BIOINTEGRATION OF BONE GRAFTING MATERIALS AND OSSEOINTEGRATED IMPLANTS IN ORAL AND MAXILLOFACIAL SURGERY

Semmelweis University PhD School Thesis

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1. INTRODUCTION

The reconstruction of large skeletal deficiencies presents a challenging problem to the oral and maxillofacial surgeon and surgical community. Such defects in the facial skeleton can be the result of trauma, infection, congenital defects, cranio-facial syndromes, severe periodontitis, or tumor resection. In the reconstructive process there is often a need to create new bone. 

A solely prosthetic approach to management of alveolar bone loss frequently leads to esthetic and/or functional compromises. Today, specific surgical techniques extend implant options and optimize their final results: extraction and immediate implant placement, tuberosity and pterygomaxillary implants, partial intrasinus and nasal fossa implants, sinus grafting, onlay bone grafts, dental nerve repositioning, guided bone regeneration, tissue engineering procedures, alveolar distraction osteogenesis, osteotomies and bone grafts.

A frequently occurring clinical situation that causes significant problems for reconstruction is the atrophic edentulous jaw, since the introduction of reliable oral implant techniques, partially or totally edentulous patients can be successfully treated with jawbone-anchored prostheses. However, a prerequisite for the use of oral implants is a sufficient amount of bone to fully cover the implant and to allow the implant to support a fixed prosthetic restoration. Even a minor lack of bone, either horizontal or vertical, may cause a significant problem. A narrow or buccally concave alveolar ridge may result in exposed threads at the alveolar crest or at bone fenestrations. Anatomic restrictions, such as the nasal cavity, maxillary sinuses, and inferior alveolar nerve, in combination with insufficient amounts of bone may dictate a less advantageous placement of the implants, compromising the final restorative result.

Numerous methods have been used in an attempt to solve this problem. One of the most common methods involves the harvesting and implantation of fresh autogenous bone grafts, taken from the same person. However, this is an expensive procedure that requires hospitalization as well as the potential risk for donor site morbidity. Other types of grafts available for the maxilla and mandible are the allogeneic, alloplastic and xenogeneic ones. The use of bone grafts involves three mechanisms: conduction, induction, and guided tissue regeneration. All are involved in bone regeneration. Sinus elevation has become one of the most commonly performed routine surgical procedures in preprosthetic surgery. The essence is that the alveolar process of the atrophic maxilla is made thicker towards the maxillary sinus, and made suitable to receive the implant.

Ectodermal dysplasias are a large, heterogeneous group of inherited disorders that involve primary defects in the development of two or more tissues derived from ectoderm.

The typical dysmorphic facial features include frontal bossing, malar hypoplasia, a flattened nasal bridge or saddle nose, prominent supraorbital ridges, wrinkled, hyperpigmented periorbital skin,
thick, everted lips, and prominent low-set ears. The dental findings range from complete anodontia to hypodontia of the primary or permanent teeth, widely spaced, peg-shaped, or conical teeth, delayed eruption, and defective enamel of the permanent teeth. When teeth are missing, the jawbone alveolar processes do not develop properly, so the skeletal vertical dimension is reduced, resulting in protuberance of the lips. This leads to a typical old-age appearance of the face. The palatal arch is frequently high and a cleft lip and palate may be present. Congenital absence of the teeth is more frequent in the lower jaw and affects the growth of the jawbones, leading to a lack of alveolar bone in both height and width.

2. AIMS

The purpose of this work is to show the role of the implant osseointegration associated to bone regeneration and to the reconstruction of large skeletal defects used in oral and maxillofacial surgery, for restoring function and esthetics in edentulous patients. The resorbed ridge may compromise loading and function of the implants because of off-axis loading, compromising the predictability of implant therapy. Ridge augmentation and sinus elevation procedures are now being employed to regain lost alveolar structures. These surgical procedures include the use of autogenous, allogeneic and xenogeneic bone grafts, synthetic bone substitutes, non-resorbable or resorbable barrier membranes as described in the guided bone regeneration principle. So they have expanded the treatment modality for patients whose ridges are not ideal for implant placement. The preferred bone graft material during a bone reconstructive procedure, as in ridge augmentation and sinus elevation, is autogenous bone, as it carries proteins such as bone-enhancing substrates, minerals and vital bone cells, but this often needs hospitalization, other surgical operations and it has a potential risk for donor site morbidity.

