Hydroxyapatite/Collagen Composite Is a Reliable Material for Malar Augmentation

Antonio D’Agostino, MD,* Lorenzo Treviistol, MD,† Vittorio Favero, MD,‡
Michael J. Gunson, DDS, MD,§ Federica Pedica, MD,∥ Pier Francesco Nocini, MD, DDS,¶
and G. William Arnett, DDS#

Purpose: To evaluate the long-term results of cheekbone augmentation using porous hydroxyapatite granules mixed with microfibrillar collagen in a large group of patients.

Materials and Methods: Four hundred thirty patients who underwent zygomatic augmentation and intermaxillary osteotomy were evaluated clinically, radiologically, and histologically.

Results: Complications were found in 13 patients (1.56%). There were no relevant radiologic differences in prosthesis volume after 1 month (T1) or after 24 months (T2) in any patient; there were no clinically relevant differences in 110 patients after 36 months. At T1, the prosthesis had a granular structure and the granules had not migrated; at T2, the prosthesis was staunchly adhering to the underlying bone. Over time, the radiopacity of the material increased. Histologic results of 19 biopsy specimens obtained from 8 patients 2 years after the procedure showed prominent ossification with low inflammation, confirming new bone formation over time. According to the visual analog scale, the patients were generally satisfied with the aspects that were considered.

Conclusion: Hydroxyapatite and collagen composite used during malarplasty produced a successful outcome. Its main drawback is a learning curve that is longer than for more frequently used implantable biomaterials.

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Functional and esthetic facial rehabilitation has become an important sector of maxillofacial surgery. Harmonic facial features and natural proportions favor self-confidence and psychological health. Facial defects or asymmetries can result from soft tissue asymmetry or bony framework alterations. Intermaxillary osteotomy corrects skeletal malocclusions, aligns the upper incisor sagittal and vertical planes, and improves the esthetics of the lower third of the face, including the paralateronasal area, the upper and lower lips, and the chin. While the osteotomy procedure is being carried out, some patients also might require contouring of the malar soft tissue complex or other facial areas to improve midface definition and to obtain greater facial harmony.

*Associate Professor, Department of Surgery, Unit of Maxillofacial Surgery and Dentistry, University of Verona, Verona, Italy.
†Associate Professor, Department of Surgery, Unit of Maxillofacial Surgery and Dentistry, University of Verona, Verona, Italy.
‡Clinical Assistant, Department of Surgery, Unit of Maxillofacial Surgery and Dentistry, University of Verona, Verona, Italy.
§Private Practice, Arnett and Gunson Facial Reconstruction, Santa Barbara, CA.
∥Clinical Assistant, Department of Pathology and Diagnostics, University of Verona, Verona, Italy.
¶Professor and Chief, Department of Surgery, Unit of Maxillofacial Surgery and Dentistry, University of Verona, Verona, Italy.
#Private Practice, Arnett and Gunson Facial Reconstruction, Santa Barbara, CA and Assistant Professor, Department of Oral and Maxillofacial Surgery, Loma Linda University, Loma Linda, CA.

G. William Arnett is the assignee of U.S. patent 6506217 B1 (moldable postimplantation bone filler and method).

Address correspondence and reprint requests to Dr Favero:
Department of Surgery, Unit of Maxillofacial Surgery and Dentistry, University of Verona, P.le LA Scuro, 10, Verona 37134, Italy; e-mail: Vittorio_favero@yahoo.it

Received December 9 2015
Accepted January 28 2016

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0278-2391/16/00144-0
http://dx.doi.org/10.1016/j.joms.2016.01.052
HYDROXYAPATITE FOR MALAR AUGMENTATION

The present study followed the Declaration of Helsinki on medical protocol. This study was approved by the institutional review board of the Verona Hospital (Verona, Italy) and all participants signed an informed consent agreement. Over a 7-year period (2005 through 2012), 430 patients (270 women and 160 men; mean age, 28 yr; range, 18 to 45 yr) underwent procedures using porous HA granules to augment the zygomatic region (total, 860 prosthesis) and optimize facial esthetics during orthognathic surgery. All procedures were carried out in the Arnett-Gunson Center for Corrective Jaw Surgery (Santa Barbara, CA) or the Unit of Dentistry and the Maxillofacial Surgery Unit of the University of Verona Medical Center (Verona, Italy). The treatment plan, which aimed to achieve functional and esthetic improvement, was to enhance the zygomatic region of patients with inadequate cheekbone projection or facial asymmetry of the zygomatic arch.

