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KEY WORDS
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Case series

HORIZONTAL AND VERTICAL COMPUTER GUIDED BONE REGENERATION WITH SLOW-RESORBING BOVINE PERICARDIUM MEMBRANE: CASE SERIES RESULTS ONE YEAR AFTER LOADING

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PURPOSE. To assess, 1 year after placement of definitive prostheses, the performance of implants inserted via a computer guided bone regeneration approach on ridges horizontally and vertically reconstructed with 50% bovine bone and 50% autologous bone, covered with 0.8-mm-thick slow-resorption bovine pericardium membrane.

MATERIALS AND METHODS. In this case series, severe horizontal bone defects in the posterior mandible (Cawood and Howell class IV) or maxilla were treated using a 1:1 mixture of autogenous bone and bovine bone, covered by slow-resorbing bovine pericardium membrane. Six months after augmentation, implant placement via a computer guided pilot drill approach was planned, based on a 3D reconstruction of the cone-beam computer tomography (CBCT) scan to assess the amount of regenerated bone. Patients were monitored for one year after the fitting of definitive prostheses. Primary outcome measures were implant and prosthesis survival rates and complications. Secondary outcome measures were horizontal and vertical dimensional changes and peri-implant marginal bone loss.

RESULTS. Twelve consecutive patients were enrolled, and 31 implants were inserted. One year after loading, no patients had dropped out. No implants or prostheses had failed during the entire follow-up, with only one early exposure of the membrane occurring. Six months after the regenerative procedure, the mean horizontal augmentation, measured at the middle of the augmented area, was 5.28 ± 1.81 mm (95% CI 4.26-6.30 mm), while the mean maximum horizontal augmentation was 5.39 ± 1.85 mm (95% CI 4.34-6.44 mm). The mean vertical augmentation, measured at the centre of the augmented volume, was 2.01± 1.06 mm (95% CI 1.41-2.61 mm), and the mean maximum vertical augmentation was 2.05 ± 1.04 mm (95% CI 1.46-2.64 mm). One year after loading, the mean marginal bone loss from implant placement was 0.36. ± 0.11 mm (95% CI 0.30-0.42 mm).

CONCLUSIONS. Within the limitations of the present case series, the use of slow-resorbing pericardium membrane combined with autologous bone and particulate bovine bone in a 1:1 ratio seems to permit the alveolar reconstruction of medium to severely horizontally resorbed ridges and provide minor vertical bone augmentation.

CONFLICT OF INTEREST STATEMENT

This case series was partially supported by the companies Ubgen and 3P Implafavourite. Silvio Mario Meloni, Marco Tallarico and Milena Pisano are scientific consultants to Ubgen. Silvio Mario Meloni and Milena Pisano are scientific consultants to 3P Implafavourite company. Computer Guided Bone Regeneration is a registered trademark.

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INTRODUCTION

Guided bone regeneration (GBR) is one of the most applied and viable methods of reconstructing alveolar bone and obtaining horizontal and vertical bone regeneration[1-4]. The use of membranes as a barrier has the ultimate goals of protecting the blood clot, preventing the invasion of non-osteogenic cells, and maintaining adequate and proper biological space for the regeneration of new bone[5-7]. Membranes can be resorbable, for example collagen membranes, or non-resorbable, for example PTFE membranes[8], and associated with heterologous and/or autologous bone grafts to obtain new bone formation[9,10].

The ideal desirable characteristics of membranes for GBR are: biocompatibility, cell occlusion properties, and capacity to integrate with the host, but also clinical manageability, space-maintaining capabilities, and appropriate mechanical and physical properties[11,12].

Non-resorbable membranes represent the first generation of barriers used in GBR[13]. These barriers meet all the previously listed requirements; however, they have the major limitations of the need for a second surgery to remove them and a high possibility of infection in the event of exposure[14-16]. Resorbable membranes, on the other hand, resorb rapidly when exposed, thereby reducing the risk of bacterial infection. Unlike non-resorbable membranes, they do not require a second surgery[17,18] the main limitation of resorbable membranes is their fast degradation rate, especially in vertical bone augmentation, which could lead to insufficient bone regeneration[19,20].

That being said, the use of collagen resorbable membranes in one- and two-stage horizontal augmentation procedures has been well documented by several studies[21-25]. Nowadays, research is focused on the use of potentially better performing membranes of animal origin, such as those in bovine pericardium. In addition to properties such as acellularity, biocompatibility and resorption capacity, bovine pericardium seems to have the additional advantages of easy handling and elasticity[26].

Moreover, the cross-linking process improves the stability of collagen matrices, without interfering with cellular ingrowth and angiogenesis[27,28]. Bovine pericardium has long been used in vascular surgery, for cardiac repairs and valve reconstruction and repair[29,30], but has only recently been introduced in bone regeneration procedures. As such, the literature in humans is scarce, although results from an animal study were promising[26].

