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Bone formation in sinus augmentation procedures using autologous bone, porcine bone, and a 50 : 50 mixture: a human clinical and histological evaluation at 2 months

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Key words: autologous bone, bone regeneration, histology, porcine bone, sinus augmentation

Abstract
Objectives: The aim of this study was to perform a 2 months clinical and histological comparison of autologous bone, porcine bone, and a 50 : 50 mixture in maxillary sinus augmentation procedures. **Materials and methods:** A total of 10 consecutive patients, undergoing two-stage sinus augmentation procedures using 100% autologous bone (Group A), 100% porcine bone (Group B), and a 50 : 50 mixture of autologous and porcine bone (Group C) were included in this study. After a 2-month healing period, at the time of implant insertion, clinical evaluation was performed and bone core biopsies were harvested and processed for histological analysis. **Results**: The postoperative healing was uneventful regardless of the materials used for the sinus augmentation procedures. The histomorphometrical analysis revealed comparable percentages of newly formed bone, marrow spaces, and residual grafted material in the three groups. **Conclusion:** The clinical and histological results of this study indicated that porcine bone alone or in combination with autologous bone are biocompatible and osteoconductive materials and can be successfully used in sinus augmentation procedures.

The rehabilitation of the distal edentulous maxillary area is often a problem due to the significant resorption following teeth extraction and the pneumatization of the maxillary sinus, which may lead to a lack of primary stability of dental implants (Froum et al. 1998; Artzi et al. 2002; Scarano et al. 2006; Mangano et al. 2007). Maxillary sinus augmentation procedures have been used to obtain a sufficient volume of bone tissue to allow a successful implant placement. Several biomaterials have been proposed and used for this procedure, but it is still not clear which graft materials are clinically the most suitable for bone regeneration (Artzi et al. 2002; Hallman et al. 2002; Wallace & Froum 2003; Mangano et al. 2007; Nannmark & Sennerby 2008). The ideal bone substitute must be biologically safe demonstrating biocompatibility, reliable reproducibility, and absence of toxicity (Arcuri et al. 2005). Moreover, it has to satisfy three fundamental mechanisms for a successful bone regeneration such as: osteogenesis, osteoinduction, and osteoconduction. Autologous bone is the only biomaterial showing all these properties, and therefore, it is still the gold standard for successful bone regeneration (Constantino & Freidman 1994; Cypher & Grossman 1996). However, it has still different disadvantages such as: limited intraoral availability, tendency to undergo partial resorption, the need for an additional surgery in case of extra oral donor sites, prolonged operation time, which in turn contributes to the high cost of the surgery (Van den Bergh et al. 1998). Therefore, surgeons have attempted to circumvent these disadvantages using several bone substitutes. These materials appeared to be only osteoconductive, and the addition of autologous bone could eventually improve their properties, resulting in composite grafts. This means that harvesting of autologous bone is still necessary, but the amount of bone needed and donor site morbidity is considerably decreased. Analysis of both clinical results and the commercial diffusion of the different products developed by

the biomedical industry shows a greater osteoconductivity of bone substitutes of natural origin over derivative substitutes (Trisi et al. 2003; Santos et al. 2010). In particular, there is one animal species with a genotype close to human – the pig – that has been used as a source of xenografts, and these materials have provoked a great deal of research due to their potential as adequate substitutes for bone regeneration (Borie et al. 1998; Barone et al. 2012). Various studies have shown their efficacy as osteoconductive matrices (Orsini et al. 2006; Nannmark & Sennerby 2008; Ramırez-Fernandez et al. 2011; Scarano et al. 2010, 2011; Cassetta et al. 2012; CalvoGuirado et al. 2009, 2010; Calvo-Guirado et al. 2011; Calvo Guirado et al. 2013). However, all aspects of a bone substitute must be thoroughly studied in order to make predictive risk assessment possible (Arcuri et al. 2005). To the author best knowledge does not exist a study where regeneration capacity of porcine bone alone or a 50 : 50 mixture with autologous one is evaluated only 2 months after sinus lift procedures. The purpose of this human study was a histological, histomorphometrical, and clinical comparison of the outcomes, after a 2-month healing period, of autologous bone, porcine bone, and a 50 : 50 mixture of the two in maxillary sinus augmentation procedures, in order to better understand the bone substitute behavior in early stages of bone regeneration.