All procedures were carried out using general anesthesia after prophylactic antibiotic administration (ampicillin and sulbactam 1.5 g intravenously 1 hour before surgery). In accordance with the patent of G. William Arnett (U.S. patent 6506217), the prostheses, which were handmade, were prepared by mixing HA granules 5 mL (Pro-Osteon 200, Interpore Cross International, Irvine CA), microfibrillar collagen hemostat flour 1 g (Avitene, Davol Inc., Warwick, RI), and sterile saline solution 5 mL (Fig 1A,B).

The mixture is shaped using sterile instruments and according to the desired result in relation to the patient’s features. Initially, the material is very malleable. After it has been shaped, it is warmed for at least 150 minutes under a 150-W heating lamp and allowed to stiffen. Shaping is carried out at the end of an orthognathic procedure (Le Fort I), because the same upper vestibular incision is used after debridging the area between the infraorbital nerve medially and the zygomatic arch laterally, creating pockets (whose sizes should match those of the prostheses) within the zygomatic bones (Fig 2A,B); this is a very important detail that will prevent prosthesis displacement. Careful hemostatic control of the recipient site is
extremely important. If the prosthesis is positioned more laterally, then the more the inter-zygomatic diameter will be augmented. Likewise, if the prosthesis is positioned more medially, then the sagittal projection will be improved. No internal fixation is needed to stabilize the prostheses; instead, extraoral compressive dressings are applied to stabilize the implants.

All patients included in the study underwent a clinical assessment and participated in at least a 3-year follow-up (mean follow-up, 6 yr; range, 3 to 10 yr). Clinical evaluations consisted of quantifying short- and long-term complications linked to inflammatory or infectious problems or the need for other procedures, implant stability (absence or presence of clinically appreciable signs of resorption), and photographic records taken 1 to 3 years after surgery.

Seventy-six of the 430 patients agreed to complete the visual analog scale (VAS), a psychometric response scale that measures a continuum of values on a scale of 0 to 100. In this study, patients were asked to judge the naturalness of the facial contour of the zygomatic arch: they were instructed to give a grade of 0 if they judged the prosthesis appeared unnatural and to give a grade of 100 if they were completely satisfied with their new profile. They also were asked about symmetry: they were asked to give a grade of 0 if one side seemed different from the other and a grade of 100 if the 2 sides were exactly the same. The third parameter was the implant’s natural feel: they were asked to give a grade of 0 if the prosthesis seemed foreign to their body and a grade of 100 if it seemed part of their body. The patients were asked to define their satisfaction with the implant as a grade of 0 if they were entirely dissatisfied and 100 if they were completely satisfied.

All patients underwent imaging after 1 month (T1) and after 24 months (T2). One hundred ten of the 430 patients also agreed to undergo cone-beam computed tomography (CBCT; NewTom 3G device; QR srl, Verona, Italy) at least 36 months after surgery (T3). Signs of resorption of native bone and variations in the structure and radiopacity of the implanted prosthetic material were evaluated by a blinded observer (the radiologist who analyzed the CBCT); these phenomena were evaluated over a long period (≥36 months) in 110 of the patients studied.