The aim of this case series was to assess the performance of implants inserted via a computer guided bone regeneration approach[31] on alveolar ridges horizontally and vertically reconstructed with 50% bovine bone 50% autologous bone covered by 0.8-mm-thick slow-resorbing bovine pericardium membrane.

This paper reports the results 1 year after loading with the definitive prostheses in accordance with the STROBE guidelines (https://www.strobe-statement.org/checklists/).

MATERIALS AND METHODS

This case series aimed to assess patients treated for severe horizontal bone defects in the posterior mandible or maxilla via computer guided bone regeneration, 6 months before implant placement. Patients were selected and treated at one private centre in Sardinia (Italy) from December 2019 to October 2020. One clinician performed all surgical procedures (S.M.M.). Another clinician (M.P.) fitted all prosthetic restorations. All patients gave their informed written consent to treatment.

Any patient aged 18 years or older affected by partial or total posterior edentulism of either the mandible or maxilla with a residual horizontal ridge thickness of 4 mm or less (Cawood-Howell Class IV)[32] who requested implant-supported restoration and were able to understand and sign informed consent was treated.

Patients were not treated if any of the following exclusion criteria applied:

- American Society of Anesthesiologists (ASA) class III or IV;
- Pregnancy or nursing;
- Alcohol or drug abuse;
- Heavy smoking (>10 cigarettes/day);
- Radiation therapy to head or neck region in the previous 5 years;
- Absence of teeth/denture in the opposing jaw;
- Untreated periodontitis;
- Implants to be fitted immediately post-extraction;
- Full mouth bleeding and full mouth plaque index of 25% or higher;
- Unavailability for regular follow-ups.

Surgical and prosthetic protocol

Patients' medical history, photographs and study models were collected at the first visit. A pre-operative cone-beam computed tomography (CBCT) scan was obtained for the initial screening (**FIGS. 1, 2**), and a virtual wax-up was generated to evaluate the ideal implant position and the bone volumes to be regenerated (**FIG. 3**).

Patients received 2 g amoxicillin plus clavulanic acid (Augmentin, GlaxoSmithKline, London, UK) 1 hour before augmentation surgery, and 1 g twice daily for 1 week thereafter. In the event of penicillin allergy, 600 mg clindamycin was administered 1 hour before surgery, and 300 mg four times a day for 1 week after surgery.

Patients were instructed to rinse with 0.2% chlorhexidine solution (Curasept, Curaden Healthcare, Saronno, Italy) for 1 minute before surgery, and a sterile surgical drape was applied to minimize potential contamination from extra-oral sources. Oral sedation with triazolam 0.50 mg (Triazolam Ratiopharm, Milan, Italy) was given prior to surgery, which was carried out under local anaesthesia (Septanest with adrenaline, 1/100,000, Septodont, Mataró, Spain).

A midcrestal incision was made into the keratinized tissue using a surgical blade No. 15, and a full-thickness flap was raised beyond the mucogingival junction, at least 5 mm beyond the bone defect. Two vertical incisions were placed at least one tooth mesial and distal from the area to be augmented, while, in edentulous areas, vertical incisions were placed at least 5 mm away from the planned surgical site, into the retromolar pad. In the posterior mandible, a lingual flap was raised safeguarding sensitive anatomical structures. Before bone collection, the recipient site was debrided by removing soft tissue remnants.

