolar width increased by 6 mm (range, 4–7 mm). Histopathological analysis revealed that newly formed bone was detectable throughout the implantation sites of sinus biopsies. The analysis of vascularization of the implant bed revealed large numbers of high-lumen vessels, in addition to moderate numbers of smaller blood vessels within the connective tissue. The histomorphometrical analysis of the tissue distribution showed that the amount of newly formed bone was 20.39 ± 4.95%, the amount of the remaining bone substitute was 41.85 ± 11.97%, and connective tissue was 37.76 ± 8.82%. The overall dental implant success and survival rates were 100% and remained unchanged at a follow-up period of 3 to 12 years.

Conclusions: The results of this study demonstrated that a composite graft of rhBMP-2/ACS and DBBM can result in predictable reconstruction of a large bone volume of the maxilla for dental implant placement and functional loading.

Keywords: *Recombinant human bone morphogenetic protein-2, maxillary sinus floor augmentation, guided bone regeneration, dental implant survival rate, dental implant success rate*

Introduction

Prosthetic rehabilitation of the severely resorbed posterior maxilla requires restoration of a large volume of bone that is sufficient for accommodation and osseointegration of dental implants [1,2]. In addition, impaired blood supply in these defects due to previous inflammation, unsuccessful surgeries, or aging poses a major challenge to successful bone augmentation [3,4]. Therefore, despite the availability of numerous grafting materials, autogenous bone is still the "gold standard," as it has prominent osteogenic and osteoinductive properties [4,5].

However, bone harvesting is associated with increased operating time, morbidity, additional costs, and the risk of potential complications. Moreover, the amount of bone in the donor sites could be limited by anatomical features or previous surgeries [6,7]. Thus, it is advantageous to choose alternative reconstructive procedures that reduce or eliminate the use of autogenous bone but provide comparable treatment results. It is especially important to consider alternative approaches for the treatment of patients with impaired health and compromised healing potential [4].

Growth factors and bone morphogenetic proteins (BMP) are potential next-generation agents that can be used extensively for sinus floor augmentation and posterior maxillary reconstruction [8,9]. BMPs belong to the transforming growth factor beta superfamily and may initiate, stimulate, and amplify the normal bone formation cascade and may also induce differentiation of mesenchymal cells into osteogenic cells when implanted into a tissue [10-12]. The osteogenic activity achieved by rhBMP-2 resulted in bone apposition comparable to that of the autogenous bone [9,13].

BMP-2 is an excellent growth factor; however, its efficacy in humans remains unclear. RhBMP-2 in an absorbable collagen sponge carrier was approved by the FDA in 2002 for orthopedic indications [14] and for oral and maxillofacial indications in 2007 [15]. Long-term implant survival and success rates in the reconstructed posterior maxilla vary and largely depend on a higher initial bone height, preferably > 5 mm [16]. It is also unclear what long-term implant survival and success rates would be in rhBMP-2-induced bone.

The aim of this study was to analyze the efficacy of the clinical application of rhBMP-2 in the reconstruction of the resorbed posterior maxilla for dental implant placement in patients with altered healing potential due to systemic diseases (diabetes and rheumatoid arthritis) or local factors (severe atrophy and previous unsuccessful surgeries complicated with osteomyelitis).

Methods

A retrospective evaluation was performed on 13 patients with edentulous posterior maxilla (Class IV–VI according to Howell–Cawood classification) who were treated from April 2010 to September 2018. Two subjects included in the study had type 2 diabetes (glycated hemoglobin [HbA1c] level < 6%), and one subject had rheumatoid arthritis. The other patients did not have any known medical conditions [Table 1]. Bone height between the sinus floor and residual alveolar crest was measured using cone-beam computed tomography (CBCT). The defects were grafted with a composite graft consisting of a combination of rhBMP-2/ACS manufactured by Infuse Bone Graft (Medtronic, Memphis, TN, USA) and deproteinized bovine bone mineral (DBBM) Bio-Oss spongiosa granules of 1–2 mm (Geistlich AG, Wolhusen, Switzerland).

The operations were performed under a combination of local anesthesia and intravenous sedation. A mid-crestal incision was made to expose the edentulous alveolar crest and the lateral bony wall of the maxillary sinus. An antrostomy was performed with a piezoelectric saw or round bur, creating a bony window in the lateral wall of the sinus. The Schneiderian membrane was then elevated from the bony floor, and the created space was augmented with a composite graft. The graft consisted of a mixture of an acellular collagen sponge soaked with solubilizing rhBMP-2 and cut into 0.5-cm square pieces and DBBM particles in a 1:1 ratio. The osteotomy window was covered with a collagen membrane Bio-Guide (Geistlich AG, Wolhusen, Switzerland), and the mucoperiosteal flaps were repositioned and sutured with resorbable sutures [Fig.1-10]. Additional horizontal bone augmentation was performed in 10 cases simultaneously with sinus floor augmentation using guided bone regeneration (GBR) with the same composite graft and Bio-Guide resorbable collagen membrane fixed with tacks [Fig.11-18].

Postoperative CBCT scans were obtained immediately after bone augmentation and at the time of implant placement after six months of healing. Core bone biopsy specimens were harvested using a trephine bur (outer diameter: 3.0 mm) at the time of implant placement. Biopsies were taken perpendicular to the alveolar ridge, 6–8 mm in depth, at the future implant positions. The specimens were fixed in 10% formalin and submitted to histologic analysis.

Table1: Local and systemic factors contributing to posterior maxillary deficiency.