Biopsy samples were obtained from implants in 8 patients who required removal of fixation screws from the upper jaw 2 years after surgery. Once the patients gave informed consent, biopsy samples were taken using trephine burs (inner diameter, 2 mm; outer diameter, 3 mm) and 19 samples of prosthetic material were collected. Each sample was taken so that a portion of the prosthesis in the entirety of its width from the periosteum to the native bone could be collected, and the periosteum side was marked with a pen. The material collected was fixed in formaldehyde buffered with 4% phosphate and washed in the buffer. After decalcification with Osteodec (Bio-Optica Milano Spa, Milan, Italy), the sample was dehydrated using increasing concentrations of alcohol and xylene and then embedded in paraffin. Morphologic and immunohistochemical analyses of bone samples were performed to evaluate remodeling and eventual osteogenesis. Four-micrometer-thick sections were stained with hematoxylin and eosin, and immunohistochemistry was performed on subsequent sections using 2 monoclonal antibodies specific for cathepsin K (clone CK4, Novocastra, Newcastle, UK; clone 3F9, Abcam, Cambridge, UK) to stain osteoclasts and for CD56 (clone 123C3.D5, 1:100; Thermo Scientific, Grand Island, NY) to stain osteoblasts, as previously described. Cathepsin K is fundamental for the degradation of type 1 collagen in bone resorption mediated by osteoclasts21 and CD56 stains resting and
activated osteoblasts. Vital areas were identified by checking the section stained with hematoxylin and eosin under an optical microscope and looking for nucleated osteocytes. Then, applying immunohistochemical analysis, the presence of osteoclasts was evaluated by staining of cathepsin K.

**FIGURE 2.** A, Placement of the implants in the subperiosteal pockets. B, Cone-beam computed tomogram showing final position of the prosthesis in the malar area. Prostheses differ in shape and size owing to the asymmetric nature of the defect to recontour.

antibody and osteoblasts reactive to CD56. Percentage of new bone formation, percentage of fibrous tissue, and presence of the biomaterial also were investigated.

Results

Clinical Evaluation

Clinical evaluation (Table 1) of patients showed that prosthesis malposition, which was noted in 6 cases, was probably due to excessively large subperiosteal pockets in which the prostheses were positioned. The inappropriate dimension led to a caudal rather than contralateral slippage of the prosthesis. Five cases of partial resorption were noted; all were linked to inadequate hemostasis of the recipient site or in some cases to massive bleeding at the patient’s awakening. There were 2 cases of early infection (<30 days) requiring removal of the prosthesis. There were no cases of late-onset infection, dehiscence, fistula, or thinning or alteration of overlying soft tissues. Comparison of photographs taken 1 and 3 years later confirmed the registered clinical data (Figs 3-6). Some patients reported bilateral edema and pain in the zygomatic region during the first month after surgery. Thirteen patients (1.56%) had some kind of complication; 2 (0.2%) had infectious complications.

The VAS was completed by 76 of the 430 patients (Table 2). The patients substantially agreed on their perception of the primary parameters characterizing the result. On a scale of 0 to 100%, the average judgment about the natural contour of the zygomatic profile was 85.83 ± 22.22 of 100 (median, 95.19). The average judgment about symmetry was 85.68 ± 23.00 (median, 96.44). The average judgment about the implant’s natural feeling was 80.30 ± 26.28 of 100 (median, 92.10). The patients’ average general satisfaction with the result was 84.41 ± 23.96 of 100 (median, 96.72).

Radiologic Evaluation

Except for the cases of partial or complete resorption (n = 5; 0.64%), the imaging data collected at T1 showed that the prosthesis maintained its granular structure and that the granules had not migrated to the surrounding soft tissues (Fig 7). The structure of the prosthesis was radiotransparent compared with the compact portion of the zygomatic bone. At T2, the prosthesis seemed to adhere staunchly to the underlying zygomatic bone in all patients. The granular structure was still distinguishable, although it was less evident, and the partial radiotransparency had evolved to a radiopacity similar to that in the compact part of the native bone, making it impossible to distinguish the interface between the prosthesis and bone (Fig 8). That tendency continued, according to the imaging data available at T3, toward progressive loss of definition of the granular architecture and an almost complete radiopacity and apparent corticalization of the bone in contact with the prosthesis. The interface between the prosthesis and bone at T3 appeared indistinguishable (Fig 9).

Histologic Evaluation

The persistence of porous HA and of macrophages, although without inflammatory infiltrate, was found in all samples (Table 3). Fibrous stroma was found in 50%, and the presence of new osteogenesis and mature bone was found in 70% of cases. According to biopsy findings, the presence of mature bone was found only at the periosteal side (marked with a pen), and the presence of new formation of immature bone was found entirely on the deep side of the native bone with a bone maturation gradient proceeding from the periosteal to the deep side (Fig 10). Immunohistochemical investigations uncovered some cathepsin K protease contained in the cytoplasm of the macrophages, thus indicating the presence of osteoclast activity localized around the HA residues (Fig 11). The anti-CD56 antibodies indicated greater new osteogenesis activity at the side of the biopsy sample adjacent to the native bone (deep), confirming the results of histomorphometric analyses (Fig 12).