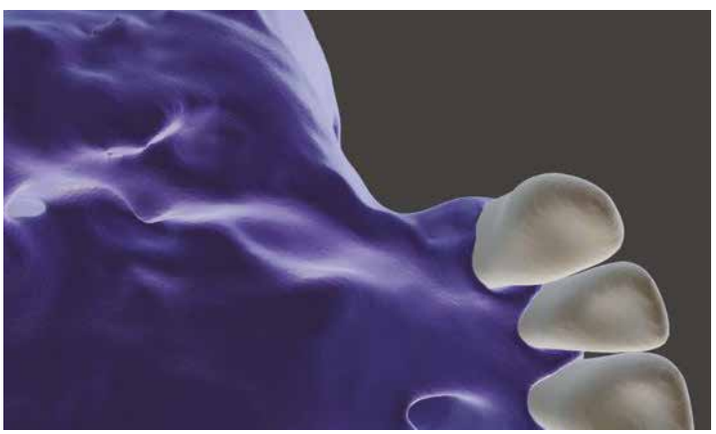

FIG. 1: *Pre-operative 3D CBCT reconstruction, occlusal view*

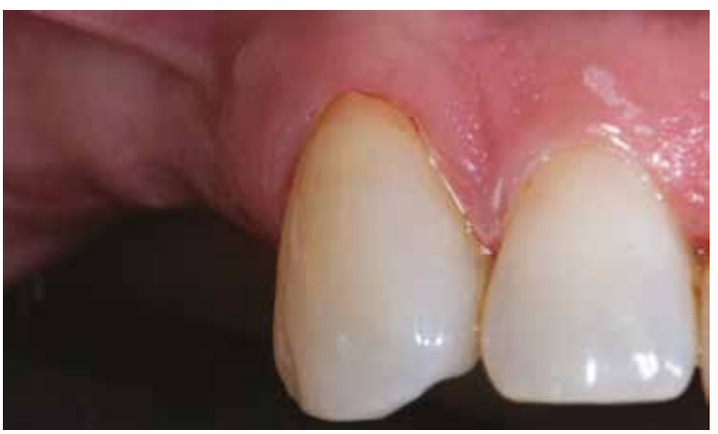

FIG. 2: *Pre-operative clinical view*

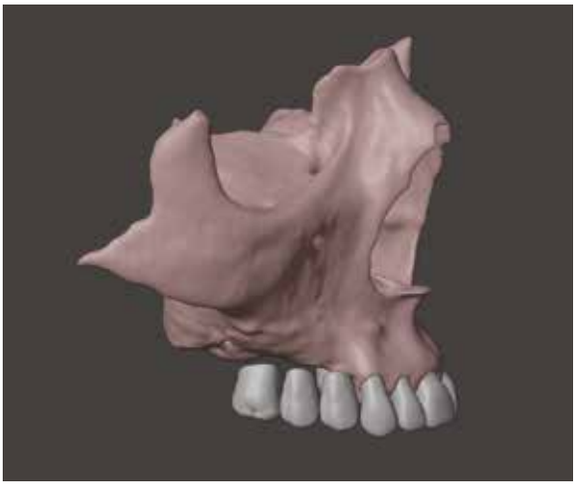

FIG. 3: *Pre-surgical virtual wax-up to visualize the bone augmentation requirement, lateral view*

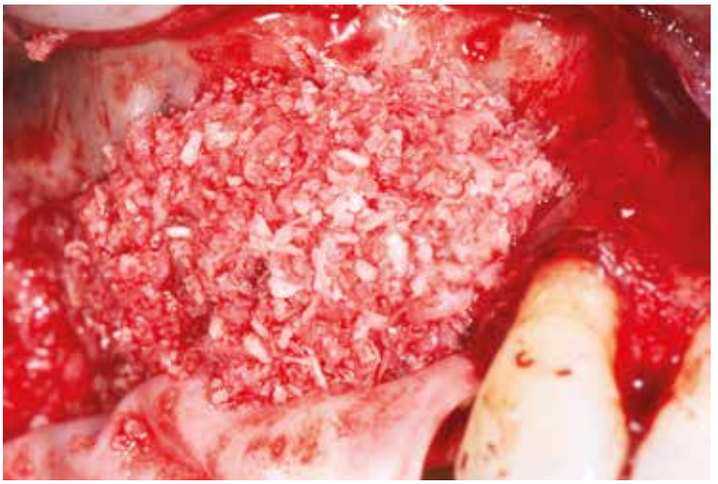

FIG. 4: *Autologous bone mixed with bovine bone (50 to 50%) and pericardium membrane*

Autogenous bone was harvested from the retromolar regions of the mandible using a minimally invasive cortical bone collector (Micross, Meta, Reggio Emilia, Italy). At maxillary sites, an additional flap was raised for the bone harvesting procedure. After that, multiple decortications were made at the recipient site with a 2 mm round bur. A slow-resorption 0.8-mm-thick cross-linked bovine pericardium (Ubgen, Vigonza, Italy) membrane was then fixed using two lingual/palatal titanium pins (3P Implafavourite, Scalenghe, Italy).

The harvested particulate autogenous bone material was mixed with bovine bone (Re-bone Ubgen) in a 1:1 ratio, and placed at the buccal and lingual/palatal sides of the defect and carefully packed vertically over the crest (**FIG. 4**).

At this stage, the bovine pericardium membrane was trimmed to cover the entire volume of the graft, and two additional titanium pins were placed on the buccal side to fix the membrane. After pushing the graft material over the native crest, a third pin was placed in the mid-buccal side to prevent apical movement of the bone graft (**FIG. 5**).

Where indicated, maxillary augmentation was combined with a conventional lateral sinus lift procedure to achieve additional apical bone height for subsequent implant placement.

Finally, a periosteal incision was performed between the two vertical incisions to allow completely tension-free flap closure. In the mandible, both the lingual and the buccal flaps were released with respect of the anatomical structures. The flaps were sutured in two layers to prevent exposure of the membrane; horizontal mattress sutures were first placed 4 mm from the incision line, and then single interrupted sutures were placed to close the edges of the flap. Vertical incisions were sutured with single e-PTFE 4-0 interrupted sutures (Elastin, Braun Italia, Milan, Italy).

Postoperatively, 80 mg of ketoprofen (Oki, Dompé, Milan, Italy) as needed was prescribed. A four mg/day regime of betamethasone (Bentelan, Glaxo, Verona, Italy) was administered for two days. The patient was instructed to rinse with 0.2% chlorhexidine (Curasept) three times per day for two weeks, and to eat only soft food for 30 days.