	Gender	Age	Systemic factors	Characteristics of the recipient site	History of teeth loss
1	Male	62	Type 2 diabetes	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses. Bone defects at the area of #14,16, 17	Teeth #14,16,17 lost due to advanced periodontitis
2	Male	66	none	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses.	n/a
3	Female	65	Type 2 diabetes	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses.	All the upper teeth lost due to advanced periodontitis
4	Female	57	Rheumatoid arthri-tis	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses. Bone defects at the area of #13,16	Teeth # 13,16,17 lost due to advanced periodontitis
5	Female	59	None	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses.	n/a
6	Female	53	None	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses.	n/a
7	Female	64	None	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses.	n/a
8	Female	65	None	Severe atrophy of the posterior maxilla with hyperp-neumatisation of the maxillary sinuses.	Two unsuccessful previous surgeries. Severe inflammation resulting in loss of the grafting material in the left maxillary sinus.
9	Male	50	None	Severe bone defect of posterior maxilla with chronic inflammation	Severe bone loss after chronic osteomyelitis and sequestra-tion of lateral wall of the maxilla after previous unsuccessful implant surgery attempts
10	Female	63	None	Bone defect of posterior maxilla with chronic inflammation	Severe bone loss after chronic osteomyelitis and sequestration of lateral wall of the maxilla after previous unsuccessful implant surgery attempts
11	Male	57	None	Bilateral bone defects in posterior maxilla with chronic inflammation	Severe bone loss after chronic osteomyelitis and sequestration of lateral wall of the maxilla after previous unsuccessful implant surgery attempts
12	Male	54	None	Extensive sinus pneumatization	n/a
13	Female	58	None	Severe atrophy of the posterior maxilla with hyperpneumatisation of the maxillary sinuses	History of oroantral fistula (OAF) after molar extraction, subsequent OAF closure with Caldwell-Luc operation

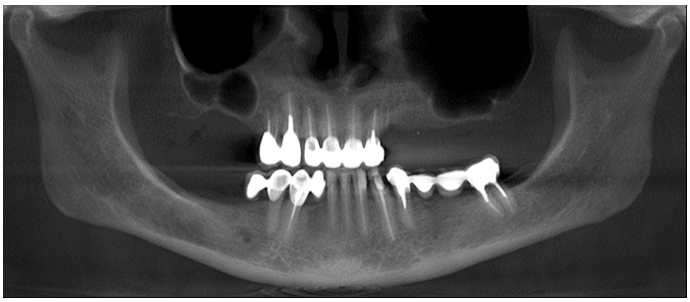


Figure 1: *Preoperative panoramic radiograph showing deficient bone in posterior maxilla.*

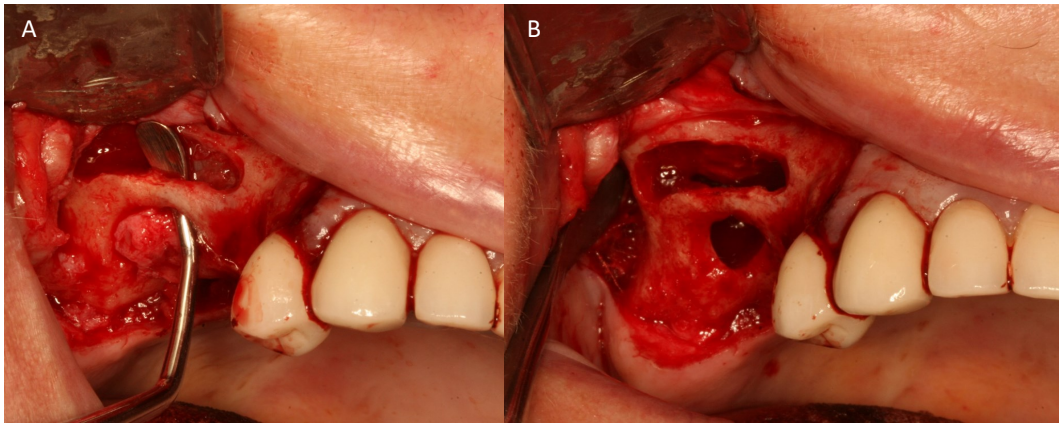


Figure 2A: *The edentulous alveolar crest is exposed. Note a bone defect after previous surgeries and management of oroantral fistula.*

Figure 2B: *An antrostomy is performed creating a bony window in the lateral wall of the sinus. The Schneiderian membrane is elevated from the bony floor.*

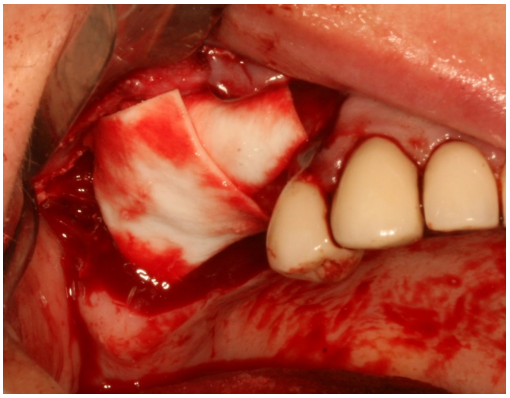


Figure 3: *Right maxillary sinus is augmented with a composite graft consisting of a combination of rhBMP-2/ ACS and Bio-Oss. The osteotomy window is covered with collagen membranes.*