Two different studies have been performed.
1. The objective of the former was to determine whether during sinus elevation the donor site morbidity could be avoided by using pure-phase $\beta$-tricalcium phosphate.
2. The objective of the latter was to verify if it is possible to achieve an optimal bone reconstruction through osseointegrated implants, bone grafts and guided bone regeneration also in patients affected by severe orofacial syndromes as Ectodermal Dysplasia.

3. MATERIALS AND METHODS

Sinus Elevation

Twenty edentulous patients were scheduled for bilateral sinus floor grafting at the following 4 centres: 1. Semmelweis University, Department of Oral and Maxillofacial Surgery, Budapest, Hungary; 2. Dental and Stomatologic Clinic, Department of Oral Surgery and Oral Implantology,
University of Milan, Italy; 3. Department of Oral and Maxillofacial Surgery, Manchester Royal Infirmary, Manchester, United Kingdom; 4. Periodontology, Oral Implantology, Dento-Alveolar Surgery Clinic, Brugge, Belgium.

At each centre, identical protocols were followed for patient selection, preoperative examinations, surgical procedure, implantation, biopsy specimen removal, postoperative treatment, and patient follow-up. In 10 cases, the operation was combined with onlay bone grafting. All of the patients had conventional denture retention problems because of severe anterior and posterior maxillary alveolar ridge atrophy. All had a residual sinus floor less than 5 mm high. In 10 patients, the maxilla was atrophied to such an extent that sinus grafting alone was insufficient; in these case, a large section of the residual alveolar arch had thinned to a knife edge in the horizontal and sagittal directions. The patient population consisted of 9 men and 11 women who ranged in age from 38 to 67 years (mean 52 years). After routine oral and physical examinations, the patients were selected and bone reconstruction procedures were planned. In 10 patients, the reconstruction included only bilateral sinus floor grafting; in the other 10 patients, bilateral sinus grafting was performed, with onlay bone grafting in the anterior and part of the posterior maxilla, followed by implant placement 6 months later. All of the patients were healthy, with no disease that might influence the treatment outcome. The patients were fully informed about the procedures, including the surgery, bone-substitute material, and implants. They were asked for their cooperation during treatment and research; all gave their written informed consent. The ethics committees of the various institutions approved the research protocol. Routine panoramic radiographs were obtained in all cases pre- and postoperatively, 6 months after the first surgery (prior to implant placement), and immediately after implant placement. Additional panoramic radiographs were taken at 6-month intervals after implant placement. Moreover, in the 10 patients in which onlay bone grafting was performed, 2D and 3D examinations were performed pre- and postoperatively and 6 months after implant placement, using a General Electric Pro-Speed Plus (General Electric Medical Systems, Milwaukee, WI). The lateral exposures were taken in the same plane and direction as the preoperative ones. In all 20 patients, surgery was performed under general anesthesia. Before or at the time of sinus grafting, 5 to 6 cm³ of spongious bone were harvested from the left iliac crest by a second team of surgeons. In the cases that included onlay grafting, the spongiosa was removed together with a piece of cortical bone about 3 cm wide and 4 to 6 cm long. The bilateral sinus grafting procedure followed Tatum’s classical description. In brief, a door was created with a round hollow bur in the lateral maxillary sinus wall. After mobilization, the door was reflected inward. On one site, the sinus-elevation space was filled only with 1.5 to 2 g of β-TCP (particle size 1,000 µm); on the other side, it was filled with 3 to 4 cm³ of autogenous bone. The TCP side was the experimental side; the autogenous bone side was the control side. The choice of sides was randomized using the coin-toss method. In 12 of
the 20 patients, the experimental side was on the right; in 8, it was on the left. In 10 of the 20 patients, it was necessary to widen the alveolar crest, which had become extremely thin in places. This was performed at the same time as the bilateral sinus grafting. The harvested cortical bone was attached to the buccal side of the compromised maxilla using microscrews. Next, the uneven bone edges were smoothed with spongiosa, the buccal and labial periosteum was extended in the customary way, and the wound was closed in a tension-free manner. No membrane was used to cover the bone. The sutures were removed 7 to 10 days later. The following postoperative regime was applied to avoid infection: ciprofloxacin 500 mg 2 times daily for 5 days and ibuprofen 400 mg 3 times daily to reduce pain and swelling. The patients were instructed not to wear removable prostheses for 30 days and not to blow their noses for 7 days. After 6 months of healing, the patients received implants. Eighty cylindric bone biopsy specimens were taken from the grafted posterior maxilla (2 from the experimental side and 2 from the control side in every patient) using a trephine but with an inner diameter of 2 mm and an outer diameter of 3 mm. After biopsy specimen removal, osteotomy sites were prepared for implant placement. In 4 patients, 16 Protetim implants were placed at the sinus elevation sites. In the other 16 patients, 64 Ankylos implants were used. In addition to the 80 implants placed at the sites of the β-TCP or autogenous bone grafts, many more implants were required for the complete rehabilitation of the edentulous maxillae of the 20 patients, but the remaining implants were not directly related to this study. The bone biopsy samples contained both the grafted area and the previously existing area of sinus floor, but the residual native crestal bone was not included in the histologic and histomorphometric examinations. Cortical bone in samples from patients with onlay grafts was not included either. Biopsy samples from all 4 centres were fixed in 4% formaldehyde and then submitted for histologic examination to the oral pathology unit of the Department of Oral and Maxillofacial Surgery of Semmelweis University. The bone samples were processed and stained as reported earlier. Briefly, they were fixed in 4% formaldehyde in phosphate buffer, dehydrated in an ascending series of graded alcohols, and embedded in methylmethacrylate resin at 4°C. Five-μm-thick histologic sections were cut in the longitudinal plane with a diamond knife and stained with toluidine blue and hematoxylin-eosin. Goldner’s trichrome method was used for light microscopy.

