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

Semmelweis University PhD School Thesis

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LIST OF ABBREVIATIONS

Guided Bone Regeneration  GBR
Scanning Electron Microscopic  SEM
Transmission Electron Microscopic  TEM
Titanium Plasma-Sprayed  TPS
Hydroxyapatite  HA
Bovine Spongiform Encephalopathy  BSE
Particulate Marrow Bone Cancellous  PMBC
Tricalcium Phosphate  TCP
Recombinant Human Bone Morphogenetic Protein  rh-BMP
Deoxyribonucleic Acid  DNA
Hard Tissue Replacement  HTR
Polyhydroxyethyl Methacrylate  PHEMA
Computerized Tomography  CT
Ectodermal Dysplasia  ED
Expanded Polytetrafluoroethylene  e-PTFE
Probing Depth  PD
Modified Plaque Index  mPLI
Modified Sulcus Bleeding Index  mSBI
Tricalcium Phosphate Granule  CG
Osteogenic Mesenchyme  OM
Bone Graft  BG
Anorganic Bovine Bone  ABB
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 (GBR)
- osteotomies and bone grafts
- tissue engineering procedures
- alveolar distraction osteogenesis

A main hindrance for successful bone healing and for creation of new bone is the rapid formation of the soft connective tissue. Ingrowth of soft tissue may disturb or totally prevent osteogenesis in a defect or a wound area. The mechanisms behind the influence of soft connective tissue on osteogenesis are not yet fully understood. Experiments in vitro have demonstrated that fibroblasts produce one or more soluble factors that are inhibitory to bone cell differentiation and osteogenesis.1 Another possible explanation suggested by Schmitz et al2 is that a bony non-union development may be due to the failure of the cells that are present to calcify the matrix, perhaps caused by the lack of appropriate bone derived growth and differentiation factors in large bony defects. Another 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.3 (Figures 1., 2., 3., 4.)

Fig. 1. A narrow alveolar ridge
Fig. 2. Bilateral harvest from mental symphisis
Fig. 3. Autogenous grafts fixed by mini screws and covered by anorganic bovine bone
Fig. 4. After reconstruction of bone defect, optimal for implant insertion
However, this is an expensive procedure that requires hospitalization as well as the potential risk for donor site morbidity. Even though similar methods have been used in more advanced situations of oral reconstructive therapy, only limited scientific data exist regarding the long-term outcome of such treatment. Other methods use bone powder implants or various commercially available allografts. Most of these materials act as passive scaffolds, and it is questionable whether such techniques have any real inductive effects on osteogenesis at the cellular level.

In recent years, much research has been focused on the osteogenic potential of demineralised bone powder implants. The stimulatory effects appear to be due to local morphogenic factors inherent in the implanted bone matrix. In general the technique has shown good experimental results, but more research is necessary before it can be applied routinely in patients.

Thus, whereas many different methods to improve bone healing and regenerative capacity have been tested, with varying degrees of success, few have reached the stage of routine clinical application. While the future holds promise for new ideas in this area, it is tempered by the realization that the restoration of a deficient skeleton by natural bone remains the ultimate goal.

Autogenous graft or allogeneic graft? For many years, the reconstruction of bone defects has been achieved using a variety of bone substitute materials. The question of the “best” graft material has been addressed intensively by researchers, and as a result, a large number of experimental and clinical publications have appeared on this topic. In 1996, a Consensus Conference on sinus grafting made an attempt to summarize and evaluate the research findings.

One of the most important conclusions of the conference was that retrospective analyses did not reveal any bone substitute material that was equivalent to autogenous spongiosa. Accordingly, “…many participants believed that autografts were the most efficacious…” and “the doubts raised revealed the need for controlled prospective multicenter clinical trials”.

In essence, the question lies in how to avoid morbidity at bone graft donor sites. It is increasingly clear that, in addition to basic animal experiments, there is a need for clinical investigations that apply the gold standard principle to compare autogenous bone and various bone substitute materials. (Figures 5., 6., 7.)
An important publication in this respect is that of Groeneveld and coworkers. 23 They compared 4 materials: osteogenic protein 1 (on a collagen carrier), human freeze-dried demineralized bone matrix, autogenous bone, and nongrafted alveolar crest. In a total of 12 patients (3 for each of the materials), histologic and histomorphometric methods were used to detect new bone formation during sinus floor elevation and implantation. All grafted sinuses exhibited an increased proportion of osteoid, as compared with nongrafted sinuses. It was concluded that in human sinus floor elevation, osteogenic protein has a potential bone-inductive capacity; however, the results with this material were inconsistent.

Yildirim and associated 24 used a combination of Anorganic Bovine Bone (ABB) and venous blood as a graft material. Six months after sinus floor augmentation, they found 14.7% new bone, 29.7% ABB, and 55.6% soft tissue in the tissue samples (soft
tissue=blood vessels and connective tissue composed of various proportions of fibroblasts and collagenous fibres). It is interesting to compare these results with the data reported in 1991 by Schenk,\textsuperscript{25} who found that the bone content of the human iliac crest was 20% to 25%, depending on age. Naturally, one of the problems to be considered in this regard is the extent to which Anorganic Bovine Bone (ABB) is resorbed.

In the literature, the resorption of bovine bone substitute materials has been the subject of controversy. Schlegel and Donath\textsuperscript{26,27} were able to identify the presence of ABB granules even after a resting time of up to 7 years. It was demonstrated histologically by Skoglund and colleagues\textsuperscript{28} that ABB particles could be found in the maxilla 44 months after implantation. Some publications based on animal experiments have furnished histologic evidence of the resorption of ABB.\textsuperscript{24,29-31}

An example of control is provided by the paper by Tadjoedin and coworkers.\textsuperscript{32} Bilateral sinus grafting was performed on 10 patients; 1:1 mixture of autogenous bone particles and bioactive glass particles was used on the experimental side, and autogenous bone alone was used on the control side. At 6 months, bone tissue on the experimental side had increased to 32%, differing only slightly from the control side, which contained 38% bone by volume. At 16 months, the total bone volume on the experimental side was similar to that on the control side. After 16 months, the quality and density of bone in the augmented sinus floor were similar, regardless of whether or not bone particles or a mixture of bone particles and bioactive glass particles had been applied.

In addition to histology and histomorphometry,\textsuperscript{33-38} modern imaging procedures\textsuperscript{39-47} are being applied more frequently for sinus graft examination. At the Sinus Consensus Conference,\textsuperscript{20} panoramic radiographs appeared logical for the comparison of a large number of patients. Long-term results of sinus grafting may be monitored by a number of known computer tomographic methods, but these have seen limited use. Kent,\textsuperscript{40} for example, examined bone levels from the new sinus floor to the alveolar crest and the apex of the implant. Alveolar bone height was considered satisfactory if the new bone exceeded the apex of the implant by at least 2 mm even after 5 to 10 years.

These data and the Consensus Conference\textsuperscript{20} have raised the question (among others) of how the immediate and long-term success of planned sinus grafting can be monitored, not only histologically, as with delayed implant placement, but also more accurately.
The significance of pure-phase $\beta$-tricalcium phosphate as a bone substitute material has increased in recent years. It has been used in maxillofacial preprosthetic surgery, implant dentistry, traumatology, orthopedics, and hand surgery.\textsuperscript{48-55} The treatment modes in maxillofacial surgery have included the filling of large cysts, sinus grafting, augmentation, and the filling of periodontal lesions. It has been demonstrated that $\beta$-tricalcium phosphate is fully resorbed in 12 to 18 months and is replaced by bone that is similar both functionally and anatomically to the original bone. In view of these favourable properties, some Authors sought to determine whether this bone substitute alone is an appropriate sinus graft material and whether it is suitable for the filling of large bone cysts.\textsuperscript{55} Accordingly, prospective controlled studies were planned in selected patients.
2. – AIM

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, and non-resorbable or resorbable barrier membranes as described in the guided bone regeneration (GBR) 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. – OSSEΟINTEGRATION IN IMPLANT DENTISTRY

Based on fundamental experimental studies performed by the research teams of P.-I. Brånemark from the University of Göteborg, Sweden, and A. Schroeder from the University of Berne, Switzerland, the use of dental implants has become a scientifically accepted treatment concept in dentistry to replace lost or missing teeth in fully and partially endentulous patients. This breakthrough in implant dentistry was initiated by the discovery that dental implants made of commercially pure titanium can be anchored in the jawbone with direct bone contact. In a landmark paper published in 1969, Brånemark et al\textsuperscript{56} described this phenomenon for submerged titanium implants from a clinical point of view and with decalcified histologic sections (the implants had to be removed before sectioning).