Material and methods

Study design

Ten consecutive patients (six women, four men; age range 43–55 years; mean age 50.3 years) were selected at the Department of Oral Sciences of “Sapienza” University of Rome, Italy, between February 2008 and June 2012. A total of 10 sinus elevation procedures (all unilateral) by means of a Piezosurgery device (Easy Surgery, BioSafin, Ancona, Italy) were performed (Vercellotti et al. 2001). All the patients included in this study were systemically healthy and completely edentulous in the posterior maxilla with a residual bone crest of approximately 4 mm. Maxillary bone atrophy was scored (as Class V) on the basis of the Cawood and Howell classification (Cawood & Howell 1991) and assessed by either preoperative orthopantomography (OPT) or computed tomography (CT). The following exclusion criteria were used to select the patient population: unhealthy systemic health status that would contraindicate surgical treatment, parafunctional habits, poor oral hygiene, uncontrolled diabetes mellitus, current irradiation to the head or neck, psychological disorders and alcohol or drug abuse, history of maxillary sinus, nose, or throat pathologies. With respect to tobacco use, six patients were nonsmokers and four smoked more than 10 cigarettes per day. All patients were informed of the study protocol, of the therapeutic alternatives to sinus elevation, and of the possible complications of such an intervention, and they all signed an informed written consent. The patients were randomly assigned to three groups using CLINSTAT (Martin Bland, York, UK) software. The study protocol was scrutinized and approved by Ethical Committee of “Umberto I” University Hospital, Rome, Italy, and was carried out in accordance with the fifth revision of the World Medical Association Declaration of 2000. The surgical interventions were performed by the same clinician (MC), specialized in implant dentistry. Before treatment, radiographic examinations, such as OPT and CT scans, were carried out to assess anatomical conditions, position, and dimension of the bony window. In addition, CT was also used to determine the absence of sinus pathology. Surgical technique All patients underwent oral hygiene procedures prior to surgery. Antimicrobic prophylaxis was obtained with 1 g of amoxicillin (Glaxo-SmithKline, Verona, Italy) 1 h before intervention and twice a day for 5 days. Patients’ mouths were rinsed with chlorexidine digluconate (Corsodyl, Glaxo-Smithkline) 0.2% solution for 2 min. Local anesthesia was induced by infiltration with mepivacaine (Mepivacaina 20 mg/ml, Pierrel Pharma, Milano, Italy) associated with adrenaline 1 : 100.000. A horizontal crestal incision was made with two additional vertical releasing incisions, and a full thickness mucoperiosteal flap was raised to expose the complete lateral wall of the maxilla. The osteotomy for sinus access was performed using a Piezosurgery device (Easy Surgery, BioSafin). The inferior margin of the osteotomy was placed 3–4 mm above the sinus. The osteotomy was completed by rounding the angle of the bony window. The separation of the sinus membrane was performed