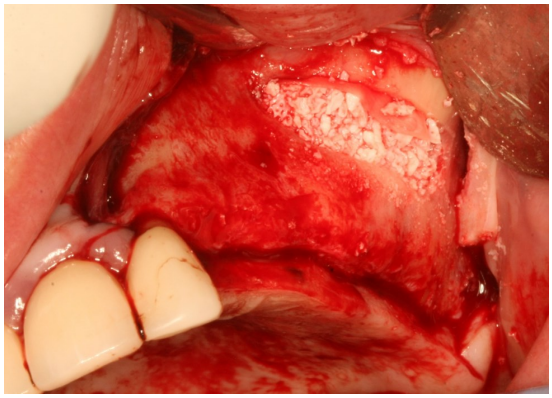


Figure 4: *Augmentation of the left maxillary sinus.*

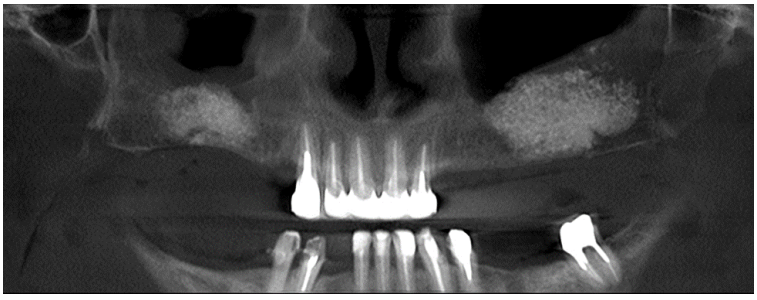


Figure 5: *Six months postoperative radiograph.*

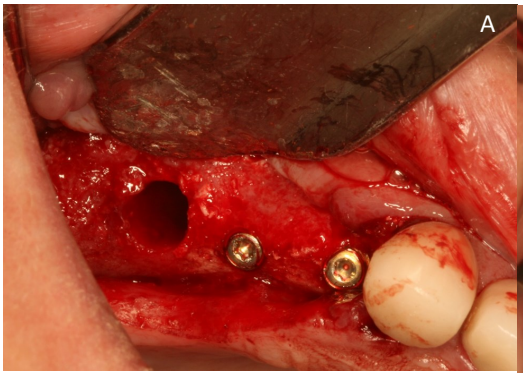


Figure 6A: *Six months after bone augmentation. Placement of dental implants. Core bone biopsy speciment was harvested using a trephine bur (outer diameter: 3.0 mm) at the time of implant placement.*

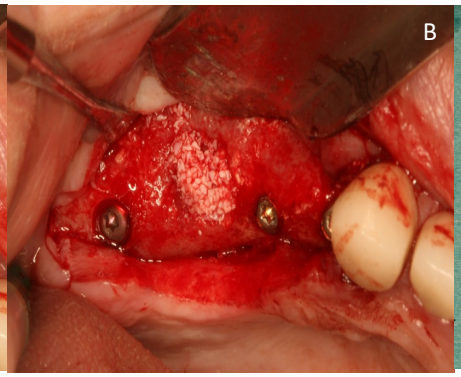


Figure 6B: *Right side. Implants are inserted, bone defect after biopsy is filled with Bio-oss.*

Figure 6C: *A trephine bur with with a core bone biopsy specimen.*

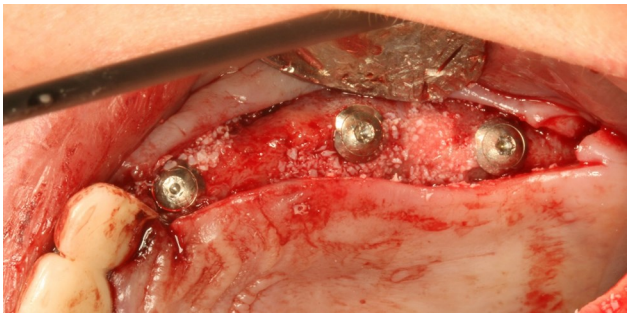


Figure 7: *Left side. Implants are inserted, bone defect after biopsy is filled with Bio-oss.*