Seven years later, Schroeder et al\textsuperscript{57} provided the first true histologic evidence of direct bone-to-implant contact for nonsubmerged titanium implants using nondecalcified histologic sections with the titanium implant still present in the specimens. Later, these authors created the terms osseointegration and functional ankylosis\textsuperscript{58} to describe this phenomenon. In the past 10 years, the terms osseointegration and osseointegrated implants have been widely used in the literature.

An osseointegrated implant is characterized in light microscopic analysis by a direct apposition of bone to the titanium surface without evidence of a separating connective tissue layer between the bone and the implant. Hereby, the bone has all characteristics of living bone, such as osteocytes or blood vessels, close to the implant surface. (Figure 8.)

![Osseointegrated implant](image)

Fig. 8. Osseointegrated implant
Osseointegration has also been documented in scanning electron microscopic (SEM) studies as well as in a transmission electron microscopic (TEM) study. To achieve an osseointegrated titanium implant with high predictability, the implant must be inserted with a low-trauma surgical technique, avoiding overheating of the bone during preparation of a precise recipient site; must be placed with initial stability; and should not be functionally loaded during the healing period of 3 to 6 months. When these clinical guidelines are followed, successful osseointegration will occur predictably for nonsubmerged titanium implants (one-stage procedure) as well as for submerged titanium implants (two-stage procedure), as has been demonstrated in comparative experimental studies.

The best-documented two-stage implant system is the Brånemark System, whereas the most prominent one-stage system using nonsubmerged titanium implants with a titanium plasma-sprayed (TPS) surface is the ITI System. The basic characteristics, indications, and clinical procedures of both implant systems have been described in detail in textbooks written by Brånemark et al.

In addition to demands from patients for high reliability and optimal esthetics, it is desirable to shorten the treatment period for economic and social reasons. One way of reducing the treatment period is to use 1-stage surgery and non-submerged implants. Another way of reducing the treatment period is to shorten the time between implant insertion and the placement of a prosthetic suprastructure on the implants.

During the healing period, in cases of complete or partial edentulism, the patient usually wears some sort of removable prosthesis. Normally, the patient has to refrain from wearing the removable prosthesis during the first 2 weeks after implant placement and thereafter must wear it during the entire healing period of about 3 to 6 months. In recent studies, the problems of unfavourable loading caused by removable prostheses after 1-stage surgery have been discussed.

The idea has arisen that the prostheses cause the implants exposed through the mucosa to undergo micromotion, leading to crater-shaped marginal bone defects. One possible way to minimize micromotion is to enhance the stability of the implants by splinting the implants with a provisional, screw-retained, implant supported prosthesis in a fixed position immediately after surgery. A prerequisite for such an immediate technique is
1-stage surgery with non-submerged implants. Few studies have been published on the effects of immediate loading of implants. In the mandible, success rates similar to those with healing times of 3 to 6 months before loading have been reported. Studies on immediate loading of maxillary implants are scarce, but the results reported indicate that this method is also viable. The scientific documentation, however, is poor. Bergkvist et al. indicated that immediate splinting of the implants with a fixed provisional prosthesis might protect non-submerged implants from unfavourable and uncontrolled loading and improve the healing conditions. Immediately loaded ITI SLA solid-screw dental implants supporting fixed prostheses in the edentulous maxilla can be a viable treatment alternative when restoring the edentulous maxilla.

The long-term documentation of osseointegrated implants was first reported by Adell et al. in a retrospective clinical study treating fully edentulous patients with Brånemark implants. The authors reported estimated implant survival rates of 86% in the mandible and 78% in the maxilla at 15 years. Data published from prospective studies on fully edentulous patients by Zarb et al. have confirmed these results. Similar results of retrospective studies have also been reported for nonsubmerged ITI implants placed in fully edentulous patients by Babbush et al., Bruggenkate et al., and Krekeler et al.

In the mid-1980s, clinical investigators started to focus more on the treatment of partially edentulous patients in order to expand indications for osseointegrated implants. Although related 10 year data are still lacking for any implant system, encouraging results with ITI implants were found in a prospective study on partially edentulous patients at the University of Berne. Applying strict criteria for success, the examination up to 5 years demonstrated success rates above 95%. Mean success rates above 90% have also been reported for Brånemark implants in a prospective study by Zarb and Schmitt. 5-year results with success rates above 90% applying life table analysis, have also been presented for the IMZ system (Interpore International, Irvine, CA) for fully and partially edentulous patients.

Encouraging treatment results of patients with standard indications have, in the past 5 to 10 years, led to increasing interest in the use of dental implants in “borderline” indications, such as recipient sites with insufficient bone volume, recipient sites close to specific anatomic structures (mandibular nerve, maxillary sinus, etc), extraction sockets, and esthetically demanding sites.
One of the most important prerequisites to achieve the above mentioned success rates with any kind of osseointegrated implants is the presence of a sufficient amount of healthy jawbone at the recipient site. This does not only include an adequate bone height, but also a sufficient crest width. Clinical studies have clearly demonstrated that the success rate of Brånemark implants is compromised in areas of poor bone quality or on those with good quality but inadequate bone height. Screw-type implants with a larger, 5-mm diameter have been recommended for that special situations. An alternative solution for this problem is the use of titanium implants with a rough titanium surface in the bone-anchoring section, such as the TPS surface. Experimental studies have indicated that the anchorage of titanium implants with a TPS surface is significantly improved when compared with polished or fine-structured surfaces. Thus, titanium implants with a TPS surface, have also been successfully utilized in recipient sites with poor bone quality or reduced vertical bone height. In addition, titanium implants with a hydroxyapatite (HA) coating have been recommended for these indications, because the HA coating accelerates bone apposition to the implant surface in the early healing period and significantly improves the anchorage in bone.

However, several publications have reported that the HA coating is biologically unstable over time and shows signs of resorption in histologic studies. This observation might be a contributing factor for the increased rate of complications 3 to 5 years after implant placement, such as severe bone defects around failing or failed HA implants.

New surgical techniques have recently been developed to allow the placement of dental implants in areas with extremely reduced vertical bone height. One of these techniques is the simultaneous use of dental implants with autogenous bone grafts from the iliac crest in severely atrophied mandibles or maxillae. In the posterior maxilla, the vertical bone height at potential implant recipient sites is often limited by the extension of the maxillary sinus, and the placement of endosseous implants with a standard technique is not possible. Sinus lift procedures have been recommended to allow the placement of implants even in sites with less than 5mm of bone height. In the posterior mandible, the vertical bone height is limited by the mandibular canal with the neurovascular bundle. To overcome this anatomic limitation, nerve lateralization has been proposed. However, this technique is questionable for routine use in dental offices.
and appears to be associated with an increased risk for postoperative morbidity, such as dysfunction of the inferior alveolar nerve.\textsuperscript{85,86}

A further problem is the lack of a sufficient crest width. Clinical studies have clearly shown that the long-term prognosis of osseointegrated implants is compromised when the buccal bone wall is missing at the time of implant placement. Various surgical techniques have been developed to increase the width of the crest. One of the methods uses a split technique of the narrow alveolar crest and subsequent filling of the created gap between the two cortical bone walls with either autogenous/homologous bone grafts or hydroxyapatite.\textsuperscript{85,87} The latest surgical technique to improve the volume of jawbone at implant recipient sites involves the principle of guided bone regeneration (GBR). This principle, utilizing barrier membranes, was first evaluated in the late 1950s and early 1960s by the research teams of Bassett et al\textsuperscript{88,89} and Boyne et al\textsuperscript{90} for the healing of cortical defects in long bones and osseous facial reconstruction. These authors utilized microporous cellulose acetate laboratory (Millipore) filters to establish a suitable environment for osteogenesis by excluding connective tissue cells from bone defects. In the early 1980s, this principle was tested in a number of systematic experimental studies for the regeneration of lost periodontal tissues. In implant dentistry, such membranes have been clinically tested in various indications.\textsuperscript{91-95}

### 3.1 - SINUS ELEVATION

Sinus elevation (sinus lifting, sinus grafting) 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.

The surgical procedure is a standard aseptic procedure, carried out under local or general anesthesia. The sinus augmentation procedure was described by Boyne and James: For grafting of the maxillary sinus floor with autogenous marrow and bone, a supracrestal incision is made from the canine or first premolar area and extended posteriorly to the ipsilateral maxillary tuberosity region. Vertical releasing incisions may be made in the canine and tuberosity region. A mucoperiosteal flap is raised to expose the lateral wall of the sinus. A rectangular osteotomy is outlined with a round burr, ensuring that the inferior osteotomy is outlined with a burr, ensuring that the
Inferior osteotomy is about 5 mm above the sinus floor. The osteotomy is completed with hand instrumentation. The superior osteotomy is left intact to allow infracture of the lateral sinus wall. The sinus membrane is carefully elevated within the sinus cavity so that it is completely free inferiorly, anteriorly, posteriorly and medially. Simultaneously, the lateral sinus wall is fractured inwardly. A portion of the antral space is filled with the graft material or autogenous cancellous bone.