Discussion

Arem et al2 and Moos et al3 were among the first to describe pioneering experiences with Proplast to enhance the lower third of the face at the end of the 1970s. These procedures were followed by autologous onlay bone grafts that were initially collected from the rib and iliac crest and later from the calvarial bone. Although those grafts that were positioned for esthetic

Table 1. Clinical Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Prostheses (N = 860), n (%)</th>
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<tbody>
<tr>
<td>Malposition requiring secondary correction</td>
<td>6 (0.72)</td>
</tr>
<tr>
<td>Partial or total resorption requiring secondary</td>
<td>5 (0.64)</td>
</tr>
<tr>
<td>correction</td>
<td></td>
</tr>
<tr>
<td>Dehiscence</td>
<td>0</td>
</tr>
<tr>
<td>Fistula</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Thinning of overlying soft tissue</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>13 (1.56)</td>
</tr>
</tbody>
</table>


FIGURE 5. Patient 2 at preoperative assessment. A-C, Class I dentoskeletal malocclusion with vertical excess, mandibular left deviation, and asymmetry in soft tissues and hard tissues of the right zygomatic region treated with multisegment Le Fort I osteotomy, bilateral sagittal split osteotomy, and bilateral asymmetrical malarplasty with porous hydroxyapatite prosthesis.


purposes were considered the gold standard in the 1980s, they have since been abandoned because of donor site morbidity, the difficulty in modeling non-adaptable graft materials, and, in particular, the unpredictable results of graft volumetric maintenance.\textsuperscript{5,24-27} Brusati et al\textsuperscript{7} and Denny and Rosenberg\textsuperscript{8} who proposed using Le Fort III osteotomies to obtain esthetic results initially followed the method described by Tessier\textsuperscript{6} to harmonize facial disharmonies and his suggestions on modifying and simplifying those procedures. Those methods foresaw midfacial advancement, at times in conjunction with bone grafting and stabilization. Given the high surgical invasiveness of these procedures, the need for an extraoral (coronal sub-palpebral) approach, the technical difficulty in carrying them out, and controlling occlusal problems, they are no longer used in traditional orthognathic surgery and currently are used only in cases of malformations in pediatric patients. The low zygomatic maxillary osteotomy proposed by Bell et al\textsuperscript{28} in 1988 is a technique that corrects defects in a transverse direction of the zygomatic region,

### Table 2. VISUAL ANALOG SCALE OUTCOMES

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Natural Contour</th>
<th>Symmetry</th>
<th>Natural Feel</th>
<th>Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>76</td>
<td>85.83 ± 22.22;</td>
<td>85.68 ± 23.00;</td>
<td>80.30 ± 26.28;</td>
<td>84.41 ± 23.96;</td>
</tr>
<tr>
<td></td>
<td>95.19 (88.19, 99.91)</td>
<td>96.44 (87.14, 100)</td>
<td>92.10 (70.86, 99.39)</td>
<td>96.72 (79.77, 100)</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± standard deviation; median (quartiles 1, 3).


![Cone-beam tomogram, coronal slice, at 1 month after surgery.](image)

requiring an augmentation of the bizygomatic diameter, but also necessitating grafts composed of onlay bone grafting material (eg, HA granules) if an increase in the sagittal projection of the malar bone is clinically necessary. Traditional orthognathic and plastic surgeries have moved in the direction of using allogeneic material, or rather so-called implantable biomaterials. The ideal material should be biocompatible and osteoconductive and show a high degree of reabsorption that is predictable over time. More specifically, biocompatibility presupposes an inert chemical state, an absence of toxicity, an inability to induce hypersensitivity responses, and a low rate of infections.