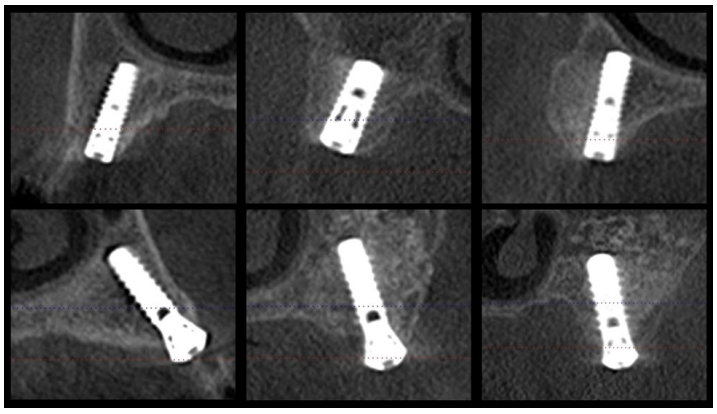


Figure 8: *CBCT scan 4 months after implant placement.*

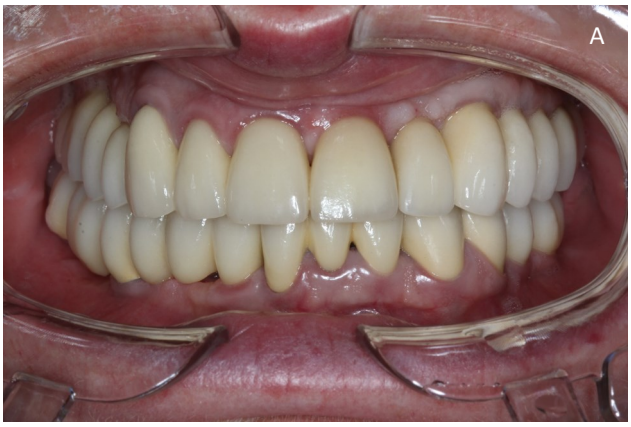


Figure 9 A and B: *Final restoration.*

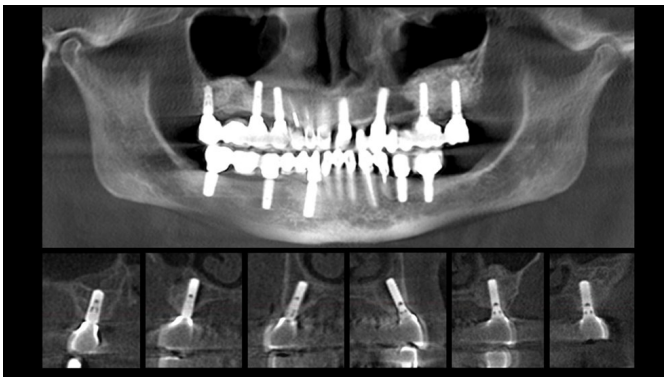


Figure 10: *CBCT scans 12 years after the delivery of the final prothesis.*

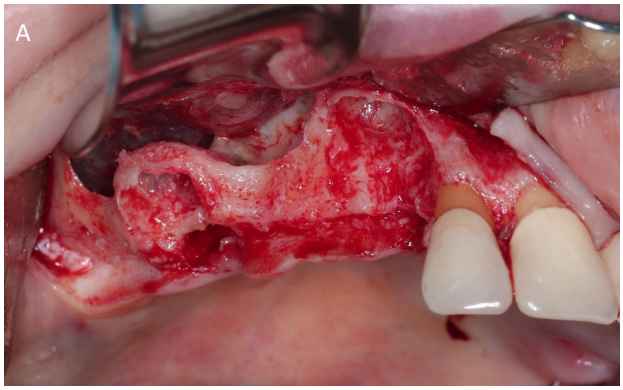


Figure 11A: *The edentulous alveolar crest is exposed. Note bone defects after previous inflammation and teeth extraction. An antrostomy is performed creating a bony window in the lateral wall of the sinus. The Schneiderian membrane is elevated from the bony floor. Right side.*

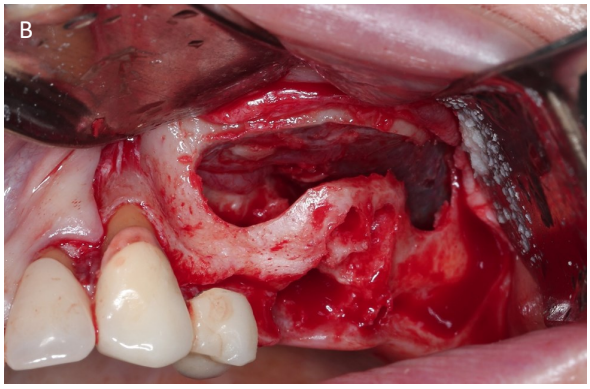


Figure 11B: *Left side.*

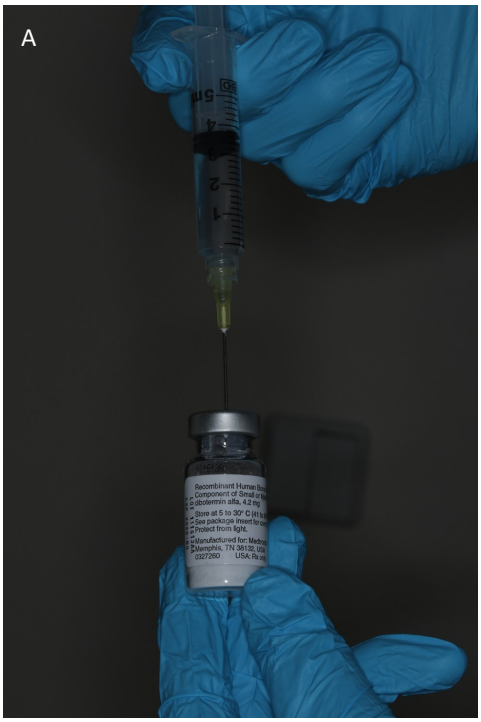


Figure 12A: *The rhBMP-2 is reconstituted with 0.9mL of sterile water.*

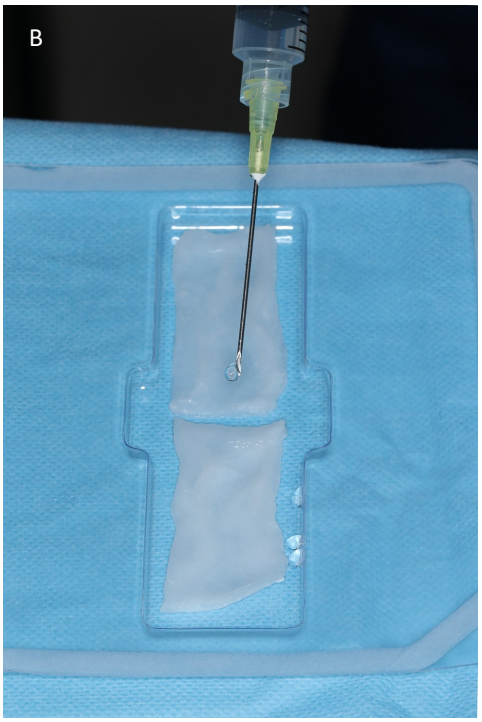
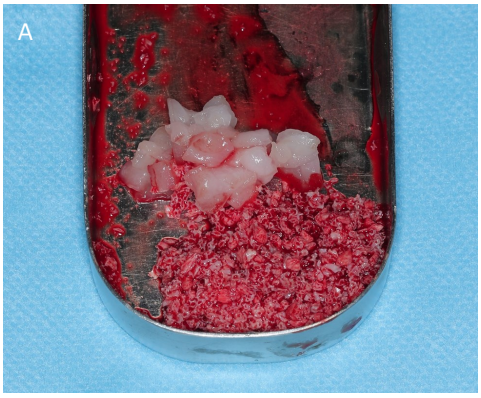