using a piezoelectric tip, which was inserted up to 2 mm into the edge of the exposed sinus membrane. Membrane elevation was completed using manual sinus elevators or a piezoelectric surgery tip as with manual procedures, and the sinus mucosa was carefully dissected. The space obtained with the sinus elevation was filled with different graft materials: 100% autologous bone (group A); 100% deantigenated-collagenated porcine bone substitute (OsteoBiol Gen-Os, Tecnoss, Giaveno (TO), Italy) (group B) or finally a 50 : 50 mixture of autologous and porcine bone (OsteoBiol Gen-Os, Tecnoss, Giaveno (TO), Italy) (group C). Autologous bone was harvested from the retromolar trigone using a trephine and then fragmented into particles (bone chips). The total amount of graft material at each site varied according to the extent of maxillary bone restoration and sinus anatomy. The mucoperiosteal flap was sutured using tension-free single sutures (GORE–TEX, W.L. Gore & Associates, Inc., Flagstaff, AZ, USA), which were removed 10 days after surgery. Patients were restricted to a soft diet for 4 weeks, and oral hygiene instructions were provided. During the postoperative healing period, the occurrence of clinical complications such as acute or chronic sinus infection or bleeding was recorded. After a period of 2 months, radiographic examinations (OPT and CT scan) were performed to evaluate the outcome of surgical procedures and the implants were inserted. A total of 17 cylindrical implants (Impladent, Formia, Latina, Italy), with an external hexagon (diameter 3.75 mm and lengths ranging from 10 to 15 mm) were inserted using twostage procedure and were distributed as follows: Six implants were inserted in four patients treated with autologous bone (group A); five implants were inserted in two patients treated with porcine bone (group B); six implants were inserted in four patients treated with the combination of 50% autologous bone (bone chips) and 50% porcine bone (group C). Two months after the insertion, at the second stage surgery, all implants were loaded with a provisional cemented acrylic resin prostheses and 6 months later a fixed permanent metal-ceramic prosthesis was delivered. The implants were clinically and radiographically evaluated at the time of insertion, 2 and 6 months after implant placement. Specimen processing At the time of implant surgery, after a 2- month healing period, bone cores were harvested using a 3.5 9 10 mm diameter trephine bur under saline solution irrigation and processed for histology. A total of 17 bone cores, one for each implant inserted, (six for group A, five for group B, and six for group C) were retrieved and were immediately stored in 10% buffered formalin. The specimens were processed using the Precise 1 Automated System (Assing, Rome, Italy) (Piattelli et al. 1997). The specimens were dehydrated in a graded series of ethanol rinses and embedded in a glycolmethacrylate resin (Technovit, Kulzer, Wehrheim, Germany). After polymerization, the specimens were sectioned, along their longitudinal axis, with a high-precision diamond disk at about 150 lm and ground down to about 30 lm with a specially designed grinding machine. Two slides were obtained from each specimen. These slides were stained with acid fuchsin and toluidine blue and examined with transmitted light Leitz Laborlux microscope (Leitz, Wetzlar, Germany). Histomorphometry of the percentages of newly formed bone, residual grafted material, and marrow spaces was carried out using a light microscope (Leitz) connected to a highresolution video camera (3CCD, JVC KY-F55B, JVC□, Yokohama, Japan) and interfaced to a monitor and PC (Intel Pentium III 1200 MMX, Intel□, Santa Clara, CA, USA). This optical system was associated with a digitizing pad (Matrix Vision GmbH, Oppenweiler, Germany) and a histometry software package with image capturing capabilities (Image-Pro Plus 4.5; Media Cybernetics Inc., Immagini & Computer Snc Milano, Italy).

Results

Clinical results

The postoperative healing was uneventful; only slight inflammation and swelling immediately after the surgical procedure were observed. During the sinus elevation procedure, neither perforations nor infections occurred. Two months after implant placement, at the radiographic follow-up, radiopacity around and above the implants in the maxillary sinus was evident; clinically, all the implants were stable, and therefore, after the abutment connection, they all received provisional cemented acrylic

resin prostheses. After further 6 months, a fixed permanent metal-ceramic prosthesis was delivered as the X-ray confirmed the presence of radiopaque material in the increased sinuses.

Histological results

In all biopsies, trabecular bone was observed over the entire grafted area; grafted material particles were always present.

100% autologous bone

In group A, it was possible to observe trabecular bone with large marrow spaces (Fig. 1).