The bone graft or/and bone-substituting material is placed in this cavity. A number of donor sites come into consideration, like the mental region, the maxillary tuber, etc. The enossal implantation may be performed at the same time; for undisturbed healing, at least 5 mm thickness of the sinus floor is necessary in order to ensure appropriate primary stability for the implants. (Figure 9.) The mucoperiosteal flap is repositioned and sutured.
Fig. 9. a-e  Outline of sinus grafting: A bone window is formed in the facial wall of the maxillary sinus; this is broken in, but maintaining the integrity of the sinus mucosa the maxillary sinus is filled. If there is primary stability, implant is inserted
3.2 – ECTODERMAL DYSPLASIA

Ectodermal dysplasias (EDs) are a large, heterogeneous group of inherited disorders that involve primary defects in the development of two or more tissues derived from ectoderm. (Figure 10.)

Fig. 10. (a) X-linked hypohidrotic Ectodermal Dysplasia: localization within the region Xq11-q21.1.

(b) Tissues derived from Ectoderm.

These tissues include the hair, teeth, nails, skin, secretory glands (sweat, eccrine, tear, and salivary glands), and mucous glands in the throat, larynx, respiratory system, and intestinal tract.

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 (Figure 11.).
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. (Figures 12., 13.)

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. (Figures 14., 15., 16.)
Figs. 14, 15, 16. Decreased edentulous alveolar bone ridge and reduced occlusal vertical dimension by clinical and radiographic points of view.

The salivary secretion rates are reduced and the salivary glands may be absent. This causes dryness of the mouth and an increased risk of caries. Mouth dryness can make it difficult to soften and swallow food, and may reduce the senses of smell and taste.98,99
4. — BONE GRAFTS AND SUBSTITUTES: MATERIALS

The types of grafts available for the maxilla and mandible are the autogenous, allogeneic, alloplastic, and xenogeneic. 

*Autogenous* grafts are taken from the same person.  

*Allogeneic* grafts are composed of tissues taken from another individual of the same species. 

*Alloplastic* materials are synthetic substances used as substitutes for bone in grafting, and *Xenogeneic* grafts are composed of tissue taken from another species (from an animal source, usually bovine). 

Characterization and analysis of any bone graft substitute prior to its use in human bone sites involves consideration of several material properties of the graft:

1. Chemical and physiologic composition.
2. Morphologic structure.
3. Physical properties.
4. Absence of xenogeneic, allogeneic, and/or other foreign protein in the material. 

Based on these properties, ideal bone substitutes should demonstrate:

1. Excellent biocompatibility, to be fully accepted by the living organism.
2. High osteoconductivity, to promote conduction of new bone formation from the walls of the host bone defect.
3. A large inner surface area, to become fully revascularized by the host bone site.
4. High porosity, to be completely incorporated in new bone.
5. Moderately slow resorption, to remain in place, promoting long-term bone remodelling.
6. An adequate modulus of elasticity, to guarantee a natural stress/strain environment.

4.1 - AUTOGENOUS AND ALLOGENEIC BONE

Autogenous bone grafts (from the patient’s own body) and allogeneic (or homologous) bankered bone (from another individual of the same species) are
frequently and successfully employed to promote regeneration of parts of the skeleton. The use of these types of grafts is limited, however, by the cost of a donor site operation for autogenous bone or by fear of the risk of infection (with human immunodeficiency virus, hepatitis) with use of allogeneic materials.85,86,101

Autogenous grafts are usually harvested from one of the following donor sites:

1. Iliac crest (anterior superior crest or posterior superior crest)
2. Rib
3. Calvaria
4. Anterior tibia
5. Intraoral sites
6. Free flaps (fibula with microvascular anastomosis)

The principal harvesting sources of bone grafting materials are selected primarily to provide the maximal amount of particulate marrow and cancellous bone (PMCB) to deliver the highest potential number of pluripotential or osteogenic precursor cells in the graft material mass. These cells are used in effecting the restoration of the deficient bone area. Although some pluripotential cells exist in the host bone wall, depending on the type of defect involved, delivery of a graft of high osteogenetic material with a great number of these preosteoblastic cells and pluripotential cells102,103,104 tends to increase the potential for success and enhance the quality of the final restorative result. Therefore, most of the donor sites used for autogenous bone grafting provide a basis for obtaining an optimally high amount of PMCB.

The iliac crest graft is considered to be the gold standard of graft materials because of the high population of pluripotential cells in the particulate cancellous bone and marrow portion of the graft. These cells are available for introduction to become osteoblasts and to form new bone. These pluripotential cells are located primarily in the vascular marrow spaces of the cancellous bone (PMCB).85,105

The principal complications of taking bone from the posterior iliac crest are adynamic ileus and hernia. However, in reviewing more than 170 cases involving posterior iliac crest harvesting performed over 18 years, some Authors have not observed a single case of ileus or bowel hernia1.
Harvesting of the anterior iliac crest has been reported to be associated with paresthesia of the lateral femoral cutaneous nerve. In an experience with more than 300 anterior iliac crest donor sites, only one patient has experienced paresthesia of the lateral femoral cutaneous nerve. This complication occurs primarily when the incision is made too far inferiorly on the lateral aspect of the thigh or too far anteriorly, involving an incision immediately below the anterior iliac spine, creating an opportunity for interdiction of the lateral femoral cutaneous nerve. Thus, the harvesting of bone from the iliac crest is, in our experience, met with very little postoperative morbidity.

Patients are usually ambulated on the first postoperative day and released from the hospital on the second postoperative day (sometimes even on the first day after surgery) and are allowed to use a cane or a walker during ambulation for the first 5 days at home. Except for not being able to climb several sets of stairs, to drive an automobile, or to elevate the leg forcefully during the first postoperative week, patients experience very little restriction in their range of motion or ambulation. The patient is allowed to ambulate at will and to move slowly during the first few days postoperatively. The principal minor complication that we have observed after this iliac crest procedure has been formation of hematomas. When a hematoma occurs following an anterior iliac crest procedure in which the medial table is allowed to remain intact, simple reapplication of a pressure dressing with or without aspiration of the hematoma or seroma suffices to treat the swelling.

If the medial table approach has been used in an anterior iliac crest harvesting procedure and a postoperative hematoma occurs, it is very difficult to reach the involved area for aspiration and also difficult to apply a pressure dressing in the correct direction to effectively control the hemorrhage. Although the medial table technique is used by many surgeons, we believe that the lateral table approach results in fewer postoperative hematomas.

If the anterior superior iliac spine is inadvertently taken in the surgical procedure, several complications can ensue. One of these is interference in the function of the sartorius muscle. This affects the patient’s walking and, particularly, the patient’s ability to lift and abduct the leg (in the manner of crossing the knees when sitting). There is also an increased incidence of postoperative hernia when the anterior superior iliac spine is taken. Additionally, the patient tends to experience considerable discomfort.
during ambulation with a full-gaited walk, experiencing a delay in final rehabilitation for a matter of 3 to 4 weeks. Therefore, we believe that the safest bone-harvesting procedure is one in which the anterior iliac crest is harvested through the lateral approach, leaving the medial table, the iliac crest itself, and the anterior superior iliac spine all intact. (Figure 17.)

Figs. 17. a-b  Iliac crest donor site

_Cranial or calvarial_ bone grafts are usually obtained by taking the outer table of the calvarium with the underlying cancellous bone and marrow. The cortical bone of the calvarial graft may be used in one piece or morselized and mixed with the cancellous bone particles. (Figure 18. a) One problem associated with calvarial grafts is that they are composed primarily of cortical bone matrix. This property makes such a graft excellent for recontouring facial bone areas. Such a graft, however, does not have the same results when applied to the alveolar bone of the mandible and maxilla, particularly when the case involves the reconstruction of the mandible and maxilla for root-form implants. The amount of PMCB obtainable from cranial grafts is limited compared to the amount found in the iliac crest. Calvarial bone grafts, when subjected to the stress of occlusal forces through conventional prostheses or root-form, implant-bone prostheses, tend to resorb and tend not to maintain the form and contour of the reconstructed bone area.
The *anterior tibial* surface can be used also as a source for cancellous bone and marrow. A moderate amount of PMCB may be obtained from the tibia and the procedure usually results in very little morbidity. Thus, as an alternative site for autogenous bone when approximately 30 to 40 cm³ of PMCB is needed, the anterior tibial surface can be used preferentially after the posterior and anterior iliac crest have been considered. (Figure 18. b) All donor sites already discussed produce PMCB graft material that can be used in reconstructing the maxilla and mandible and for the insertion of root-form implants. If small amounts of cancellous and marrow bone are needed, an intraoral source may be used.