Figure 12B: *Reconstituted rhBMP-2 is distributed on the collagen sponge.*



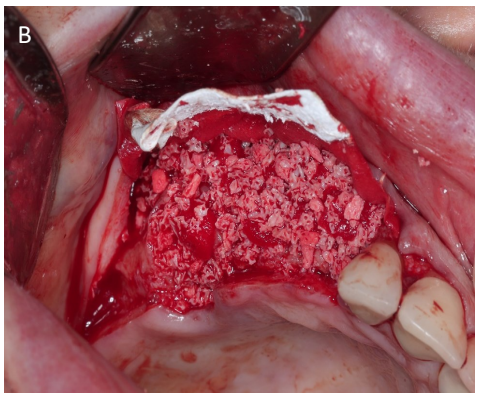
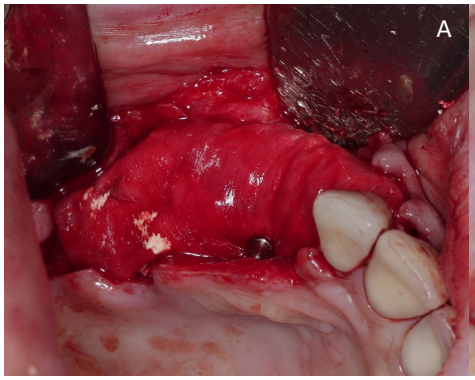
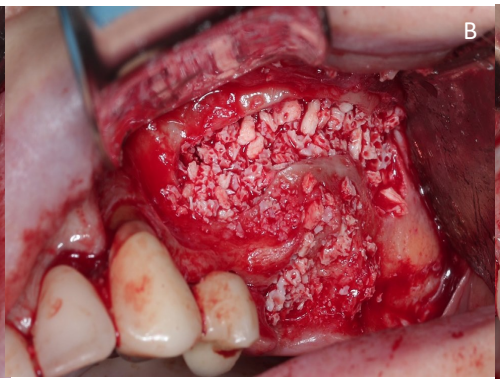


Figure 13 A, B: *ACT is cut into 0.5-cm square pieces and mixed with Bio-Oss particles in a 1:1 ratio.*





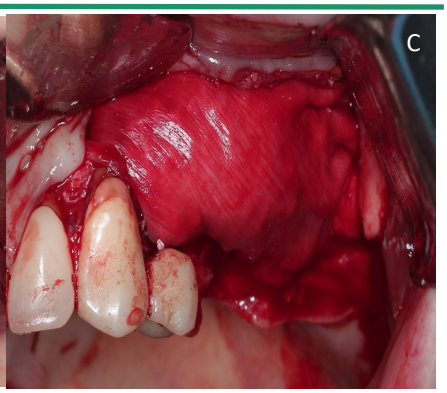


Figure 14 A, B: *Maxillary sinus and alveolar ridge are augmented with a composite graft consisting of a combination of rhBMP-2/ACS and Bio-Oss. Right side.*

Figure 14 C: *Left side.*

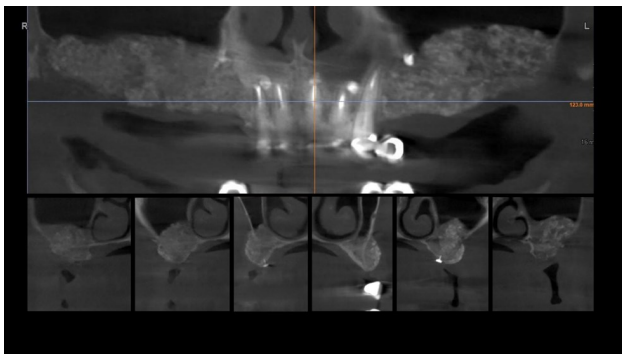


Figure 15: *Six months postoperative CBCT scans.*

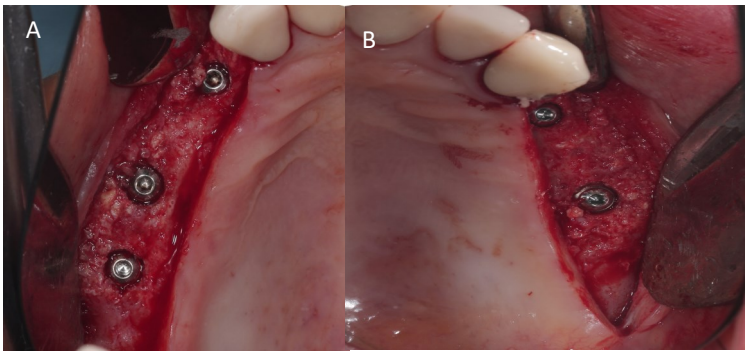


Figure 16 A, B: *Six months after bone augmentation. Placement of dental implants.*

