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Customized-3D zirconia barriers for guided bone regeneration (GBR): clinical and histological findings from a proof-of-concept case series

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ABSTRACT

Objectives. The aim of this case series was to evaluate, clinically and histologically, customized-3D zirconia barriers manufactured for guided bone regeneration (GBR) procedures. **Methods.** Seven healthy consecutive patients with severe bone atrophy (two of them with a bilateral atrophy) were selected for a GBR procedure with a zirconia barrier. In a 3D software (DentalCad, Exocad GmbH, Germany), a virtual bone graft was designed and a shell was designed covering the graft; a standard tessellation language (.STL) file was obtained and milled (M1, Zirkonzahn, Italy) using a 1200 MPa zirconia (Prettau, Zirkonzahn, Italy). Nine GBR surgeries (8 upper-posterior jaw, 1 lower-posterior jaw) were performed using autogenous bone chips mixed with xenograft (SmartBone, IBI-SA, Switzerland / BioOss, Geistlich, Switzerland) covered with a zirconia barrier, fixed by means of screws. After healing, implant sites were prepared with a trephine bur, collecting a bone biopsy, and dental implants were inserted (Neodent, Straumann Group, Switzerland). Specimens were histologically analyzed. **Results.** Eight successful surgeries were recorded; one zirconia barrier got exposed after one month of healing but no signs of infection were present till the barrier was removed. In all cases it was possible to insert implants with no additional bone augmentation procedures. Histological evaluations showed the presence of intense deposition of new bone. **Conclusions.** Within the limitations of the present case series, the tested customized-3D zirconia barriers confirmed good clinical and histological performances, and, even in case of premature exposure, did not show signs of infection. Preliminary results suggest they are effective for GBR procedures. Further research is necessary with a larger sample size. **Clinical significance.** The presented barriers could be a viable alternative to titanium-reinforced polytetrafluoroethylene membranes and customized meshes.

1. Introduction

There are several different surgical techniques available for augmenting jaw bone horizontally and/or vertically. They include osteodistraction, inlay and onlay bone grafting, and guided bone regeneration (GBR) procedures [1–4].

Guided bone regeneration GBR has become a well-established approach. Its biological rationale is based on mechanically excluding soft tissues from growing into an osseous defect and letting bone cells only grow into the defect [5]. Since its introduction, a number of technical variations have been proposed [1,6–11]. Over the recent years, a wide range of resorbable and non-resorbable biocompatible barriers have been introduced to improve new bone formation. They aim at stabilizing blood clot and at underlying bone graft, thus minimizing the risk of collapsing for the newly-formed ridge. Also, the risk of the space being occupied by ingrowing soft tissue is reduced [12–15].

Every barrier type has both advantages and disadvantages. Various resorbable and non-resorbable materials, such as polytetrafluoroethylene (PTFE), expanded PTFE (e-PTFE), high density PTFE (d-PTFE), titanium meshes, collagen, polylactic acid, polyglycolic acid, and their copolymers have been tested in several experimental and clinical studies [16–19].

As far as their capacity to grow new bone is concerned, it is well established that non-resorbable membranes are more effective than the resorbable ones [20–22]. Nowadays, the d-PTFE membranes represent the gold standard for GBR together with the increasingly popular customized-3D titanium meshes [23,24]. However, both these barrier materials are associated with complications, such as exposure and/or

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infection, which could impair the outcome of the GBR procedure [25–27]. Furthermore, both non-resorbable membranes and titanium meshes need to be removed. Such removal procedures can be time consuming and invasive because of fibrous tissue ingrowth in their micro and macroporosity.

Zirconia is a polycrystalline ceramic used in the fabrication of dental prostheses and dental implants. This material has interesting features. It is bioinert and it shows high flexural strength even at very thin thicknesses [28–31]. Compared to titanium, it induces a better fibroblast response, it shows less biofilm adhesion and less inflammation response [32].