The single interrupted sutures were removed 14 days after surgery, and mattress sutures were removed two to three weeks after surgery.

Six months after bone healing, a CBCT scan was taken and 3D rendering generated to assess the regenerated bone, and to plan implant sizes and positions. A virtual wax-up was made, taking into consideration all the anatomical landmarks and the prosthetics plan (**FIG. 6**).

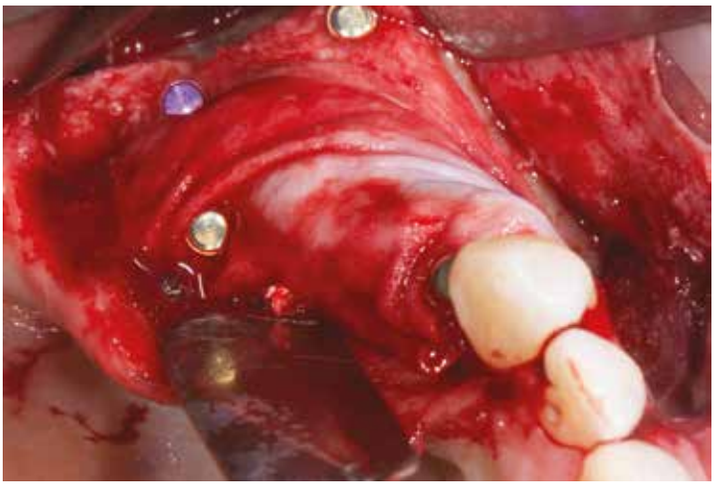

FIG. 5: *Slow-resorption 0.8 mm-thick pericardium membrane trimmed and fixed with titanium pins*

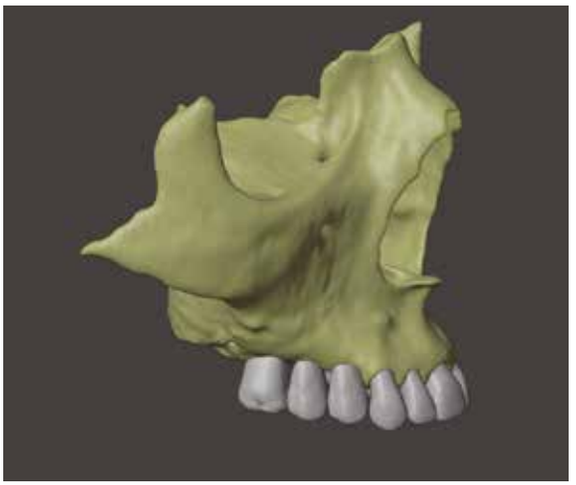

FIG. 6: *Virtual wax-up 6 months after bone regeneration, to determine the correct implant positions*

Pilot holes were drilled according to the computer-assisted implant installation plan, and implants (Cono-in 3P Implafavourite) were installed with an insertion torque of 30 to 35 Ncm (**FIGS. 7-10**).

Two to three months after implant placement, apical repositioning flaps, (**FIGS. 11, 12**) or free-gingival graft were performed, and screw-retained resin prostheses were fitted one month later. Three months thereafter, permanent zirconia-ceramic crowns were fitted.

All patients were followed up for at least one year after placement of definitive prostheses. Data were collected at implant placement and 12 months after placement of definitive prostheses (**FIGS. 13, 14**). Hygiene maintenance and occlusal checks were scheduled every 6 months.

Outcome measures

Implant and prosthesis survival rates and complications were the primary outcome measures.

- *Implant failure*: any removal of implants dictated by implant mobility, progressive marginal bone loss, infection, or implant fracture. The stability of individual implants was measured by the prosthodontist at the time of definitive prosthesis fitting, applying a removal torque of 35 Ncm. After loading, implant stability was tested manually, with two dental mirror handles, by the same prosthodontist.
- *Prosthesis failure*: any prosthesis which had to be replaced for any reason.
- *Any surgical, prosthetic or biological complications*: including membrane exposure, subsequent infection, and/or morbidity associated with the donor site, any fracture or chipping of the provisional or definitive ceramic crown, abutment mobility, wound or implant infection, mucositis, abscesses, or peri-implantitis. Complications were assessed, recorded and treated by the same clinicians who performed the augmentation and implant or prostheses placement procedures, as applicable.

Secondary outcome measures were horizontal and vertical dimensional changes, and peri-implant marginal bone loss. As regards the former, bone augmentation was measured by superimposition of two CBCT scans, one taken before the surgery and the other six months later. The DICOM files were imported into dedicated software (Relu BV, Leuven, Belgium).