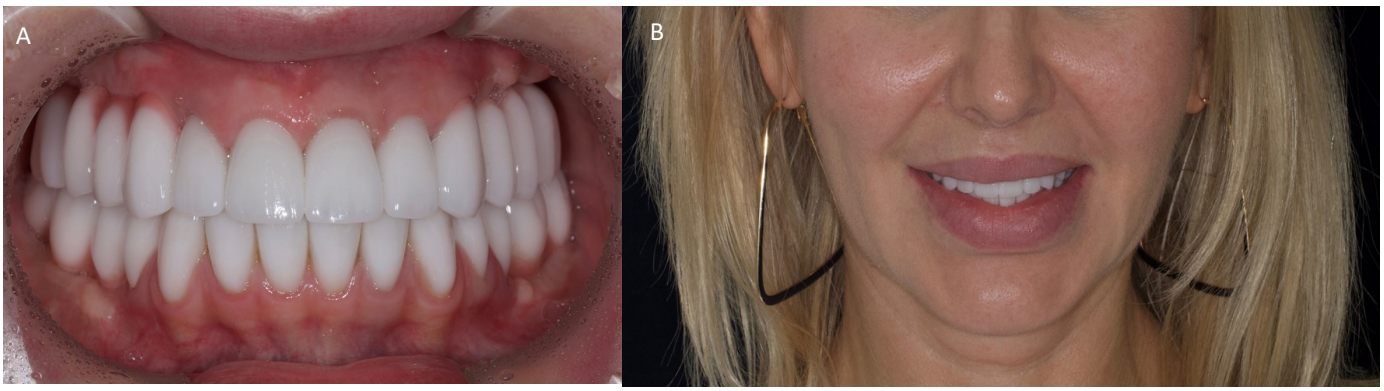


Figure 17 A, B: *Final restoration (Prosthodontist: Renat Aubov).*

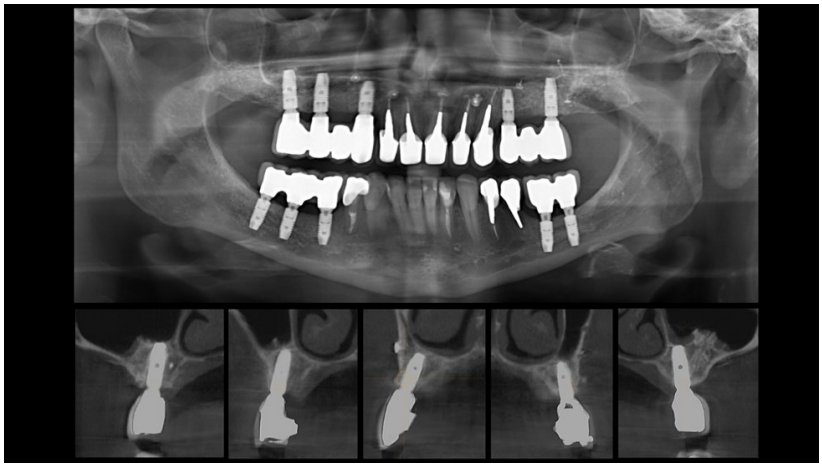


Figure 18: *CBCT scans four years after the delivery of the final prothesis. Implants on the lower jaw are placed simultaneously with inferior alveolar nerve lateralization.*

All dental implants were inserted using a two-stage approach with good primary stability (minimum insertion torque of 35 N/cm). Changes in bone quality and peri-implant crestal bone level were evaluated using CBCT images during follow-up visits for a period of 3 to 12 years.

Results

Thirteen patients (five men and eight women) were included in the study. The participants' age ranged 50–66 years. Overall, five sinus augmentations and 15 sinus augmentations simultaneously with GBR were performed. All the grafts healed uneventfully. A total of 71 dental implants were used. The residual bone height below the maxillary sinus ranged from 0.5 to 3.0 mm. The mean alveolar ridge height increased by 14 mm (range 10–18 mm) and width increased by 6 mm (range, 4–7 mm). A total of 71 implants were installed, successfully osseointegrated, and functionally loaded after 4 months. At the time of follow-up (ranging from 3 to 12 years), no implants were lost. Therefore, the implant success and survival rates, according to Albrektsson's criteria, were 100% [Table 2]. Analysis of CBCT images during follow-up visits for a period of 3 to 12 years revealed stable peri-implant crestal bone level and increased density of the augmented bone.

Table 2: Description of surgical procedures and implant survival rates.

Patients	Types of surgery	Number of sinus floor augmentations	Number of implants placed	Number of implants lost				
				1 year follow-up	2 years follow-up	3 years follow-up	5 years follow-up	12 years follow-up
1	Maxillary sinus augmentation + GBR	1	3	0	0	0	n/a	n/a
2	Maxillary sinus augmentation + GBR	1	3	0	0	0	n/a	n/a
3	Bilateral maxillary sinus augmentation + GBR	2	8	0	0	0	0	n/a
4	Bilateral maxillary sinus augmentation + GBR	2	5	0	0	0	n/a	n/a
5	Bilateral maxillary sinus augmentation + GBR	2	8	0	0	0	0	n/a
6	Bilateral maxillary sinus augmentation + GBR	2	8	0	0	0	n/a	n/a
7	Bilateral maxillary sinus augmentation + GBR	2	8	0	0	0	0	n/a
8	Maxillary sinus augmentation + GBR	1	8	0	0	0	n/a	n/a
9	Maxillary sinus augmentation + GBR	1	2	0	0	0	0	0
10	Maxillary sinus augmentation + GBR	1	4	0	0	0	0	0
11	Maxillary sinus augmentation	2	6	0	0	0	0	0
12	Maxillary sinus augmentation	1	2	0	0	0	0	0
13	Maxillary sinus augmentation	2	6	0	0	0	0	0

Histologic Examination

Histopathological analysis revealed that the newly formed bone was detectable throughout the implantation sites of the sinus biopsies [Fig.19a]. Therefore, the newly formed bone tissue was almost exclusively located on the granule surfaces of the xenogeneic bone substitute in the form of thin layers covering most of the surface areas [Fig.19b]. At the surface areas adjacent to the connective tissue, mostly mononuclear cells of the macrophage line and single biomaterial-associated multinucleated giant cells (BMGCs) were observed. Furthermore, histological signs of mild inflammation were observed within connective tissue. Thus, macrophages, besides single BMGCs, and moderate numbers of lymphocytes and granulocytes were observed [Fig.19c].