In order to overcome the limitations of non-resorbable membranes and titanium meshes, zirconia can be considered as an alternative and innovative material suitable for GBR because it has high biocompatibility, together with a scarce tissue integration. This proof-of-concept case series aims at showing how customized-3D zirconia barriers could be a predictable and alternative barrier material for GBR in terms of (i) biocompatibility, (ii) ease of use and removal, (iii) exposure management, (iv) bone regeneration outcomes.

2. Materials and methods

2.1. Study design

The present study is a case series of clinical trials conducted at one clinical center in conformity with the Good Clinical Practice Guidelines (GCPs), following the recommendations of the World Medical Association Declaration of Helsinki–ethical principles for medical research involving human subjects as revised in Fortaleza (2013). All patients had been informed about the benefits and the possible risks of the GBR procedure and its alternatives. A signed written consent was obtained from all the patients.

2.2. Case series presentation

All the surgeries were performed by the same operator (FM), an expert in oral surgery and bone regeneration. Seven healthy consecutive patients with severe bone atrophy, who needed bone augmentation and implant placement, were selected for a GBR procedure with a zirconia barrier (Fig. 1). Two of them underwent a bilateral bone augmentation. The total number of treated sites was nine: eight surgeries were performed at the upper jaw and one at the lower jaw. A cone beam computed tomography (FoV: 10 × 8 cm, 70 kV, Giano NewTom, Cefla, Imola, Italy) was prescribed as a pre-operative radiograph in order to obtain a 3D model of the alveolar jaw bone (Fig. 2A).

A bone graft was designed in a 3D software (DentalCad, Exocad, Darmstadt, Germany) according to the planned position of the prosthesis. A 0.4–0.5 mm-thick barrier was then designed (Fig. 2B). It covered the planned bone graft (Exocad GmbH, Germany) and extended a few millimeters wider than the graft perimeter. 1.6 mm-wide fixation screws were planned, according to the available bone, and holes in the mesh were created. An STL file was generated and sent to a CAM software. Next, the mesh was milled and sintered (M1, Zirkonzahn, Gais, Italy) using a 1200 MPa zirconia disk (Prettau, Zirkonzahn, Gais, Italy). After milling and finishing, the zirconia meshes were cleaned, disinfected and sterilized following the steps reported in Table 1.

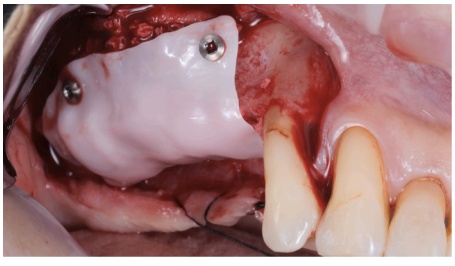

Fig. 1. Customized-3D zirconia barrier for guided bone regeneration (GBR).

2.3. Surgery

Local anesthesia with a 4% solution of articaine and 1:100.000 epinephrine was performed. Then, a full thickness flap of the atrophic area was elevated (Fig. 2C). A try-in of the barrier was performed before grafting the area in order to verify whether its adaptation to the recipient site was correct. Autogenous bone chips were collected with a bone scraper (SafeScraper, META) and mixed with a xenograft (Bio Oss, Geistlich, Wolhusen, Switzerland or Smart Bone, IBI-sa, Mezzovico-Vira, Switzerland) at a 40:60 ratio.

A part of the graft was placed into the atrophic area and the other part of it was placed into the inner side of the barrier (Fig. 2D). The barrier was then placed into the mouth of the patient and, according to the clinical situation, two or three fixation screws were tightened at 10 N/cm (Fig. 2E).

Releasing incisions of the flaps was the next step in the procedure. Then, suturing was performed with single and horizontal mattress sutures (Fig. 2F). Antibiotics (Augmentin, GlaxoSmithKline, London, Great Britain - 1 g, b.i.d., 6 days), painkillers (Synflex, Almirall, Milano, Italy - 550 mg, b.i.d., 3 days) and a 0,12% chlorhexidine rinse (Curasept, Curasept SpA, Saronno, Italy) were prescribed. Finally, sutures were removed after ten days.