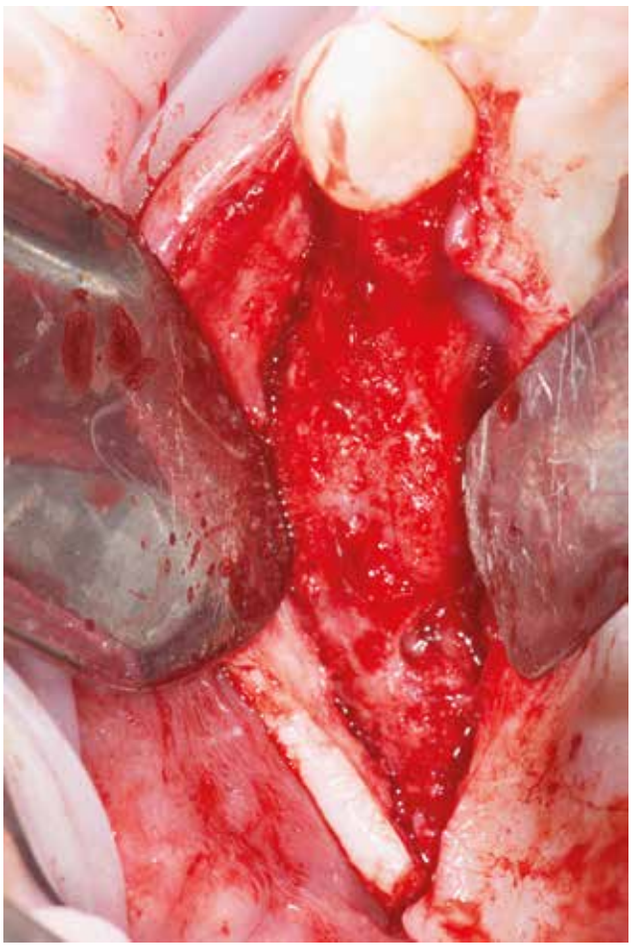

FIG. 7: *Alveolar crest before implant installation 6 months after bone reconstruction*