The β-TCP particles were achromatic. If they had broken out of the section, their places were recognizable because of their characteristic shape and size, or because of the granule remnants at the interface between the β-TCP granules and the surrounding tissue.

Morphometric studies were performed according to the principles of Parfitt and colleagues. Sections of each sample were taken for histomorphometry from 4 levels at 150-μm intervals. The samples were measured semiautomatically using an Olympus microscope connected to a computer.
using Analysis software. The total surface area of each sample, the surface area that consisted of bone, and the area that consisted of graft material were measured in mm$^2$, and bone and graft material were analyzed as a percentage of the total. Bone from the original sinus floor was not involved in the bone area measurement. The Student $t$ test was used to determine statistical significance. Values of $P<.05$ were considered significant.

**Ectodermal Dysplasia**

In Ectodermal Dysplasia study, 186 titanium implants associated with guided bone regeneration were placed in 33 patients. All the patients were nonsmokers. The ED patient group consisted of 13 patients, nine men and four women, aged 16–45 years, all with reduced vertical dimension or skeletal deep-bite. Sixty-six implants were placed in this group, 15 in the upper jaw and 51 in the lower jaw, and GBR was used for local bony dehiscence and fenestration defects. Ten bioabsorbable membranes and 21 non-resorbable membranes were used. The non-ED patient control group comprised 20 patients, 11 men and 9 women, aged 16–68 years, selected with the same dentofacial features as the ED patients: hypodontia or missing teeth with reduced occlusal and skeletal vertical dimension (15 skeletal deep-bite and five normovertibite, no open-bite), decreased alveolar bone, with a typical old-age appearance and poor aesthetics of the face. Both groups had a severe lack of the alveolar ridge in both height and width, corresponding to edentulous sites. All the mandibular alveolar ridges had a knife-edge contour, which usually makes ideal implant placement difficult without GBR and bone grafts.