After 5-8 months of a healing period, according to the extension of the atrophy, a post-operative CBCT was performed to assess the effectiveness of the GBR procedure (Fig. 2G). A second surgery was performed: a full-thickness flap was elevated, fixation screws were removed together with the zirconia barrier (Fig. 2H) (VIDEO 1).

Dental implants were placed according to the treatment plan (Fig. 2I). To prepare the implant beds, the osteotomy was initially made using a 3 mm-diameter trephine bur, instead of the pilot drill. It was finalized, as suggested by the manufacturer, by a drilling sequence with a final drill of 3.75 mm in diameter.

The bone-core biopsies were harvested from the sites where dental implants were to be inserted. A total of 17 implants were placed (Neodent GM Helix, Straumann Group, Basel, Switzerland) and flaps were closed with primary intention (Fig. 3A). After three months of healing, implants were uncovered (Fig. 3B) and an impression for provisional prosthesis was taken. PMMA provisional crowns were delivered (Fig. 3C and D) the following week and the definitive crowns were delivered after three months of functional loading (Fig. 3E, F and G).

2.4. Histological analysis

The bone cores, left inside the trephine burs to maintain the orientation, were carefully rinsed with a cold 5% glucose solution to remove blood while maintaining the correct osmolarity (278 mOsm/L).

The specimens were fixed in 10% formalin solution at pH 7.2 for a week, and dehydrated with a graded series of alcohols.

After the pre-infiltration treatment in a 50% resin/alcohol solution (Technovit 7200 VLC, Kulzer, Hanau, Germany) for ten days, the bone cores were easily removed from the trephine burs with a custom-made plunger. They were then completely embedded in 100% resin until the specimens became transparent. Finally, the bone cores were oriented and polymerized.

A high-precision cutting system (TT System, TMA2, Grottammare, Italy) with a circular diamond blade was used to prepare the sections of the specimens along the longitudinal axis of about 50 microns in thickness.

The sections were subsequently ground down to about 30 ± 10 microns under running water with a series of polishing discs, which was followed by a final polish stage using 0.1 micron of alumina particles in a micro grinding system (TT System, TMA2, Grottammare, Italy).

The prepared sections were stained with toluidine blue and fuchsin

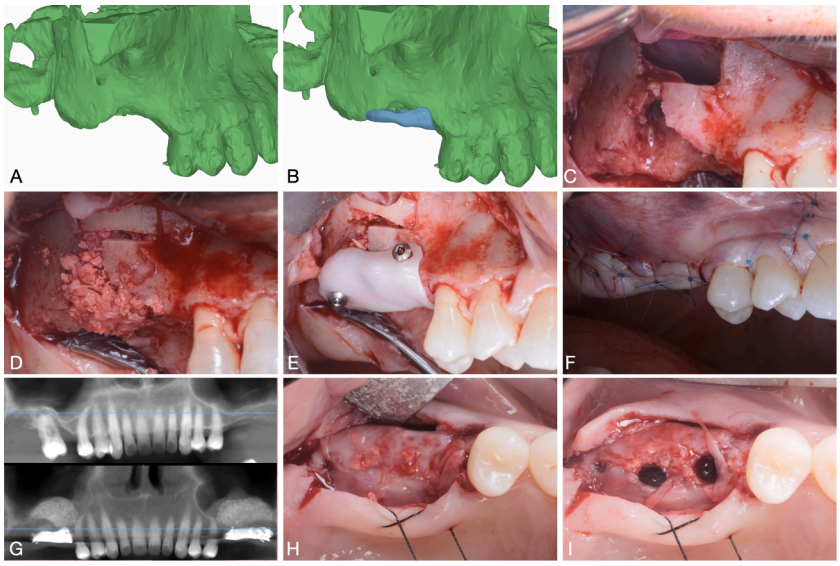

Fig. 2. Step-by-step procedure: (A) Segmentation of a pre-operative CBCT scan (B) Design of a customized-3D barrier (in blue) to correct the vertical defect (C) Flap elevation (D) Autogenous bone chips and xenograft in place (E) Zirconia barrier fixated with two screws (F) Flap suture (G) Pre- and post-operative CBCT panoramic view (H) Augmented area after barrier removal (I) Implant sites preparation (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