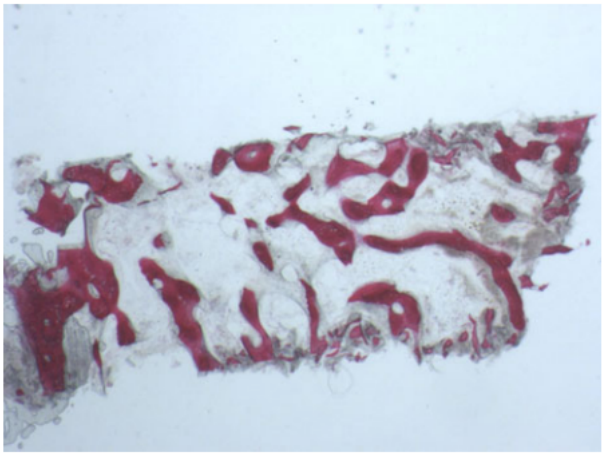

Fig. 1. Histological image 2 months after sinus augmentation with autologous bone. Trabecular bone with large marrow spaces can be observed. Acid fuchsin– toluidine blue 12X.

The affinity for the staining of the grafted autologous bone particles was very similar to that of the host bone; therefore, it was difficult to see a demarcation line between the particles and bone in low power images. While, at high power, it was clear that the grafted particles were lined by newly formed bone (Fig. 2), which showed the features of a recently formed tissue, such as wide osteocyte lacunae, high staining affinity, the presence of osteoblasts and osteoid matrix undergoing mineralization. Inflammation and multinucleated giant cells were absent.

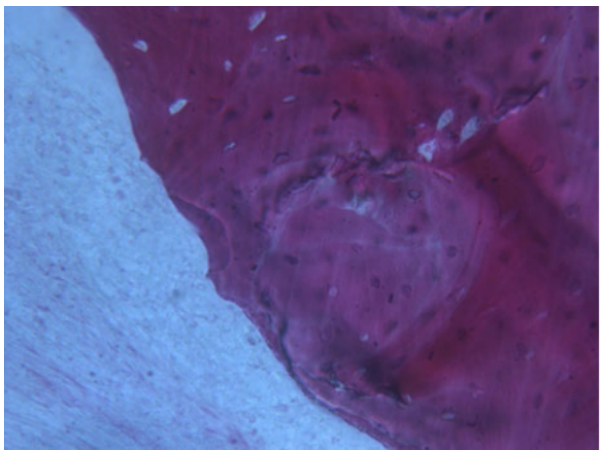

Fig. 2. The autologous bone grafted particles were in close contact with newly formed bone with large osteocyte lacunae. Acid fuchsin–toluidine blue 200X.

Histomorphometry showed that the percentage of newly formed bone was 23.2 3% (median: 23.4), of marrow spaces 60.4 2.3% (median 60.45), and of residual grafted material 16.4 3.8% (median: 14.9).

100% of porcine bone

In group B, trabecular bone with marrow spaces and residual biomaterial particles was observed (Fig. 3).

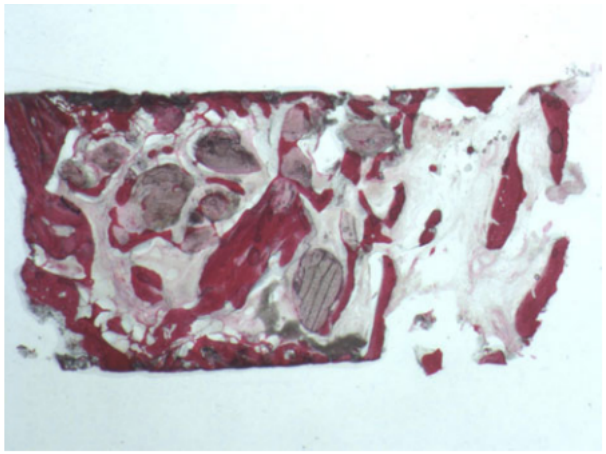

Fig. 3. Trabecular bone with large marrow spaces and residual biomaterial particles were also observed in the sites grafted with porcine bone. Acid fuchsin–toluidine blue 12X.