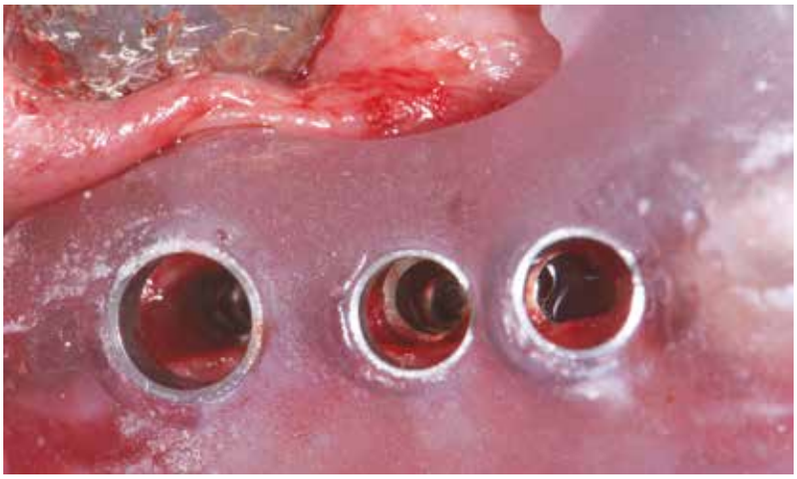

FIG. 8: *Guided implant installation*

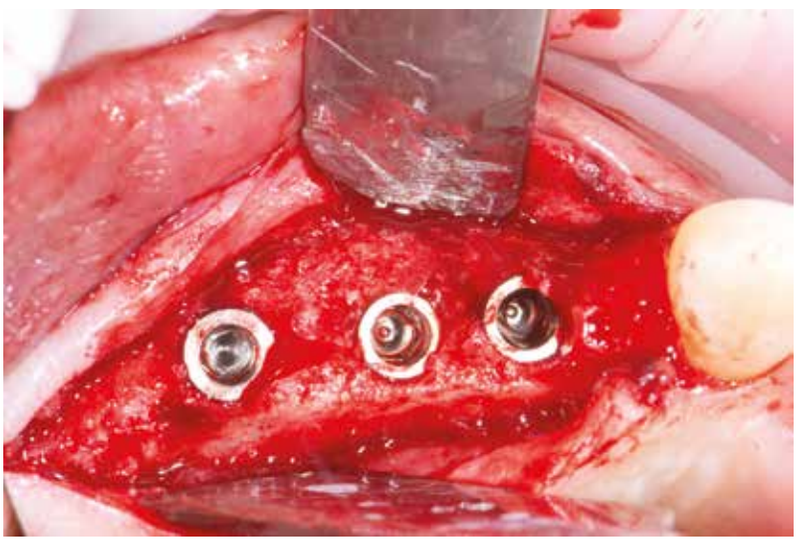

FIG. 9: *Alveolar crest after implant installation*

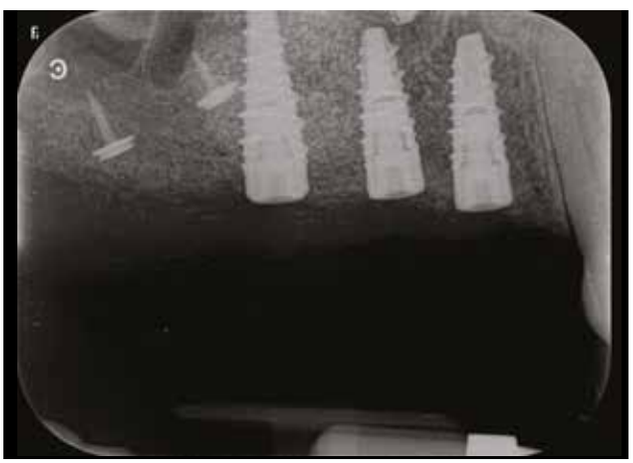

FIG. 10: *Peri-apical radiograph at implant installation*

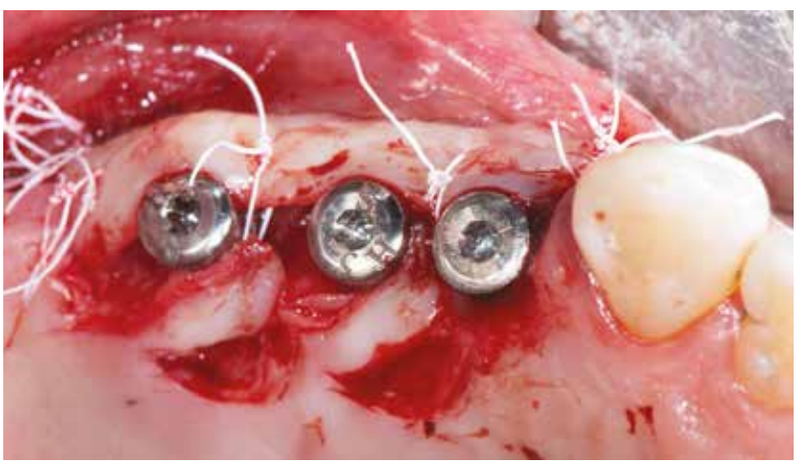

FIG. 11: *Split-thickness apical repositioning flap to increase the keratinized tissues*

FIG. 12: *Soft tissue after healing*

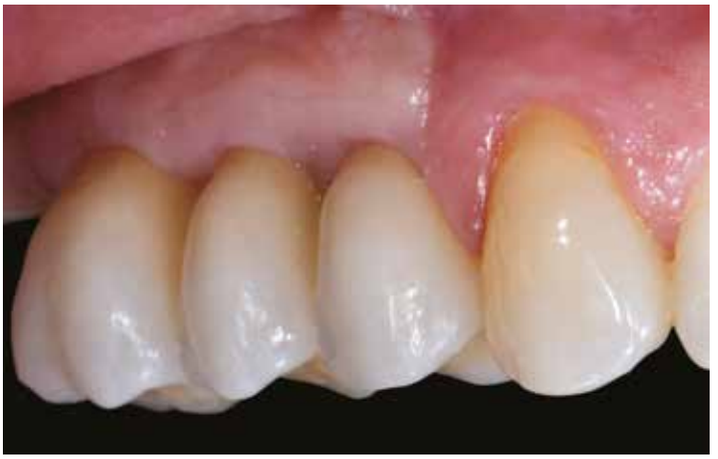

FIG. 13: *Screw-retained zirconia-ceramic prosthesis 1 year after placement of definitive prostheses*

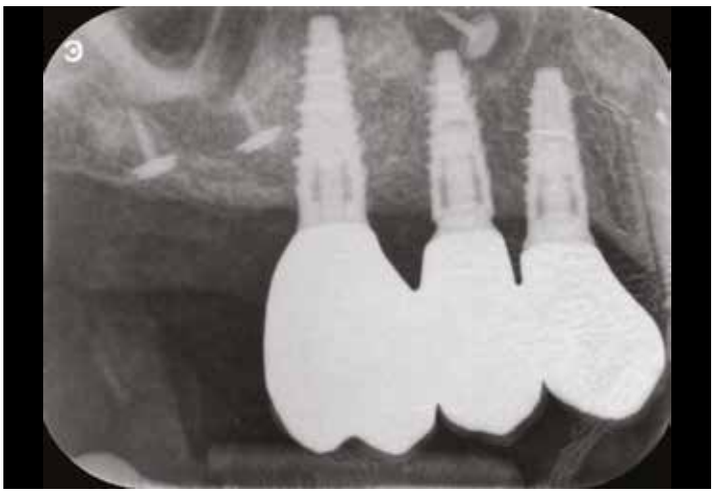

FIG. 14: *Peri-apical x-ray 1 year after placement of definitive prostheses*

Segmentation of the DICOM data was performed to create STL files. Then, the 3D mesh objects generated were matched point by point using the same regions of interest. The matching was then improved using a best-fit algorithm (Ortogonblender, Blender, Amsterdam, Holland). Finally, horizontal and vertical augmentation were measured at the centre of the augmented volume and at the the greatest horizontal and vertical dimensions (3D Clinical Viewer, Sassari, Italy) (**FIGS. 15, 16**).