![Figs. 18. a-b  Calvaria and anterior tibia harvests](image)

A *fibular bone* transfer, when used as a free graft with microvascular anastomosis, tends to produce a very successful soft-tissue graft transfer. However, the osseous portion of the composite graft is composed, for the most part, of thick cortical bone and as a result does not usually offer a high quantity of viable cells for facilitating osseointegration with titanium root-form implant surfaces. Root-form implants placed in such grafts require a longer period of time for integration than do similar implants placed in PMCB grafted areas. Once implants are well integrated, however, the result can be prosthetically satisfactory.
The intraoral sites most frequently used are the mentum, which contains mostly cortical bone; the area behind the mandibular third molar; mandibular tori, which also contain largely cortical bone and the maxillary tuberosity. The intraoral site mostly prefered is the retromolar area of the mandible. This site can be entered by simply using a small, round bur to perforate the cortical bone of the anterior surface of the ascending ramus posterior to the third molar. The small cortical bone plate is elevated to expose the underlying cancellous bone, which is then curretted in a horizontal direction posteriorly into the ramus. The curette is always kept in a plane parallel to the occlusal surface of the mandibular teeth to prevent injury to the mandibular canal and the inferior alveolar nerve. These is little chance of postoperative morbidity if care is taken measuring from the anterior border of the ramus to the mandibular canal. The procedure can be used bilaterally if additional graft material is needed.\textsuperscript{1,85,86}

The symphysis region is an intraoral donor site of choice. The advantages of this site versus an extraoral site are:\textsuperscript{105-111}

- surgery time is shorter
- easy access
- more rapid healing
- absence of visible scars
- the postsurgical effects are well tolerated
- surgery may be performed under local anesthesia

The disadvantages of this donor of this donor site are:

- a limited quantity of bone to harvest
- risk of loss of sensitivity on the mandibular incisors

Following local and regional anesthesia (Spix’s spine), a linear incison is performed on the mucosa between the respective distal aspects of the two canines. Reflection of a full-thickness flap gives access to the symphysis bone. Osteotomy is performed using a bone bur. The upper limit must be located 5 mm under the teeth apices. The depth of the bone graft depends on the width of the symphysis and on the bony defect to be treated. The use of osteotomes allows mobilization and harvesting of the graft. The graft is then adapted to the recipient site. The donor site may be filled using a bone substitute or bone hemostatic wax. The flap is repositioned and sutured using a resorbable suturing material. (Figure 19. )
4.2 - SYNTHETIC BONE SUBSTRATES MATERIALS: ALLOPLASTIC GRAFTS

The use of modern bone substitutes allows regeneration to occur without scar formation and interstitial reconstruction, in contrast with the spontaneous healing process. The implanted materials must satisfy a number of conditions. They should not damage the host organism, they should not contain any infective agent, and thus they cannot transmit any type of infection. If possible, they should be fully resorbed and should progressively be replaced by newly-formed bone tissue, these processes proceeding synchronously. The principle of remodelling should hold, and the bone formed should be similar to the original bone. The process of ossification should not be slowed down, but if possible be influenced in a positive manner, by osteoconductive means. These materials should or give rise to the formation of bone at sites where there was originally no bone, outside the periosteum. In this work a 99% pure phase β-Tricalcium phosphate (beta-TCP) has been used for the regeneration of bone defects. β-Tricalcium phosphate exists in α and β phases. These are identical chemically, but under physiological conditions they behave differently. α-Tricalcium phosphate is resorbed only very slowly, and can be detected in the new bone even years after its implantation, whereas the β form is fully resorbed after a few months, being replaced by...
new bone. A certain proportion of the β phase enters the tissues, so that phosphate ions are present in the implanted area. The β-TCP – ceramic phases are very stable chemically, they are integrated into the bone without causing any reaction, on operated site heals with scar formation and connective tissue formation. β-TCP is fully resorbed and replaced by new bone within a few months. It has osteoconductive effects. It is manufactured in various grain sizes. Neither the bone-substitute material itself nor any of its breakdown products is toxic or contains any virus, prion or other protein. It has coherent porous structure, into which the new bone tissue (osteon) may grow. It breaks down synchronously with the bone regeneration, and the resulting bone tissue exhibits a structure similar to the original. It is transformed quantitatively into functioning bone. TCP gives an X-ray shadow, whereby its fate can readily be followed. Collagen fibres and blood vessels invade the interconnecting micro-pores of the TCP granules (micro-pores) and the intergranular cavities (macropores). The collagen fibres serve as a guide-rail for capillaries and newly formed bone and stimulate the taking of the bone on the implant surface prior to the beginning of its resorption. Despite its high porosity, TCP possesses optimal stability and high abrasion resistance. Its purity of phase provides a stable structure and homogenous solubility under physiologic conditions. The primary-grain size of 10-63µm does not provoke phagocytosis by macrophages. As a purely synthetic material TCP is free from any risk of material-induced infection. There is no immunologic defence reaction. The rounded surface of the TCP granules prohibits mechanical irritation of the surrounding tissue and reduces inflammatory reaction. The physiologic pH-value in aqueous solution results in excellent biocompatibility. The high mechanical stability of TCP prevents the premature degradation of the material into micro particles and thus avoids undesirable macrophage activity. TCP is integrated into the natural bone without connective tissue encapsulation or tissue degeneration. β-Tricalcium phosphate is a highly osteoconductive material.
4.3 - XENOGENEIC BONE MATERIAL

When the organic material is removed from xenogeneic bone, a special mild treatment must be used to preserve the original composition and structure of the inorganic substance.

The technical process used in producing the xenograft from a bovine bone source makes possible the removal of all organic components of the bone product, leaving a pure, nonorganic bone matrix in unchanged inorganic form avoiding the risk of BSE or other virus transmission too.

Anorganic Bovine Bone (ABB) is a finely crystalline, carbonated apatite practically identical to natural human bone mineral.\textsuperscript{1,115,116} The chemical extraction process makes possible the desirable properties of this material. The implantation of ABB in surgical sites leads to ample formation of well-vascularised new bone, which integrates with the ABB particles to restore proper structure and function in the defect site.

The resulting high bone-to-matrix ratio gives the surgeon an excellent basis for operations involving use of titanium root-form implants or orthopedic devices in reconstructive or orthognathic surgery.
The chemical composition of a graft material influences the rate and extent to which it is incorporated into the host tissue and the subsequent physical characteristics of the graft site.

Even more important is the crystalline structure of biomaterials. ABB bone consists of very tiny crystals similar to those of human bone. The small crystals are represented in x-ray diffraction analysis by broad spectrum. (Figure 22.)

Absence of any protein in the bone substrate materials is important to be certain that no allergic or immunologic reaction occurs after implantation of the xenograft material in human patients. The complete removal of all organic materials is confirmed for each batch of ABB material produced.

Investigations have shown ABB to have a natural morphologic structure; a chemical composition identical to that of bone; a large inner surface and porosity comparable to that of bone; a crystalline structure identical to that of bone tissue; and a composition that is purely anorganic.

The biologic character of the xenograft has been examined in a number of animal and clinical experiments. The ABB spongiosa offers greater space for the regeneration of new bone tissue and seems to be one of the best materials of choice for the regenerative process in the maxilla and the mandible. The enlargement of histologic views showed, for both ABB spongiosa and ABB cortical bone, internal pores that are filled by new bone. Porous areas with diameters of approximately 80 μm and more were invaded by new bone.
To distinguish between the blood vessels from ABB and those newly formed bone, Schenk used a different staining method. The number of blood vessels penetrating a ABB cortical particle was impressive and demonstrated the revascularizing and remodelling of the anorganic material through the invasion of blood vessels and new bone. Spector implanted ABB in 30 rabbits and evaluated the results after 10, 20, and 40 days. As a control, synthetic calcium phosphate was used. These results were evaluated by histomorphometric methods.