Some particles were completely surrounded by newly formed bone and frequently bridged by thin bone trabeculae (Fig. 4), while others were only partially in contact with the regenerated bone, although not rarely inside those particles newly formed bone areas were detected.

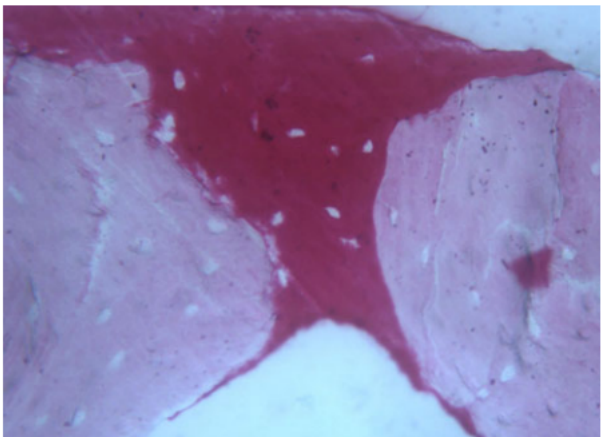

Fig. 4. Porcine bone particles were completely surrounded by newly formed bone and bridged by thin bone trabeculae. Acid fuchsin–toluidine blue 200X.

Neither osteoclasts nor inflammatory infiltrate were observed around the grafted particles. Histomorphometry showed that the percentage of newly formed bone was 21.6 3.4% (median: 21.6), of marrow spaces 56.1 3.2% (median: 56), and of residual grafted material 22.3 3.5% (median: 22.2).

50 : 50 mixture of autologous and porcine bone
At lower power magnification, it was possible to observe trabecular bone with marrow spaces (Fig. 5) presented wide osteocyte lacunae and a high affinity for the fuchsin, typical of a recently mineralized

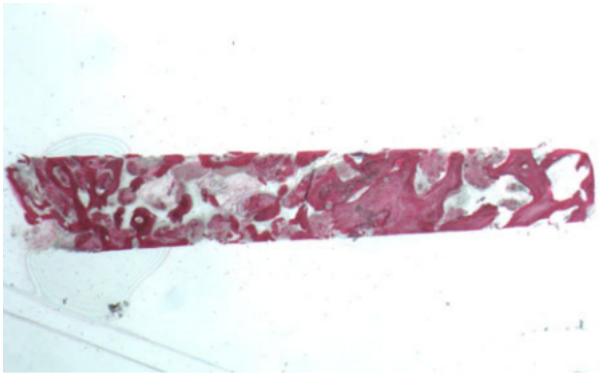

Fig. 5. Porcine bone particles were completely or partially surrounded by newly formed bone. Acid fuchsin– toluidine blue 8X.

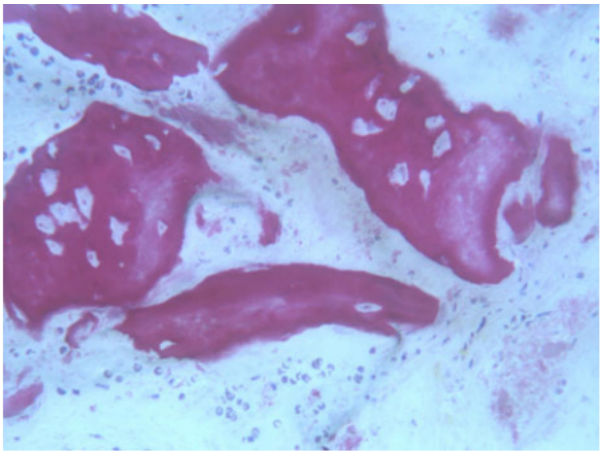

Fig. 6. Large osteocyte lacunae and a high affinity for the stain can be observed in the specimens retrieved from sites grafted with the 50 : 50 mixture of autologous and porcine bone. Acid fuchsin–toluidine blue 200X.