In the non-ED group, 36 fixtures were placed in the maxilla and 84 in the mandible. Ninety-three of the recipient sites were associated with localized bone defects or insufficient alveolar ridge width resulting in exposed fixture threads at installation. Twenty-two bioabsorbable membranes and 34 non-resorbable expanded polytetrafluoroethylene membranes were adapted to cover the exposed threads at buccal fenestration and dehiscence defects. To produce bone regeneration, GBR was applied in combination with autogenous bone and Anorganic bovine bone. Together with radiographic evaluations, the following clinical parameters were assessed around the fixtures: probing depth; peri-implantitis; mucosal recession; modified plaque index (mPLI) and modified sulcus bleeding index (mSBI); clinical mobility; and Periotest value before final prosthetic rehabilitation and after 3 years, when implant bridge removal was possible. After delivering the prosthetic-implant reconstructions, the patients were involved in a maintenance care program, in accordance with individual needs.
4. RESULTS

Sinus Elevation

After sinus elevation, no postoperative complications occurred in any of the patients. Normal wound healing was observed after both the first and second operations (graft harvesting/sinus elevation and implant placement). Minor nose bleeds occurred in 3 patients. One patient had permanent sensory loss in the distribution of the lateral femoral cutaneous nerve, and 2 patients had prolonged wound drainage (2 to 3 weeks). No other postoperative complications were observed in conjunction with the donor sites. Three panoramic radiographs were compared for every patient: 1 taken shortly after graft implantation surgery, 1 taken at 6 months postoperatively (at implantation), and 1 taken 12 months postoperatively (ie, at suprastructure fabrication). These radiographs clearly showed the positions of both types of graft material and the height of the new sinus floor. The autogenous bone was initially less visible than the β-TCP, but new bone formation was clearly observed for both materials. The consecutive images also revealed changes in the graft materials and their incorporation. β-TCP was markedly more radiopaque than autogenous bone. After 6 months, the β-TCP had changed slightly in the radiographs: the contour of the bone around the graft became more defined. After 12 months, the graft was similar to bone because of absorption of the β-TCP and the simultaneous formation of new bone. A comparison of the panoramic radiographs and CT images in 10 patients revealed the advantages of supplementing the panoramic radiographs with 2D CT images. In planning the surgery, the thickness and width of the alveolar bone and the process of new bone formation could be better assessed in this way. The 3D CT reconstruction best revealed the postoperative sinus graft height and new sinus floor, as well as the ossification process. In the biopsies from the experimental side, the β-TCP graft was identified as achromatic rounded or scalloped granules, depending on the phase of resorption. They were partially embedded in newly formed bone, which was predominantly lamellar bone. Bone formation was preceded by the abundant proliferation of a cell-rich osteogenic mesenchyme and a new capillary network in the pores of the resorbing granules. Newly formed bone replaced the resorting β-TCP particles continuously. Bone deposition characteristically occurred along the surface and in the pores of the disintegrated graft material. There was no foreign body-type giant cell reaction in the grafted samples. In 1 sample, there was a focal lack of bone formation and an intense inflammatory reaction, suggesting a local infection. The majority of the biopsy samples from the control side contained mature lamellar bone. The bone trabeculae contained osteocytes in their lacunae. Signs of dynamic bone formation with osteoblast activity or lacunar osteoclastic resorption were rare. The remnants of the autogenous bone grafts could be seen in several foci as homogeneous tissue fragments that stained like living
bone. In these samples, there was intimate contact between the graft particles and new bone. Several samples were typified by torpid bone formation, a predominantly fibrous bone marrow, and a diffuse, thin network of bone trabeculae. The mean percentage of bone area for the 20 patients was 36.47% ± 6.9% on the experimental side and 38.34% ± 7.4% on the control side; the difference was not significant (P = .25).