The structure of the material varies significantly from the surrounding bone spongious structure. In contrast, 1 week after implantation of ABB, osteoblasts are lining up and starting the mineralization process to form new matrix. A line of osteoid tends to form, embedding the osteoblastic cells in the mineral matrix. The osteoid covers the ABB surfaces and represents the first immature bone. This bone formation continues and will lead to the union of bone matrix and ABB particles across the defect to the walls of the host defect. Six weeks after implantation, the newly formed bone is interconnecting the ABB particles. The bridging by new bone is leading to the stabilization of the host bone in the defect area. The particles are difficult to recognize and distinguish from the surrounding bone tissue because of the intense proliferation of new osseous repair matrix.

Indications of the resorption process can be identified by osteoclasts on the Anorganic Bovine Bone surface next to areas of bone formation. Bone is a living tissue that usually is transformed by approximately 2% to 3% per year by a constant remodeling process. In surgical defects, however, the bone may remodel faster from the woven bone, and the transforming process to lamellar bone may occur completely within several months, depending on various factors involving graft site, vascularity, and functional forces. Resorption lacunae were also reported in human histologic specimens examined by Shenk. The cylinder shows reconstruction of the cortical crest with underlying spongiosa structures. ABB is integrated in the newly formed lamellar bone. The lacunae in the ABB particles are filled with new bone next to osteoclasts, indicating an ongoing remodeling process.

These data indicate that the resorbing remodeling process may go on for years. This has also been confirmed in various investigations of humans material. The initial integration of ABB into lamellar structures can be seen in the specimens. Later the resorbing
process follows, involving the surrounding bone in a delayed remodeling process. The resorption, remodeling and new bone formation process is prolonged by the presence of residual ABB particles, thus assuring a constant bone matrix density, an increase in bone density, and an increase of the thickness and quantity of osseous trabeculae and bone cortex. Boyne has shown that the slow resorption and remodeling of porous bone mineral imparts a high degree of permanency to the restored mandibular edentulous area. The physical and chemical properties of porous bone mineral (ABB) are host compatible, offering excellent conductive surfaces for the promotion of bone repair. (Figure 23.)

Fig. 23. Xenogeneic graft: Anorganic Bovine Bone.
5. – BONE GRAFTS AND SUBSTITUTES: MECHANISM

The use of bone grafts involves three mechanisms: conduction, induction, and guided tissue regeneration, which formerly was termed osteophylic response. All are involved in bone regeneration.1,85,117

5.1 – BONE CONDUCTION

Conduction involves the use of inert bone substitute materials or nonviable autogenous and allogeneic banked bone grafts, which offer little or no inductive stimulation to the pluripotential cells of the host defect but do serve as scaffolding over which the bone-forming cells of the host may grow. Particulate conductive materials can be placed, for example, between the root-form implant and the tooth extraction socket wall so that the bone repair can more rapidly proceed from the socket wall to the implanted surface, stimulating bone formation and integration of the root-form implant. Thus, conduction is used mostly in those defects in which there are three bony walls and in surgical sites in which a good supply of osteoblastic cells is provided by the bony walls.

Conductive materials alone should not be used on single bony surface, such as the crest of the alveolar ridge, in an effort to encourage bone to grow outwardly from that bone interface. In this situation, the supply of osteoblasts available is not able to produce the osteogenesis necessary to regenerate bone on the surface of the edentulous alveolar ridge; therefore, a highly inductive bone graft material that supplies the pluripotential cells necessary to regenerate the area should be used. Thus, for example, an iliac-crest bone graft with cancellous bone and high inductive capacities should be used to regenerate the ridge height of large edentulous areas. Therefore it is felt that inductive autograft material, in conjunction with conductive material, should be considered a necessary part of such grafting procedures.118

If bone grafts are used in children for cleft palate repair, the growth of the child and the large numbers of pluripotential cells available in the growing child’s bony surfaces are conductive to “induction” of the bone graft material, and to a favourable result. Thus,
the bony recipient site itself can be “inductive”. Clinicians are conditioned to think that it is necessary to add something to the bone graft (eg, exogenous growth factor materials) to produce the inductive effects. However, the recipient site itself may serve as an inductor of the bone reparative cells.101

Conductive materials are used in three major areas of clinical concern:
1. In two- or three-walled bony defects with ample supply of pluripotential cells
2. As a carrier for bone inductors, eg, as a substrate for rhBMP-2 that releases the inductor over an appropriate period of time
3. To increase bone density and to produce slow remodeling in the area. This remodeling ensures both the prolonged presence of bone mineral and a thickened trabecular pattern for a protective response to the occlusal and functional changes that may occur in the lifetime of the root-form implant.

5.2. – BONE INDUCTION (PROTEIN-BMP)

One of the bone growth factor materials that can bring about induction of bone in areas in which bone regeneration would not normally occur (the crest of the ridge of the maxilla) is rhBMP-2. This material can be obtained in a highly refined form by genetic engineering using recombinant DNA.119 This growth factor, when used in a surgically appropriate manner, is able to stimulate the pluripotential or precursor cells of the existing host wall and even the pluripotential cells in the cancellous portion of any bone graft that may be placed along with the inductor material. In addition, rhBMP-2 may be simply placed on a carrier without any concomitant use of autogenous cancellous bone at the time.

Regeneration of large critical sized discontinuity defects by use of rhBMP-2 in a simple collagen sponge has been demonstrated. Such restored hemimandibulectomy defects in Macaca fascicularis have been shown to support root-form implants in full function for 6 to 8 months. Bone morphogenetic protein-induced bone in the antral floor of patients also has supported implants for prostheses. In the past, demineralized freeze-dried bone has been used by some surgeons on the premise that it is an “inductive material”.10,15 However, there is very little inductive capacity in demineralized freeze-dried bone, because there is very little BMP in the product. Therefore, the effect of demineralized
bone powder is primarily one of conduction and not induction. This material should not be used in an effort to build bone superiorly on the crest of the ridge of the maxilla or the mandible, unless it is used in conjunction with the autogenous bone grafts of the type previously described or as a carrier for true BMP in the concentrated, recombinant-DNA-produced biologic form (rhBMP).

The growth factor rhBMP-2 is both a mitogen and a morphogen, and its functions are both to recruit progenitor cells and to morphologically change cells to the osteoblastic line of cellular maturation to produce bone. Such an effect may be needed for a short or long period, depending on the defect being regenerated. Carrier materials for rhBMP can be designed for a short-term, a medium-term, or a long-term effect, depending on the desired time of release of the rhBMP in the regenerating area.

Examples of materials that will carry rhBMP and be degraded over a short period (2 to 4 weeks) are collagen sponge and various degradable alloplastic materials (eg, polylactic acid and polyglycolic acid). Carriers that will release rhBMP over a slightly longer period are more slowly degradable. This class of materials would include such substances as calcium carbonate and tricalcium phosphate. Carriers that will release rhBMP over a long period are those that are slowly remodeled and resorbed, such as porous bone mineral (ABB).

Examples of carriers that are relatively inert and degraded very slightly, or not at all, HTR (hard tissue replacement), which is a polyhydroxyethyl methacrylate (PHEMA) product in the form of beads, and certain types of porous hydroxyapatite. Thus, a significant part of the clinical effect of the use of rhBMP may be determined by the degradability and other characteristics of the carrier itself. It is believed that the best type of carrier for rhBMP surrounding a root-form titanium implant may be a material that is slowly degradable, providing prolonged bone induction and availability for remodeling to obtain a higher density of cancellous bone resistant to future bone resorptive processes.²⁸,⁸⁵

5.3 - GUIDED TISSUE REGENERATION

The term guided tissue regeneration is now used to describe the phenomenon in which alloplastic membrane surface exclude various types of cells from a surgical
defect site.\textsuperscript{1,120} This phenomenon, formerly called osteophytic response, was used extensively, beginning in 1965, in connection with bone grafting of large trauma-induced, and postoncologic defects. The effect of the membrane depends on its pore size. If the pores are large, many of the cells (including fibroblasts) that the surgeon usually wishes to exclude will migrate through, allowing soft tissue, instead of new osseous matrix, to form in the bony defect. Normally a membrane with pores on the order of 0.5 µm is used; one with pores of 100.0 µm or more would allow a great many unwanted cells to enter the regenerating defect area. Whether a membrane-type barrier should be used in bone grafting for regeneration of the maxilla, for example, depends on the type of prosthetic restoration to be used. If the area is to be restored with a removable prosthesis requiring a deep vestibule for retention, a membrane should not be used because membranes tend to prevent a new periosteum from forming underneath the titanium next to the generating bone. Without the new periosteum, it is not possible to reposition the oral mucosa by suturing the mucosal flap at a superior level to reconstruct the vestibule after the removal of the titanium mesh.\textsuperscript{121,122} If a membrane is not used with the titanium mesh, a new periosteal surface forms beneath the metal and overlying the regenerating bone. This newly formed periosteum will be thick and nonfrangible and will retain the sutures used to attach the mucosa to produce an excellent vestibular height when the metal mesh is removed after 3 to 5 months. This vestibule-producing technique is really a secondary epithelialization procedure. If the surgeon and the prosthodontist are restoring the area with root-form implants and a fixed prosthesis, a deep vestibule is of lesser importance. If root-form implants are being used, a membrane may be placed inside the titanium mesh and the mucosa merely closed over to the crest of the ridge following the removal of the mesh. The optimal effect of the membrane is to exclude the ingrowth of fibrous tissue, thereby increasing bone formation. However, if the use of the membrane would prevent the surgical development of a desirable vestibule, then the membrane should not be used. Membranes should not be used when there are insufficient bony walls to provide the critical mass of precursor cells necessary to form bone. If the surgical defect has only one bony wall with very few cells available for osseous regeneration, the effect of the
membrane would be to exclude the pluripotential precursor cells from the periosteal flap, thus excluding the necessary additional pool of cells that would be available if the membrane were not used. Therefore, the filter or membrane should not be used when there is only one bony wall with a poor blood supply that offers a diminished number of cells to regenerate the defect.\footnote{118}