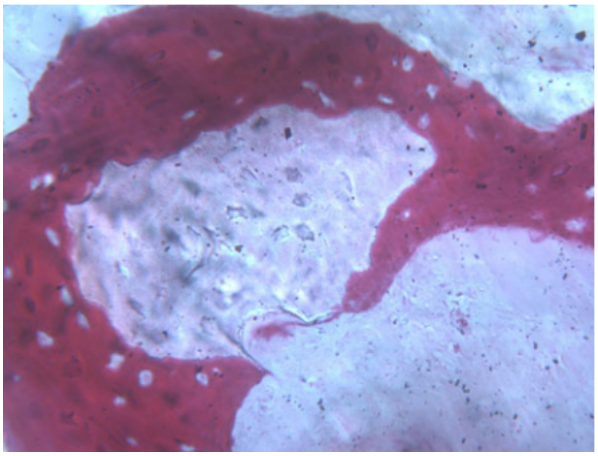

Fig. 7. A porcine bone particle was completely surrounded by newly formed bone. Acid fuchsin–toluidine blue 200X.

tissue (Fig. 6). All the specimens showed autologous bone and porcine bone particles completely or partially surrounded by newly formed bone (Fig. 7). No signs of a cellular inflammatory infiltrate were observed. Histomorphometry showed that the percentage of newly formed bone was 24.5 3.4% (median: 24.5), of marrow spaces 55.1 3.7% (median: 55.1), and of residual grafted material 20.4 3.2% (median: 20.4).

Discussion

Modern implant dentistry aims at a reduction of loading and bone healing times in the reconstruction of posterior maxillary edentulous patients. New implant surfaces, surgical techniques, and biomaterials are being investigated in order to achieve this goal. Scarano et al. (2010), in a 4- and 6-month histological and histomorphometrical evaluation of cortical porcine bone in humans, concluded that this bone substitute was biocompatible and osteoconductive and that it could be used for maxillary sinus augmentation procedures without interfering with the normal reparative bone processes. Moreover, in a 5-year clinical investigation of the resonance frequency analysis (RFA) of implants inserted, only 2 months after the regeneration procedures, in sites grafted with autologous bone and with a 50 : 50 mixture of autologous and porcine bone, no differences between the two groups were reported over the long term (Cassetta et al. 2012). Based on the abovementioned results, the present study was performed to assess the clinical and histological behavior of the porcine bone vs. a 50 : 50 mixture of autologous and porcine bone 2 months after sinus augmentation procedures and compare with autologous bone. The histomorphometrical analysis at 2 months revealed that, in the augmented regions, the percentage of newly formed bone was similar for the three groups, indicating that porcine bone alone or mixed with autologous bone could be successfully used for maxillary sinus augmentation procedures. Indeed, in all biopsies obtained after only 2 months, most of the grafted biomaterial particles were in contact with newly formed bone, and no gaps or connective fibrous tissues were found at the biomaterial– bone interface. In agreement with a previous 4- and 6-months investigation conducted in our laboratory, the present study confirmed the good biocompatibility and high osteoconductivity of the porcine biomaterial at an earlier stage. Barone et al. (2005) compared autogenous bone with a combination of autogenous and porcine bone particles, and no significant differences were found 5 months after treatment. Furthermore, the present results are consistent with a number of recent reports in which successful regenerative procedures were observed in patients treated with maxillary sinus augmentation using porcine bone (Barone et al. 2005; Barone et al. 2012; Orsini et al. 2006; Scarano et al. 2011) at longer time periods. However, to the best of the authors knowledge, this is the first study where the porcine bone alone or in combination has been investigated at such an early stage, and therefore, no comparison with other studies conducted at the same time point and with the same material can be undertaken. Within the limits of the present study, due to the relatively small number of enrolled patients, the clinical and histological outcomes indicated that the porcine bone material alone or in combination could be used with success in highly resorbed maxillae. However, these findings need to be supported over the long term with a larger number of patients, implants, and a longer follow-up.

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