Peri-implant marginal bone loss was calculated on digital periapical radiographs taken using a film-holder (Rinn XCP, Dentsply, Elgin, Illinois, USA) via the paralleling technique, first at implant placement (baseline) and then at one year after placement of definitive prostheses. The radiographs were accepted or rejected for evaluation based on the clarity of the implant threads. The distance from the most coronal margin of the implant collar to the most coronal point of bone-to-implant contact was calculated. All readable radiographs were displayed by an image analysis programme (DFW2.8 for windows, Soredex, Tuusula, Finland) on a 24-inch LCD screen (iMac, Apple, Cupertino, CA, USA) and evaluated under standardized conditions (SO 12646:2004).

The software was calibrated for each single image using the known distance between two adjacent implant threads. Measurements of the mesial and distal bone crest level adjacent to each implant were made to the nearest 0.01 mm, and averaged at patient level.

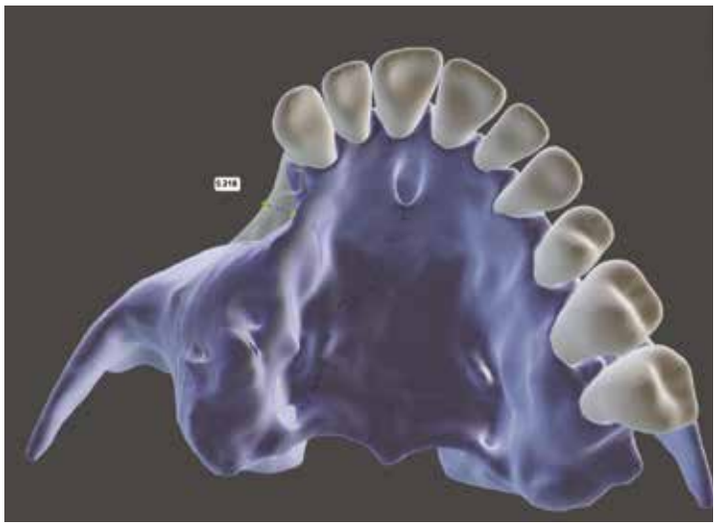

FIG. 15: *3D reconstruction of horizontal bone augmentation, maximum value measurement*

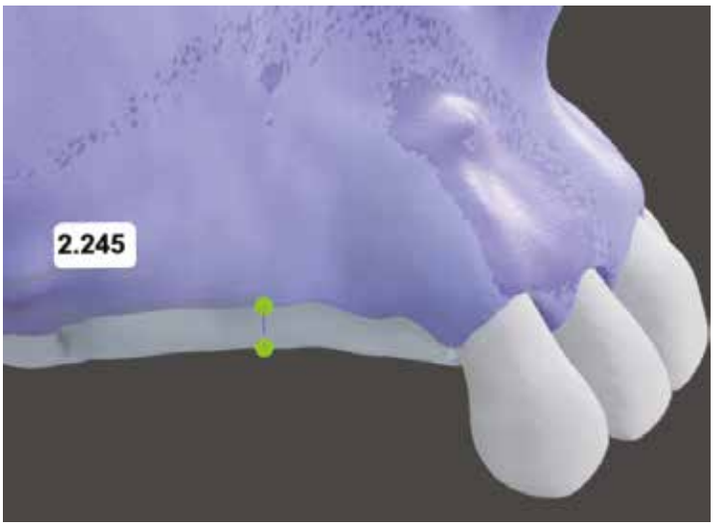

FIG. 16: *3D reconstruction of vertical bone augmentation, maximum value measurement*

Statistical analysis

All analysis was carried out according to a pre-established analysis plan using SPSS software for Mac OS X (version 22.0; SPSS, Chicago, Illinois, USA). A dentist (M.T.) analysed the data. Descriptive analysis was performed for numeric parameters using mean ± SD and 95% confidence interval (CI). Difference in mean marginal bone levels over time was compared using paired t-tests.

The patient was the statistical unit of the analyses. Multiple implants were averaged at patient level. All statistical comparisons were conducted at the 0.05 level of significance.

RESULTS

Twelve consecutive patients (3 males and 9 females) with a mean age of 53.2 years received one GBR procedure each. Overall, 31 implants of diameter 4.5 or 3.8 mm and length 12 to 8 mm were inserted. Four procedures were performed in mandibles and eight in maxillae. Of these, five procedures were combined with sinus lift.

No patient dropped out before the follow-up examination 1 year after placement of definitive prostheses. No implants or prostheses failed during the entire follow-up. Only one early surgical complication occurred, with the bovine pericardium membrane becoming exposed about 10 days after augmentation; the area was treated via local application of chlorhexidine gel 0.5% (Curasept ADS 0.5%) twice per day for 3 weeks. Complete soft tissue healing was observed. No other biological or technical complications were recorded during the entire follow-up period.