Additionally, analysis of the vascularization of the implant bed revealed large numbers of high-lumen vessels beside moderate numbers of smaller blood vessels within the connective tissue [Fig.20].

The histomorphometrical analysis of the tissue distribution showed the amount of newly formed bone was 20.39 ± 4.95%, amount of the remaining bone substitute was 41.85 ± 11.97%, and amount of connective tissue was 37.76 ± 8.82%.

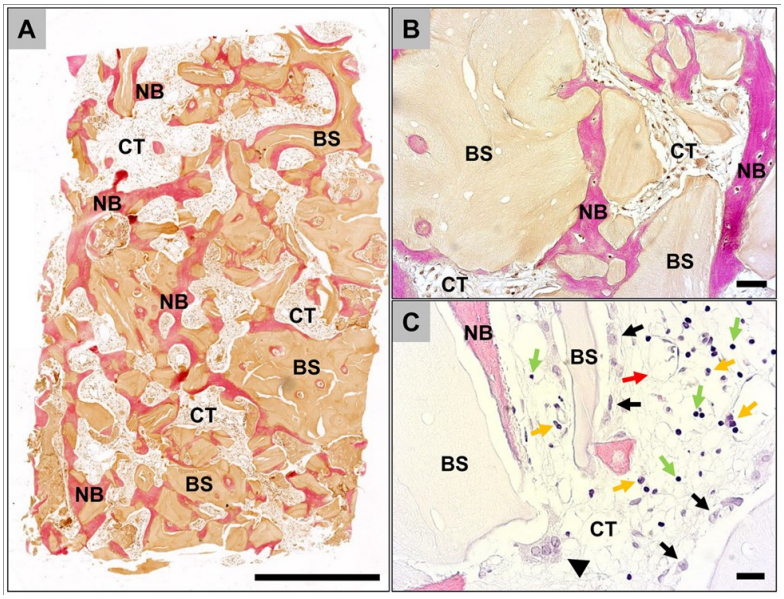


Figure 19A: *Overview of a complete sinus biopsy ("total scan") that shows the complete bony integration of the xenogeneic bone substitute (BS) within newly formed bone tissue (BT). CT = connective tissue (von Kossa-staining, 100x- magnification, scalebar = 1 mm).*

Figure 19B: *The surfaces of the xenogeneic bone substitute (BS) were nearly completely covered by thin newly formed bone (NB). CT = connective tissue (von Kossa-staining, 200x - magnification, scalebar = 20 µm).*

Figure 19C: *Tissue reactions to the xenogeneic bone substitute (BS) involving macrophages (black arrows), biomaterial-associated multinucleated giant cells (black arrowhead), lymphocytes (green arrows) and granulocytes (yellow arrows). NB = newly formed bone, CT = connective tissue (HE-staining, 400x-magnification, scalebar = 20 µm)*

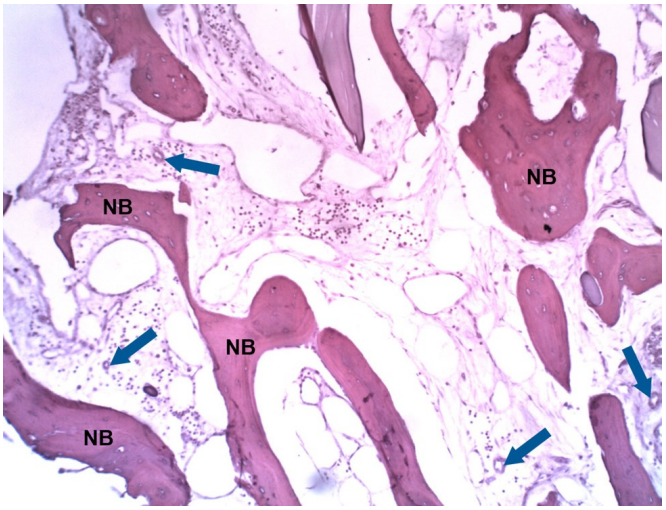


Figure 20: *Large numbers of blood vessels (blue arrows) within the connective tissue. NB = newly formed bone (HE -staining, 60x-magnification)*

Discussion

According to R.E.Marx, the mechanism of tissue regeneration is based on the presence and mutual collaboration of three elements: cells, signals, and matrices. If the components of the "tissue regeneration triangle" are missing or malfunctional, tissue regeneration will be compromised or terminated [4,13]. Therefore, autogenous bone is the gold standard in bone engineering. Cells of the autogenous bone graft are primarily endosteal osteoblasts and cancellous cellular marrow; the mineral components of the graft itself, fibronectin, vitronectin, and fibrin of the blood clot represent the matrix, and BMP-2, insulin-like growth factors 1 and 2 (IGF-1,2), and platelet-derived growth factors represent the signal. Thus, the "tissue regeneration triangle" was complete [4,5].

However, autogenous bone grafts have their limitations and disadvantages:

1. Bone harvesting is often associated with extended surgical intervention, additional costs, risk of specific complications, and prolonged recovery, especially when extraoral donor sites are utilized [6,7].
2. The osteogenic potential of autogenous bone significantly declines with age due to the reduction of osteoprogenitor cells in the bone marrow and their replacement with fibro-fatty marrow [3,4, 17].
3. The amount of bone in intraoral donor sites is often limited because of anatomical variations or previous surgery [18].
4. Autogenous bone grafts can be extensively resorbed over time. The volume loss varies from 8.3% to 42% and can be attributed to several factors, such as age, type of bone defect, embryological similarity of autograft (intramembranous vs. endochondral) [19,20].

Furthermore, vascularity of the recipient bed is one of the main prerequisites for successful bone augmentation [4,18]. It was compromised in all patients in our study owing to systemic or local factors. [Table 1].