Table 1
Cleaning, disinfection and sterilization procedures applied to customized-3D zirconia barriers.

Procedure	Step 1	Step2	Step3
Cleaning	Rinsing under flowing water with adequate brushes in outer and inner sides.	Ultrasonic bath for 15 min at 35 °C in a enzymatic detergent solution (Cidezyme, Johnson & Johnson) 8 ml/liter in deionized water	Rinsing under fresh water to remove residual detergent
Disinfection	Immersion for 12 min at 20 °C in pure CIDEX® OPA Disinfectant Solution (Johnson & Johnson)	Rinsing at least three times with highly purified deionized water.	Packaging: Insert the cleaned and disinfected zirconia mesh in a single-use sterilization package
Sterilization	Autoclave (moist heat) with fractionated pre-vacuum at 134 °C, for 18 min. Drying time: 15 min.		

acid.

The investigation was conducted in a transmitted brightfield/circularly polarized light microscope (BX 51, Olympus America, Center Valley, USA) connected to a high-resolution digital camera (FinePix S2 Pro, Fuji Photo Film, Minato, Japan).

The histologic analysis was performed by means of a software package with image capturing capabilities (Image-Pro Plus 6.0, Media Cybernetics Inc, Bethesda, MD, USA) carried out by a trained and experienced operator (TT).

To ensure accuracy, the software was calibrated for each experimental image using 'Calibration Wizard', a feature that reports on the number of pixels between two selected points of a micrometer scale. The linear remapping of the pixel numbers in microns was used to calibrate the distance.

3. Results

A total of seven patients, 5 females, 2 males (mean age: 63.1 years

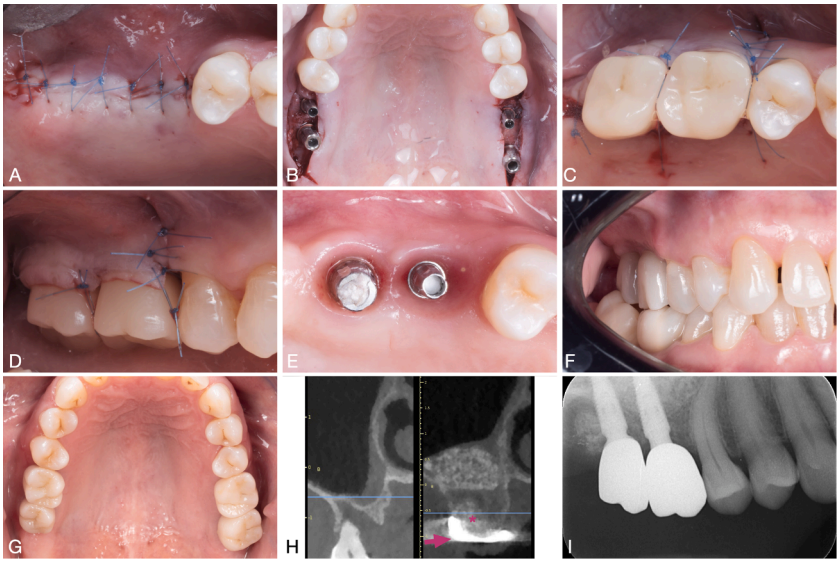

Fig. 3. (A) Flap suture after implants placement (B) Second stage surgery 3 months after implants insertion (C,D) Immediate provisional crowns in place with no occlusal contacts (E) Soft tissue appearance before cementation of definitive crowns (F, G) Definitive crowns in place (H) Side-by-side comparison of a pre- and post-operative CBCT section: arrow indicates the zirconia barrier; * vertical bone regeneration. (I) Periapical *x*-ray of the definitive crowns.

old, standard deviation: 6.2 years, range: 55 – 72 years), were consecutively enrolled in this case series study. The mean follow-up time was 4 months (range: 3–7 months).