In a majority of the patients (n = 13), the intensity of new bone formation was similar on both sides. When the volume occupied by the graft remnants was considered, these data suggest that the bone density was sufficient on both sides. Nevertheless, the new bone was markedly less dense on the experimental side in 4 of the 20 cases compared to the control side. In 1 of these patients, the lethargic bone formation process could be explained by a local inflammatory reaction. In the other 3 cases, the percentage of the graft area was quite high, i.e., the graft material took up too much space in the bone samples. The bone-forming capacity on the control side was more sluggish than on the experimental side in 3 cases. In these cases, no inflammatory reaction or delayed graft resorption hampered bone regeneration. In 2 cases, the ossification process was uniformly weak on both sides; the respective percentages of newly formed bone were 25.6% and 27.5% on the experimental side and 24.0% and 28.1% on the control side. In these 2 cases, the new bone trabeculae were uniformly thin, with no focal inflammatory lesion. The rate of graft resorption was generally lower on the experimental side than on the control side. The mean graft area percentages were 13.95% ± 5.38% and 8.47% ± 3.17%, respectively, and the difference was highly significant (P< .001). The mean areas of the biopsy samples taken from the 2 sides were quite similar: 9.18 ± 2.42 mm² on the experimental side and 8.98 ± 1.76 on the control side. In the 6-month period between implantation and loading of the implants, 2 of the 80 implants were lost; 1 on the experimental side and 1 on the control side. Both were replaced, but delivery of the definitive restoration was delayed by 3 to 6 months.

Ectodermal Dysplasia

In the Ectodermal Dysplasia study group, the patients were evaluated at the second-stage surgery, after prosthetic reconstruction, and after 1-, 2-, and 3-year follow-ups. Almost all of the patients had a good level of oral hygiene, which was reflected by the low mPLI and mSBI scores. Peri-implant mucosal complications, in which the implant threads were not covered, were observed in patients with less-optimal oral hygiene. In the ED patient group, of the 66 fixtures inserted, 60 were associated with clinically healthy peri-implant soft tissues, low bleeding scores, and minimal probing depths, without signs of inflammation, suppuration, mucosal irritation, or increased mobility. Radiographic evaluation demonstrated that these 60 fixtures were osseointegrated because of the absence of peri-implant radiolucency. Only three membrane-treated implants showed
mucosal recession and intraoral exposure of the first buccal fixture thread. Six implants were lost: two in the upper jaw and four in the lower jaw; four during the healing period and two following functional loading. In this clinical study, the ED patients had a 91% successful osseointegration rate of the installed fixtures. In the non-ED control group, 115 osseointegrated implants showed no signs of pathology, despite the intraoral exposure of threads in six cases. Only five fixtures showed increased mobility and clinical instability at the second-stage surgery (three in the maxilla and two in the mandible); these five fixtures failed. The exposure of six membranes before complete healing led to observation of the threads of the fixtures, indicating a loss of buccal bone. In another six fixtures, the first thread was exposed, but without inflammation, mucosal irritation, or mobility. In the non-ED control group, the 95.8% osseointegration rate was confirmed by the radiographic evaluation and Periotest values. The two groups were compared statistically using the chi-square test. The regenerated bone at peri-implant bony defects in the experimental group using GBR and bone grafts responded in a similar way to the control group. The osseointegration rate and failure frequency of the two groups did not differ significantly ($\chi^2=1.86, p=0.1731; \chi^2$ with the Yates continuity correction=1.08, $p=0.2996$).

5. CONCLUSIONS

About sinus elevation, it was concluded that the grafting of $\beta$–TCP was followed by the formation of new bone of similar quality and quantity to that observed after grafting with autogenous bone. Comparisons with other studies reveal that $\beta$-Tricalcium Phosphate is a satisfactory graft material, even without autogenous bone. Since a second operation is not necessary, donor site morbidity can be avoided by using $\beta$–TCP.

Notwithstanding the anatomic restrictions, titanium screw implants may be inserted successfully in Ectodermal Dysplasia patients in association with GBR and bone grafts to provide a very stable dentition, and improved chewing ability, speech, and psychological and emotional well-being.

The novelty and originality of this research:
1. For the first time a multicenter study on a broader basis was organized to examine whether $\beta$-TCP alone is a suitable graft material for sinus elevation.
2. Concomitantly on the same patient, two sinus elevations by two different bone grafting materials were performed: $\beta$-TCP alone as the experimental side and autogenous bone alone as control side.
3. Donor site morbidity was avoided by grafting $\beta$-TCP alone.
4. For the first time a study to assess the possibility to insert osseointegrated implants associated to bone grafts and guided bone regeneration also in Ectodermal Dysplasia patients was performed.

5. For the first time in a study about ED patients, implants also in the upper jaw were included.

6. The improved appearance and self-confidence, with a better function helped ED patients to become accepted by their friends and families and resulted in a better quality of life.
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