In light of the abovementioned limitations of autogenous bone grafts, alternative treatment options are attractive, especially for patients with impaired healing potential.

According to the results of our study, a combination of rhBMP-2/ACS and DBBM can be used for the successful reconstruction of a significant volume of bone in the maxilla, which is stable over a follow-up period of 3 to 12 years.

A combination of rhBMP-2 /ACS and DBBM completes the tissue-engineering triangle, where the rhBMP-2 signal attracts mesenchymal stem cells and hematopoietic stem cells, providing cellular proliferation, capillary ingrowth, and osteoid formation [10-13]. An acellular collagen sponge (carrier) and DBBM (xenograft) represent an upregulated matrix that attaches cell adhesion molecules (fibrin, fibronectin, and vitronectin), thereby creating a framework for cell migration and subsequent tissue formation [4,8,9,13].

Additionally, rhBMP-2 promotes soft tissue healing by stimulating vascular endothelial growth factors [4,21]. Thus, its application could be beneficial for the treatment of bone defects with impaired blood supply, such as defects after osteomyelitis. Herford AS and Boyne PJ utilized rhBMP-2 in the reconstruction of large critical-sized mandibular defects secondary to osteomyelitis or neoplastic diseases. In all 14 cases of successful osseous restoration of the edentulous area, followed by prosthetic treatment, rhBMP-2 was used alone with the collagen carrier, without concomitant bone materials [21].

Torrecillas-Martinez et al. conducted a comprehensive review of three human studies and four animal trials on the effectiveness of BMP-2 in sinus augmentation. The results of all the studies demonstrated that human BMP-2 index bone formation rhBMP-2 can be considered an equivalent graft material to autogenous bone for sinus graft procedures [22].

Triplett et al. compared the effectiveness of rhBMP-2/ACS with that of an autogenous bone graft when used for two-stage maxillary sinus floor augmentation. They found that the bone formed in the rhBMP-2/ACS group was normal, mature, and 100% viable as the density increased, surpassing that of the autogenous bone graft group after functional loading [9]. Results of our study also showed increased density of the augmented bone after functional loading.

Jung et al. investigated the influence of rhBMP-2 on GBR when combined with Bio-Oss. The results of their study showed that the combination of xenorgaft (Bio-Oss) with rhBMP-2 could enhance bone maturation and accelerate GBR therapy. Furthermore, histomorphometric analysis showed that the percentage of newly formed bone at the rhBMP-2-treated sites was 37% [23]. In our study, the histomorphometrical analysis of the tissue distribution showed that the amount of newly formed bone was 20.39 ± 4.95%, the amount of the remaining bone substitute was 41.85 ± 11.97%.

However, Kao et al. claimed that combining Bio-Oss and rhBMP-2 had a negative effect on histological bone formation when compared with Bio-Oss alone. The results of their study demonstrated that the percentage of newly formed bone in the Bio-Oss and rhBMP-2 group was 16.04 ± 7.45%; furthermore, in the Bio-Oss-alone group, it was 24.85 ± 5.82% [24].

Another interesting study by Yang HJ and Hwang SJ evaluated the long-term volumetric changes after maxillary sinus floor augmentation with a combination of rhBMP-2 and hydroxyapatite (group 1) and hydroxyapatite alone (group 2). The results of this study showed that the total volume of augmented sites was initially larger when BMP-2 was applied and was accompanied by void formation. Then, osteogenesis progressed to void spaces, and eventually, bone volume was larger by 36% in group 1 (BMP-2/Bio-Oss), without significant changes during follow-up period [25].

The most notable disadvantage of using rhBMP-2 is edema, which is generally larger and persists longer than that with autogenous bone grafting. In addition, this type of edema is less responsive to steroids. This was attributed to two factors: rhBMP-2 hypertonicity and increased cellular content at the surgical site. Steroids are less effective in edemas caused by noninflammatory cells [13].

Moreover, there are some concerns among clinicians that growth and differentiation factors and rhBMP-2 could cause uncontrolled differentiation of mesenchymal cells, similar to cancer [26,27]. Several arguments have been made regarding this notion. First, growth and differentiation factors do not enter the cell or cell nucleus, releasing their effects through cell membrane receptors. They were only active for 3 weeks. Additionally, they are not mutagenic. Finally, no control studies have shown a higher incidence of cancer among rhBMP-2 users [28].

Conclusions

The current study showed that severely resorbed posterior maxilla could be successfully augmented with a combination of rhBMP-2 /ACS and DBBM. RhBMP-2/ACS has a great osteogenic potential and can be used as an alternative to autogenous bone. Advanced surgical skills and protocols for rh-BMP-2 preparation and utilization are required to perform this technique. Further studies are needed to support the safety and effectiveness of rhBMP-2 in preprosthetic and reconstructive surgeries.

Abbreviations

rhBMP-2: recombinant human bone morphogenetic protein-2; DBBM: deproteinized bovine bone mineral; ACS: absorbable collagen sponge; BMGCs biomaterial-associated multinucleated giant cells; FDA: The United States Food and Drug Administration; CBCT: cone-beam computed tomography; HbA1c glycated hemoglobin; GBR: guided bone regeneration; IGF-1,2: insulin-like growth factors 1 and 2.

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Authors' contribution

GD: conceived the presented study, performed literature search, analyzed the data, wrote the manuscript. SG: conceived the presented study, performed literature search, analyzed the data, wrote the manuscript, final approval. TK: conceived the presented study, performed literature search, analyzed the data, wrote the manuscript.

Conflict of Interest

George Deryabin, Simonas Grybauskas and Tadas Korzinskas declare that they have no conflict of interests.

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