If, however, the defect has a minimum of three bony walls with excellent vascularity and a good reservoir of pluripotential cells from the host bone available to be induced to form osteoblasts and bone, the membrane may be used. The cells from the periosteum can be excluded, because they will not be necessary for appropriate regeneration of the defect. An excellent example of a complete, functional, and anatomically correct reconstruction of a large defect is using the membrane system.\footnote{123-126}

When, cells from the mucoperiostel flap are excluded, a large amount of fibrous tissue will be prevented from entering the bone-regenerating area; this effect will contribute to an excellent result when used in an appropriate surgical bone site. For enhancement of bone density in the final reconstructive product, a 50-50 mixture of PMBC with Anorganic Bovine Bone and Tricalcium phosphate have been found to be most effective.\footnote{127} (Figure 24.)

![Fig. 24. (a) Implants inserted in a narrow alveolar ridge with exposed threads and (b) non-resorbable Titanium reinforced membrane](image-url)
6. – MATERIALS AND METHODS

6.1 - 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 (using the Cawood and Howell classification);\textsuperscript{128,129} bone loss was 3 to 4 in 3 of the 20 patients, 5 in 7 patients, and 5 to 6 Howell class in the other 10 patients). 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 cm$^3$ 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.$^{130}$ 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 cm$^3$ 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 bur 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.\textsuperscript{131} Sections of each sample were taken for histomorphometry from 4 levels at 150-μm intervals. The samples were measured semiautomatically using an Olympus microscope (Olympus, Tokyo, Japan) connected to a computer using Analysis software (Soft Imaging System, Münster, Germany). 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\textsuperscript{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.

\textbf{6.2 – MATERIAL AND METHODS: ECTODERMAL DYSPLASIA}

In Ectodermal Dysplasia study, 186 titanium implants associated with guided bone regeneration (GBR) 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 nine 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 (e-PTFE) 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. (Figure 25.)

Fig. 25. Guided bone regeneration by non-resorbable membrane and Anorganic Bovine Bone mixed to autogenous bone. (a-b-c-d)

Two-stage surgery was used, with a 6- to 8-month healing period before functional loading.

Together with radiographic evaluations, the following clinical parameters were assessed around the fixtures: probing depth (PD) (mm) (mesial, distal, buccal, and palatal); 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. (Figure 26.)
After delivering the prosthetic-implant reconstructions, the patients were involved in a maintenance care program, in accordance with individual needs. (Figure 27.)
7. – RESULTS

7.1 – 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.

Panoramic Radiograph. 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.

Computerized Tomography. 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. (Figures 28., 29.)
Fig. 28.a Preoperative 3-dimensional (3D) computerized tomogram (CT) demonstrating that a large part of the alveolar crest has atrophied.

Fig. 28.b Preoperative 2-dimensional (2D) CT. Using the classification of Cawood and Howell, the bone loss grade was 6 (the height of the residual sinus floor was less than 2 mm).

Fig. 28.c Postoperative 3D CT. The bilateral sinus grafts are clearly visible (β-TCP in the right maxilla and autogenous bone in the left maxilla).

Fig. 28.d 3D CT reconstruction. The onlay bone grafting is clearly visible.
Fig. 28.e Panoramic radiograph 6 months after the sinus grafting. Ankylos implants were placed.

Fig. 28.f One year after sinus grafting, after prosthetic rehabilitation. The $\beta$-TCP graft (right) appeared similar to bone.

Fig. 29.a and 29.b Preoperative (a) 2D and (b) 3D CT scans. The right side of the residual alveolar crest has thinned to a knife edge in the horizontal and sagittal directions. The 2D CT clearly reveals the situation of the residual sinus floor.

Fig. 29.c After sinus grafting and onlay bone graft. The heads of the microscrews are visible in the right and middle parts of the maxilla.
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. (Figure 30a.)

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. (Figure 30b.)
Newly formed bone replaced the resorbing \( \beta \)-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. (Figure 31a.)

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. (Figure 31b.)
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. (Table 1.)
<table>
<thead>
<tr>
<th>Cases</th>
<th>Total area</th>
<th>New bone</th>
<th>Residual graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>11.59</td>
<td>2.91</td>
<td>0.93</td>
</tr>
<tr>
<td>Control side</td>
<td>12.15</td>
<td>2.96</td>
<td>1.06</td>
</tr>
<tr>
<td>H2</td>
<td>7.01</td>
<td>1.23</td>
<td>1.72</td>
</tr>
<tr>
<td>Control side</td>
<td>10.00</td>
<td>4.17</td>
<td>0.86</td>
</tr>
<tr>
<td>H3</td>
<td>10.14</td>
<td>3.51</td>
<td>0.91</td>
</tr>
<tr>
<td>Control side</td>
<td>7.69</td>
<td>3.09</td>
<td>0.61</td>
</tr>
<tr>
<td>H4</td>
<td>10.74</td>
<td>4.37</td>
<td>1.41</td>
</tr>
<tr>
<td>Control side</td>
<td>9.79</td>
<td>3.83</td>
<td>0.66</td>
</tr>
<tr>
<td>H5</td>
<td>7.13</td>
<td>2.68</td>
<td>0.87</td>
</tr>
<tr>
<td>Control side</td>
<td>8.34</td>
<td>2.65</td>
<td>0.56</td>
</tr>
<tr>
<td>H6</td>
<td>8.16</td>
<td>3.31</td>
<td>0.99</td>
</tr>
<tr>
<td>Control side</td>
<td>7.19</td>
<td>2.78</td>
<td>0.48</td>
</tr>
<tr>
<td>H7</td>
<td>8.55</td>
<td>3.12</td>
<td>1.61</td>
</tr>
<tr>
<td>Control side</td>
<td>8.28</td>
<td>2.25</td>
<td>0.45</td>
</tr>
<tr>
<td>H8</td>
<td>8.36</td>
<td>3.62</td>
<td>0.93</td>
</tr>
<tr>
<td>Control side</td>
<td>11.20</td>
<td>4.62</td>
<td>0.92</td>
</tr>
<tr>
<td>H9</td>
<td>7.12</td>
<td>2.98</td>
<td>0.78</td>
</tr>
<tr>
<td>Control side</td>
<td>10.35</td>
<td>4.06</td>
<td>0.82</td>
</tr>
<tr>
<td>B1</td>
<td>6.65</td>
<td>1.83</td>
<td>0.61</td>
</tr>
<tr>
<td>Control side</td>
<td>9.52</td>
<td>2.80</td>
<td>0.46</td>
</tr>
<tr>
<td>B2</td>
<td>8.12</td>
<td>2.75</td>
<td>0.98</td>
</tr>
<tr>
<td>Control side</td>
<td>7.98</td>
<td>4.18</td>
<td>0.66</td>
</tr>
<tr>
<td>B3</td>
<td>7.60</td>
<td>2.82</td>
<td>0.68</td>
</tr>
<tr>
<td>Control side</td>
<td>11.34</td>
<td>3.43</td>
<td>1.59</td>
</tr>
<tr>
<td>B4</td>
<td>13.75</td>
<td>4.05</td>
<td>3.52</td>
</tr>
<tr>
<td>Control side</td>
<td>6.12</td>
<td>3.67</td>
<td>1.20</td>
</tr>
<tr>
<td>B5</td>
<td>14.61</td>
<td>6.29</td>
<td>1.91</td>
</tr>
<tr>
<td>Control side</td>
<td>6.69</td>
<td>2.59</td>
<td>0.78</td>
</tr>
<tr>
<td>B6</td>
<td>9.74</td>
<td>4.47</td>
<td>1.70</td>
</tr>
<tr>
<td>Control side</td>
<td>7.26</td>
<td>3.58</td>
<td>0.56</td>
</tr>
<tr>
<td>E1</td>
<td>6.18</td>
<td>2.37</td>
<td>1.15</td>
</tr>
<tr>
<td>Control side</td>
<td>9.14</td>
<td>3.66</td>
<td>0.79</td>
</tr>
<tr>
<td>E2</td>
<td>11.80</td>
<td>4.33</td>
<td>1.28</td>
</tr>
<tr>
<td>Control side</td>
<td>9.67</td>
<td>3.77</td>
<td>0.52</td>
</tr>
<tr>
<td>I1</td>
<td>6.86</td>
<td>2.33</td>
<td>1.45</td>
</tr>
<tr>
<td>Control side</td>
<td>11.63</td>
<td>4.92</td>
<td>1.23</td>
</tr>
<tr>
<td>I2</td>
<td>9.30</td>
<td>3.81</td>
<td>1.13</td>
</tr>
<tr>
<td>Control side</td>
<td>8.33</td>
<td>3.28</td>
<td>0.61</td>
</tr>
</tbody>
</table>