Gore-Tex (polytetrafluoroethylene), a widely used prosthetic bone graft material, presents a sufficient degree of volumetric stability over time. Because it is preshaped, it is easily positioned and can guarantee satisfying esthetic results. However, it needs to be stabilized with screws, it is difficult to adapt it to the recipient site, and it is characterized by a relevant rate of infectious complications. Moreover, Gore-Tex implants remain slippery because there is no host tissue ingrowth and they carry an increased risk of infections, seroma formation, and extrusion. Although rigid screw fixation is a very effective and efficient method of fixing malar implants, there are complications, such as the pneumatocele described by Garner and Jordan. The low biocompatibility of the material probably plays a part in this type of complication.

Silicone derivatives likewise present a series of advantages and disadvantages. They are available in preshaped forms, are easily positioned, and do not need to be stabilized with screws, characteristics that explain their wide use. According to many investigators, such as Metzinger et al and Mommaerts et al, the percentage of residual malposition asymmetry varies from 15 to 35%. Nevertheless, silicone implants lack the potential for vascularized healing, promote thick capsule formation, cause resorption of the underlying bone, and display a tendency of shifting or extruding over long periods. In the present study, the complications were probably linked to the limited osteoconductive properties of the...
derivatives and to a chronic inflammatory reaction to extraneous bodies (chronic inflammatory peripheral reaction).

As in the cases cited earlier, Medpor (porous polyethylene) is a material that is widely used for surgical purposes and in trauma patients. It is preshaped and stable over time, but it is difficult to position,\textsuperscript{13} because of its rigidity, and to contour surfaces of complex skeletal structures. It needs to be stabilized with screws. The complication rate varies from 5 to 20\% and it is associated with a relatively large percentage of early- and late-onset infections (1 to 12\%).\textsuperscript{33,34} Medpor creates a fibrous capsule, it is not osteoconductive, and it is not very inert with respect to immunologic responses.\textsuperscript{14}

Different researchers have described using porous HA as onlay bone grafts for the facial skeleton.\textsuperscript{35,36} In a study by Moreira-Gonzales et al\textsuperscript{17} on the use of HA in procedures to contour the face, the percentage of complications was relatively small (5.6\%); more specifically, 4.3\% had contour irregularities and 1.3\% had infection and extrusion of granules requiring overcorrection of 15\% of the required volume. An animal study showed that, in contrast to the rapid resorption of autologous grafts, porous HA matrix had long-term permanence with maintenance of contour and osseous

Table 3. HISTOLOGIC EVALUATION OUTCOMES

<table>
<thead>
<tr>
<th>2-yr Postoperative Histologic Findings (19 Specimens)</th>
<th>%</th>
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<tbody>
<tr>
<td>Hydroxyapatite granules</td>
<td>100</td>
</tr>
<tr>
<td>Macrophages (foreign body reaction)</td>
<td>100</td>
</tr>
<tr>
<td>Fibrous stroma</td>
<td>50</td>
</tr>
<tr>
<td>New bone formation and mature trabecular bone</td>
<td>70</td>
</tr>
</tbody>
</table>

incorporation. Concerning the biocompatibility of HA, the results of a study by Campioni et al. showed that porous HA plus microfibrillar collagen was characterized by a high rate of cell proliferation and favored cell adhesion (Saos-2GFP) on its own surface. This would seem to satisfy the criteria necessary for biocompatibility, that is, the absence of toxicity and being chemically inert. Concerning long-term stability, porous HA seems to be stable in some conditions, such as not being placed under a functional load, which, of course, is the case at the zygomatic region or other areas subject to facial contouring. The authors also used porous HA for mandibular recontouring and paralateronasal and infraorbital augmentation, with satisfactory results. Another condition for stability is that it should not be attained by osteosynthesis. Stability seems to depend on an adequately sized subperiosteal pocket that holds the graft in place and prevents the granules from migrating to the soft tissues and adequate hemostasis at the recipient site; this will decrease intra- and postoperative bleeding so that the initial prosthetic volume is decreased. The graft’s stability also depends on the surgeon’s proficiency in view of the findings of malposition and partial resorption found in the present sample (1.36%) that were probably linked to a too-small or too-large subperiosteal pockets or inappropriate management of hemostasis. In the present cases, secondary correction was achieved by fat grafts harvested under local anesthesia. Fat grafts represent a good option for facial recontouring in orthognathic surgery, as discussed by others. Lipofilling generally presents with low morbidity, with only superficial bruising of the harvested areas or other minor complications, such as acute edema, ecchymosis, and redness, which have been described as relatively frequent. However, major adverse effects, such as blindness, also can occur, although at a much lower rate. Firm knowledge of the vascular anatomy is mandatory to prevent related complications. A certain amount of unpredictable resorption also has been observed. Compared with HA, the indications for fat grafting focus more on minor defects and on other areas of the face, such as nasolabial folds, marionette lines, cheeks, upper and lower lips, and labial tubercles. When using fat grafts for severe malar deficiency, it is generally difficult to achieve a satisfactory and stable result in symmetry and projection. The stability of HA appears to be linked to the material’s osteoconductive properties because it is gradually replaced by native bone tissue with a colonization gradient from the periosteum to the
basal cortical bone, as shown by the study’s histologic findings, which are in accord with the morphologic volumetric data described by Mendelsson et al.\textsuperscript{18} and Grybauskas et al.\textsuperscript{45}