The mean horizontal augmentation measured at the centre of the augmented volume was 5.28 ± 1.81 mm (95% CI 4.26-6.30 mm; **TABLE 1**). The mean maximum horizontal augmentation was 5.39 ± 1.85 mm (95% CI 4.34-6.44 mm; **TABLE 1**).

The mean vertical augmentation measured at the centre of the augmented volume was 2.01± 1.06 mm (95% CI 1.41-2.61 mm; **TABLE 1**), while the mean maximum vertical augmentation was 2.05 ± 1.04 mm (95% CI 1.46-2.64 mm; **TABLE 1**).

One year after definitive loading, the mean marginal bone loss from implant placement was 0.36. ± 0.11 mm (95% CI 0.30-0.42 mm; **TABLE 2**).

TABLE 1 HORIZONTAL AND VERTICAL BONE AUGMENTATION

	Mean value at centre of augmentation	Mean of maximum values
Vertical augmentation	2.01 ± 1.06 mm (95% CI 1.41-2.61 mm)	2.05 ± 1.04 mm (95% CI 1.46-2.64 mm)
Horizontal augmentation	5.28 ± 1.81 mm (95% CI 4.26-6.30 mm)	5.39 ± 1.85 mm (95% CI 4.34-6.44 mm)

TABLE 2 PERI-IMPLANT MARGINAL BONE LEVELS/LOSS IN MM

	Implant placement (n = 12)	1 year (n = 12)
Marginal bone levels	0.01 ± 0.03 (95% CI: -0.01-0.01)	0.38 ± 0.10 (95% CI: 0.33-0.43)
Marginal bone loss		0.36 ± 0.11 (95% CI: 0.30-0.42)
P value		0.000

DISCUSSION

This case series was treated with the aim of assessing the performance of implants installed in accordance with a computer guided bone regeneration approach[31] in atrophic ridges reconstructed with 50% autologous bone and 50% bovine bone covered with 0.8-mm-thick slow-resorbing bovine pericardium membranes. The results showed a mean horizontal bone gain of 5.3 mm and vertical bone gain of 2.0 mm, and no implant failures, demonstrating the good performance of slow-resorption bovine pericardium membranes for bone regeneration purposes.

Most of the studies on bovine pericardium membranes carried out to date have been in the cardiovascular field[29]. As far as bone regeneration is concerned, these membranes have mainly previously been tested in animal models, both *in vitro* and *in vivo*[26]. For instance, Bai et al.[26] tested the capability of decellularized bovine pericardium to regenerate standardized bone defects in rabbit mandibles. They found substantially greater augmented bone volumes as compared to defects left to heal spontaneously. Thomaidis et al.[33], in a comparative study on rabbit mandibles, found that bovine pericardium had a similar bone regeneration capacity to PTFE membranes, human pericardium, and human fascia alata membranes.

To the best of our knowledge, only a couple of dentistry studies have clinically investigated the performance of bovine pericardium, one in alveolar ridge augmentation[34], and one for the treatment of dehiscence defects[35]. These studies had different designs: Steigmann[34] evaluated bone augmentation performed via a two-stage approach, combining the bovine pericardium membrane with two different kinds of xenograft, which yielded a mean horizontal bone augmentation of 3.03 mm. However, that report did not present data on implant/prosthesis success or marginal bone remodelling. Moreover, bone augmentation was evaluated using a periodontal probe, and in some cases the implant installation was associated with 1-stage bone augmentation, while in other cases the procedure was delayed. Fu et al.[35], on the other hand, studied the use of bovine pericardium on small horizontal bone defects, such as implant dehiscence, in a randomized controlled trial of allograft covered by a pericardium membrane (test group, 13 patients) *vs.* allograft without membrane (control group 13 patients). They found significantly greater bone augmentation in the test group than in the control group at points 2, 4 and 6 mm from the top of the bone crest. In the test group there were increases of 1.27 ± 0.34 mm 2 mm below the bone crest, 2.81 ± 0.45 m 4 mm below the bone crest, and 3.25 ± 0.39 mm 6 mm below the bone crest, while in the control group there were respective increases of 0.15 ± 0.26 mm, 0.60 ± 0.43 mm and 0.81 ± 0.49 mm (P value <0.05). These two reports differ from our study, which assessed severely resorbed ridges reconstructed in accordance with a well-documented surgical protocol[21,22,25].

That being said, there were several limitations associated with our case series, namely the nature of the study, the small sample size, and the relative short follow up. However, to the best of our knowledge, it is the first report documenting vertical bone augmentation using slow-resorbing bovine pericardium membrane. This data requires confirmation by comparative randomized trials.

CONCLUSIONS

Within the limitation of the present case series, slow-resorption pericardium combined with 50% autologous bone mixed with 50% particulate bovine bone seems to permit the horizontal reconstruction of severely resorbed ridges and allow minor vertical bone augmentation.

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