H = Hungarian patient; B = Belgian patient; E = English patient; I = Italian patient
Nevertheless, the new bone was markedly less dense on the experimental side in 4 of the 20 cases compared to the control side (H2, B2, B4, l1). 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 (H2 25.9%, B4 25.6%, l1 21.1%), ie, 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 (H5, H7, B3). In these cases, no inflammatory reaction or delayed graft resorption hampered bone regeneration. In 2 cases (H1 and B1), 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 (both Ankylos); 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.

**7.2 – RESULTS: 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.132

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 (Table II.). 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, $p=0.2996$)

Table II. Osseointegration Rate of ED patients vs non-ED patients.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Implants Inserted</th>
<th>Implants Osseointegrated</th>
<th>Implants Lost</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED patients (n=13)</td>
<td>66</td>
<td>60</td>
<td>6</td>
<td>91%</td>
</tr>
<tr>
<td>Non-ED patients (n=20)</td>
<td>120</td>
<td>115</td>
<td>5</td>
<td>95.8%</td>
</tr>
</tbody>
</table>
8. - DISCUSSION

8.1 – DISCUSSION: SINUS ELEVATION

One of the most important conclusions of a Consensus Conference on sinus grafting held several years ago was that, “retrospective analyses did not reveal any bone substitute material that was equivalent to autogenous spongiosa…Accordingly, many participants believed that autografts were the most efficacious…. (but) the doubts raised revealed the need for controlled prospective multicenter clinical trials”. Therefore, since some authors had achieved good results with various bone-substitute materials (especially β-tricalcium phosphate [β-TCP]), a prospective multicenter study was initiated to shed more light on this question.

In a preliminary study involving bilateral sinus elevation in 4 patients in 2001 β-TCP was used on one side and autogenous bone on the other. Sixteen bone biopsy specimens were taken at the time of implant placement. The aim of work was to compare 2 different graft materials, β-tricalcium phosphate and autogenous bone, when used in the same patient. Evaluations were performed by means of 2- and 3-dimensional (2D and 3D) computerized tomography (CT) and histologic and histomorphometric examinations. The duration of the study was 6 months, which is the usual waiting period after sinus grafting. It was concluded that the implantation of β-TCP was followed by the formation of new bone of similar quality and quantity to that observed after grafting with autogenous bone. The histologic and histomorphometric results indicated that when new bone formation was slow, it was slow on both the β-TCP side and the autogenous bone side, and when it was rapid, it was rapid on both sides. Individual patient factors strongly influenced the results.

In essence, the present study is a continuation of that previous work, but on a broader basis. A prospective, multicenter study of 20 patients was organized to confirm the findings of the initial study of 4 patients and to examine whether β-TCP alone is a suitable graft material for sinus elevation.

A number of articles have examined the significance of pure-phase β-TCP and other alloplastic materials as bone substitute materials. However, very
few studies have involved bilateral sinus elevation with 2 different materials in the same patient. Tadjoedin and associates\textsuperscript{32} applied autogenous bone mixed with bioactive glass on the experimental side and autogenous bone alone on the control side. They noted that “bioactive glass particles in the size range 300 to 355 µm clearly show a bone-augmenting capacity, and the cotransplantation of autogenous bone may not be necessary for sinus floor augmentation”. This was somewhat contradicted by 2 publications by Yildirim and colleagues,\textsuperscript{144,145} who used a xenogenic bone-substitute material, ABB first in combination with venous blood and later with autogenous intraoral bone. The combination of osteoconductive ABB and osteoinductive autogenous bone proved better for sinus floor augmentation than did venous blood and ABB. In animal experiments, Mc Allister and coworkers\textsuperscript{115} demonstrated radiographic evidence that bone density and height stability were maintained for 1.5 years after sinus grafting with ABB. Valentini\textsuperscript{116} retrospectively evaluated the rates of survival of 2 different types of implants in sinuses grafted with inorganic bovine bone alone or with inorganic bovine bone mixed with a demineralized freeze dried bone allograft. They concluded that inorganic bovine bone used alone appeared to be a suitable material for sinus floor augmentation. A meta-analysis by Wallace and Froum\textsuperscript{146} showed that there was no difference in regard to implant survival between grafting with 100% autogenous bone or grafting with composites that included autogenous bone as a component. In a pilot study, Schmelzeisen and associates\textsuperscript{147} used tissue-engineered bone for sinus floor augmentation. Their results suggested that periosteum-derived osteoblasts on a suitable matrix form lamellar bone within 4 months, which allows reliable implantation. Despite this encouraging research, in everyday practice most surgeons believe that no matter what bone-substitute material is used, the results are always better if autogenous bone is added. Since the autogenous bone must be taken from somewhere, a second operation is necessary, which puts the patient at risk of donor site morbidity. This study examined whether donor site morbidity can be avoided by using synthetic bone substitute.

The primary aim of this work was to compare the implanted graft material using clinical, radiologic, and histologic studies. Two of the 80 implants (2.5%) were lost, 1 from each side, suggesting the equivalence of the 2 materials. The comparison of the
bone-forming activity of β-TCP and autogenous bone confirmed earlier findings. New bone production was similar on both sides; the difference between the 2 sides was not significant. These results support the view that β-TCP can be a satisfactory graft material, even without the addition of autogenous bone.

Radiologic examinations indicated that the grafted area changed in contour during the period of study (from sinus floor augmentation to definitive prosthetic rehabilitation). The vertical height of the grafts was not analyzed in the present study. Several factors can influence new bone formation, in addition to the nature of the graft. In 2 cases (H1 and B1), the rate of new bone formation was low on both sides. This might be the result of general factors, such as old age, hormonal dysfunction, or disturbances in calcium metabolism.

Local factors can explain 1-sided lethargic bone formation. Disturbances in the blood supply or inflammation at the site of surgery can also delay bone regeneration. In the present study, unilateral lower rates of bone formation were seen on the experimental and control sides in different patients, which supports the important role of local factors. The size of the biopsy sample can also influence the quantitative comparison of the effects of the graft materials. The greater the area of the bone sample, the more representative the quantitative measurement. In the present study, the areas of the bone samples derived from the 2 sides did not differ significantly.

In the introduction, the question was posed whether, under certain conditions, a bone-substitute material can be equivalent to the patient’s own spongiosa. These results suggest a positive answer to this question.

In sinus elevation surgery, β-Tricalcium phosphate can be as effective as autogenous bone. Naturally, this does not necessarily hold true for other operations. For instance, inlay grafting should still be performed with autogenous bone.

This study investigated 20 patients. Strict patient selection was necessary, mainly for ethical reasons. In the 10 onlay grafting cases, which required autogenous bone, use of the control material could be justified. However, in those cases with no onlay grafting, the question was not so clear-cut. The number of cases had to be restricted to the minimum number necessary to draw reliable conclusion. The examination of the 80 biopsy samples taken from the 20 patients led to unambiguous findings. The conclusion drawn appears to be supported by the clinical and radiologic data.
Initially, more working groups had been planned. However, 2 groups were forced to withdraw from participation in the investigation because patients did not agree to the excision of autogenous bone. This further demonstrates the importance of having a suitable bone-substitute material. Onlay grafting was necessary in 10 of the 20 patients. In these cases, the alveolar crest of the maxilla was so thin at many sites bilaterally that stability of the implants could not have been ensured by sinus elevation alone. The vertical augmentation had to be supplemented with horizontal augmentation. A porous bone substitute is not very suitable for this purpose; on the other hand, cortical bone taken from the hip is integrated into the outer surface of the maxilla within a few months.