The present radiologic findings confirmed that the prosthetic material changes over time; initially, it is radiotransparent with a granular structure, but over time shows increasing uniformity and radiopacity, which presupposes that the material will be resorbed and eventually replaced by cortical bone. A volumetric reduction of approximately 10 to 20\% of the original volume 18 to 24 months after the procedure was described by Mendelsson et al.\textsuperscript{18} and Grybauskas et al.\textsuperscript{45} and this is a factor that should be considered at the preoperative planning stage. The studies cited earlier also described how the biomaterial, after an initial compaction period of approximately 4 months, tends to achieve remarkable volumetric stability, with a negligible decrease in size during the follow-up observation period. The first cases of malar augmentation using HA were reported 10 years ago; those clinical outcomes are in line with the findings of the present study. However, the data could not be considered because of the lack of adequate records, mostly because at the time standard preoperative radiographic measurements were taken in 2 dimensions. Concerning the technical characteristics, the material is shaped by hand, which implies that it is possible to achieve various forms and dimensions according to the needs of the individual patient; this is particularly useful in cases of asymmetry of the zygomatic region. On the one hand, the preparation of the prosthesis has a relatively long learning curve compared with other preshaped biomaterials; on the other hand, the resulting naturalness and symmetry are excellent given the patients’ high VAS scores. Shortening intraoperative time might be possible with the use of preoperative CT planning of custom-made prostheses, although this would increase the overall cost of the treatment plan. A possible compromise might be the adoption of a ready-to-use prosthesis that can be adapted according to the patient’s needs. In contrast to other biomaterials, HA seems to be characterized by a low rate of early- and late-onset infections (0.2\%). This finding has been confirmed by other reports\textsuperscript{17} and is in agreement with the hypothesis that porous HA has an antibacterial effect.\textsuperscript{46} Colonization of bone tissue, the fact that screws are not needed to fix the prosthesis, and a high degree of biocompatibility\textsuperscript{47} contribute to limiting the occurrence of postoperative and long-term infectious phenomena. Concerning 1-piece and segmental Le Fort I osteotomies of the upper jaw, it should be remembered that healing of the osteotome site is seldom complete because of the long-term possibility of bacterial contamination through the nasal passages.

The present results represent the conjoined efforts of 2 centers specializing in the treatment of dento skeletal deformities and harmonization of facial contours. The large number of patients makes it one of the most extensive studies on this procedure found in the literature. In light of what has emerged from this study, porous HA seems to have excellent biocompatible and osteoconductive properties. In fact, the low rate of complications found and the radiologic, histologic, and molecular biological findings support this affirmation and are in agreement with data of other studies found in the literature. Porous HA prostheses for zygomatic augmentation led to long-term stable esthetic results, and most patients expressed a high degree of satisfaction. These advantages are counterbalanced by the relatively long time needed to prepare the prostheses and the long learning curve involved in creating the subperiosteal pocket and a slight hypercorrection, which seem necessary to address the short-term volumetric reduction. Given the characteristics described in this study, porous HA granules with microfibrillar collagen seems to be an excellent choice when surgery to harmonize the zygomatic region and to correct facial asymmetry is being planned.

References