Onlay bone grafting clearly has no effect on the healing process following sinus elevation, as one of the processes occurs on the outer surface of the maxilla, while the other proceeds internally.

Regarding the question of spongiosa as the gold standard, while it is true that the quality of new bone obtained using any of the bone substitutes may be compared with this as a standard, this standard does have disadvantages. The most important of these are donor site morbidity, the relatively high number of complications, the need for general anesthesia, and the high costs of hospitalization.\textsuperscript{148}

Niedhart and associated\textsuperscript{148} have given a clear picture of the cost: removal of the bone requires an average of 30 minutes, a second surgical team, and an anesthesiologist. These costs far exceed the price of the bone substitute. With careful surgical techniques, the rate of complications may be reduced; nevertheless, it generally ranges from 20\% to 30\%. When all these factors are taken into consideration, it appears important to avoid the excision of autogenous bone whenever possible.

Mention must be made of the membrane question. On the basis of more than 40 publications, Wallace and Froum\textsuperscript{146} performed a comparative meta-analysis of the use of barrier membranes over the lateral window. They found that implant survival rates were higher when a membrane was applied. A long-term clinical, histologic, histomorphometric, and radiographic study of the sinus elevation procedure led Tarnow and coworkers\textsuperscript{149} to the following conclusions:

- Application of a barrier membrane tends to increase vital bone formation.
- Application of a barrier membrane has a positive effect on implant survival.
• Membrane application should be considered for all sinus elevation procedures. As these findings were accepted, no membrane was used in the present study. In 10 of the 20 patients, an onlay graft was applied on the lateral wall of the sinuses. This autogenous bone served as a barrier to soft tissue invasion. In the interest of comparison, in the other 10 cases no membrane was applied over the lateral window. The tissue-engineering procedures mentioned in the introduction, which also aim to minimize donor site morbidity, may be the procedures of choice in the future. Obviously, if the application of tissue engineered bone becomes as routine as the use of skin or mucosa, the debate over graft materials will become less relevant. This may take considerable time, and at present, materials are needed that avoid the excision of autogenous bone.

In addition, with regard to the publications by Skoglund and associates,\textsuperscript{150,151} Tadjoedin and associates,\textsuperscript{32} and Yildirim and colleagues,\textsuperscript{144} which consider natural bone mineral, bioactive glass, and so on, the present work did not set out to compare and contrast individual graft materials. If “remodeling” is considered, pure-phase \(\beta\)-TCP used alone appears to be a suitable material for sinus floor augmentation.

8.2. – DISCUSSION: ECTODERMAL DYSPLASIA

The dental treatment of patients with ED is important, since it involves ensuring a normal diet, optimal dentofacial aesthetics and function, good speech, and appropriate psychological and emotional development. Since this may be complicated, it requires an interdisciplinary approach involving various branches of dentistry and medicine. Prosthetic dental rehabilitation usually consists of different combinations of complete or partial removable dentures, overdentures, and fixed partial dentures. The use of dental implants has become an important, well accepted treatment for replacing missing teeth in adults. Guckes et al. reported that the clinical integration rates of fixtures in the mandibles of ED patients approached that of non-ED patients.\textsuperscript{152} Some years ago, the implant position was often determined by the alveolar ridge anatomy, which sometimes presented aesthetic problems and resulted in mucosal inflammation because of this unfavourable position.\textsuperscript{153-155} Today, prosthetically guided implants are usually used to improve the hard and soft tissue aesthetics. Many authors have obtained successful
clinical outcomes with guided bone regeneration (GBR) using the barrier membrane technique, in combination with autogenous or heterologous bone during implant insertion. The use of a space-maintaining biomaterial, such as autogenous bone or Anorganic Bovine Bone, has increased the volume and stability of regenerated bone. The length of time required for maturation of newly regenerated bone before functional loading depends on the morphology and dimensions of the lesion, vascularization, surrounding bone quality, and optimal oral hygiene. In larger defects, the use of a non-resorbable membrane together with a bone graft and an extended healing period is indicated.

Ectodermal dysplasia is diagnosed from the patient’s appearance and symptoms. An early diagnosis of Ectodermal Dysplasia in infancy or childhood is very important to avoid severe complications and to improve the quality of life. The morbidity and mortality depend on the absence or presence of eccrine and mucous glands. Recurrent high fever (hyperpyrexia) may lead to brain damage, neurological complications, and a mortality rate of up to 30% in infancy. Beyond early childhood, the life expectancy is normal or slightly reduced. Both the oral and maxillofacial surgeon and the pediatric dentist can help to detect these syndromes using clinical observations and radiographic imaging. Jaw radiography is indicated for infants with a fever of unknown origin and possible hypohidrotic ED. The teeth buds may be absent. If unusual dental abnormalities and hypodontia are present at an early age, panoramic radiographs, intraoral dental radiographs, teleradiographs, and radiographs of the hands and feet may detect specific deformities.

Other general medical examinations used to reach the diagnosis include sweat pore counts, the perspiration test, and a skin biopsy to demonstrate the absence or hypoplasia of the sweat glands, hair follicles, and sebaceous glands; genetic studies to localize genes or mutations in ED families; and the prenatal diagnosis of hypohidrotic ED using fetal skin biopsies. A detailed anamnesis with a family history of Ectodermal Dysplasia in other family members may lead to an early diagnosis. Arriving at the diagnosis requires a multidisciplinary approach, since the treatment will involve many specialists, including pediatricians, dermatologists, dentists, and oral maxillofacial surgeons. Children with ED often have serious dental disease requiring necessary and
timely rehabilitative therapy beginning at the first phase of the manifestation of this pathology.\textsuperscript{158-162}

The precocious dental treatment is finalized to improve both functional and aesthetic aspects, which include nutrition, phonetics, and emotional and psychological factors. The disease involves growing children in whom the restoration of masticatory function leads to remarkable benefits in their subsequent growth and development. The absence of numerous dental elements inevitably involves an alteration of the articulation of words, and numerous sounds are altered. The absence or reduction of dental elements accents the sensation of difference felt by patients with Ectodermal Dysplasia with respect to their peers. The goal of the dentist and oral surgeon is to recreate a harmonic smile that gives a natural, pleasant appearance to the face.
9. - CONCLUSIONS

About sinus elevation, it was concluded that the grafting of β–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 β-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 β–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 β- 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: β- TCP alone as the experimental side and autogenous bone alone as control side.
3. Donor site morbidity was avoided by grafting β- 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.
10. - SUMMARY

Two different studies have been performed. The objective of the former was to determine whether donor site morbidity could be avoided by using pure-phase $\beta$-tricalcium phosphate ($\beta$-TCP). Bilateral sinus grafting was performed on 20 selected patients; $\beta$-TCP was used on the experimental side, and autogenous bone was used on the control side. In each patient, one side was randomly designated the experimental side. In 10 of the 20 patients, the maxilla reconstruction included sinus grafting and onlay bone grafting. Implants were placed 6 months after the procedure. Eighty bone biopsy specimens were taken at the time of implant placement. Histologically and histomorphometrically, there was no significant difference ($P=.25$) between the experimental and control grafts in terms of the quantity and rate of ossification. Comparisons with other studies reveal that $\beta$-TCP is a satisfactory graft material, even without autogenous bone. The objective of the latter was to verify if it is possible to use osseointegrated implants in Ectodermal Dysplasia Syndrome (EDS) patients. Dental and surgical-implantological treatment for EDS patients may be very complicated. Guided Bone Regeneration (GBR) membrane technique associated to bone grafting was used to facilitate placement of osseointegrated implants in a guided prosthetically position. Two groups with the same bony anatomical features were assessed. The first consisted of 13 Ectodermal Dysplasia patients, where 66 implants together bone grafts and membranes were inserted. In the second control group 120 implants with GBR were placed in 20 patients. The implants were controlled at second stage surgery, and at a follow-up of a 1 year, 2 and 3 years functional loading period. The results showed no statistically significant difference in the osseointegration rate between the two groups. Despite anatomical defects associated with decreased occlusal vertical dimension and the diminished edentulous alveolar ridges, both in height and in width, osseointegrated implants together GBR and bone grafts may be successfully used in EDS.


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Notes

83
12. – LIST OF AUTHOR’S PUBLICATIONS

12.1 – LIST OF PUBLICATIONS CONNECTED WITH THE TOPIC


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   Quintessence Int 2006 (in press)  \textbf{IF: 0.540}

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