From an overall point of view, 8 completely successful surgeries with zirconia meshes were performed and recorded (Fig. 4); one zirconia barrier got exposed after one month of healing (Fig. 5A) but no signs of infection were present when the barrier was removed four months after the GBR procedure (Fig. 5B). Complete ossification was recorded during the implant placement procedure (Fig. 5C). No failures, nor accidents, nor adverse events nor poor results were recorded.

All GBR procedures healed uneventfully. The patients were visited every week for four weeks. Then, they were visited after two months and, once again just before the placement of the implants. CBCT was performed five/seven months after the GBR procedure (Fig. 3H). Seventeen implants were placed and all of them osseointegrated (Fig. 3I). Implants were rehabilitated with cemented crowns.

Histological evaluations (Figs. 6 and 7) showed the presence of an intense deposition of new bone in all the analyzed fields. There are, in fact, many osteogenic cells and a high number of vessels.

4. Discussion

GBR procedures have evolved greatly over the last decades. A standard GBR procedure involves the use of a long-lasting barrier material to isolate the site, protect the underlying blood clot and the bone graft [6,14,16,33].

It was reported that an ideal barrier stabilizes the graft and acts as a scaffold to facilitate the diffusion of osteoprogenitor cells and blood vessels at the same time. In addition, it blocks the epithelial and connective tissue cells migrating from the surrounding soft tissues into the grafted site [17,34]. If the wound heals uneventfully, GBR has a high degree of predictability. A passive flap closure must be obtained during the surgery and the wound should stay closed throughout the healing period. Any barrier device, resorbable or not, needs to be covered with soft tissue primary closure to prevent microbial contamination and severe inflammatory reactions that could seriously compromise the procedure [35–37]. To this end, in complex GBR procedures, it is advisable to continue the systemic administration of antibiotics in the post-operative period [38,39]. However, even if the aforementioned factors are the well-known basis of any bone augmentation procedure, membrane or mesh exposure and infection are one of the most commonly reported complications during the healing process after horizontal and/or vertical GBR procedure [17,25–27]. In the event of an acute infection or exposure, a non-resorbable membrane or titanium mesh often have to be removed, especially if the complication occurs early.

The outcome of GBR procedures, especially with vertical defects, is strongly related with operator skills: the most time-consuming and critical aspect of the surgery is adapting and trimming a non-resorbable membrane or mesh. The barrier needs to be shaped three dimensionally to recreate a lost alveolar process, without sharp edges that could cause early or late wound dehiscences. After shaping, a barrier should be fixed by means of screws or pins: this step too requires skills and good teamwork with the assistant. For this reason, customized meshes can be considered a huge advantage, dramatically reducing surgical time, thus letting the surgeon focus on passivating and suturing the flap [40–42]. Less surgical time means less complications. In addition, with customized barriers, the anatomy - not only the volume - of the bone to be regenerated is planned before the surgery, working on a CBCT scan matched with an intraoral scan of the patient, with a digital wax-up layered on top: additional time is saved, compared to a traditional procedure, because there is no need to make calculations during the surgery and a really “prosthetically-driven” bone augmentation can be obtained.

In this case study series zirconia was used as a barrier material for GBR. These zirconia scaffolds are customized and they are obtained through a digital, CAD-CAM workflow, starting from patients’ CBCTs. Zirconia was used as a barrier material because it has interesting features and, if compared to titanium, it induces a better fibroblast response. It also shows less biofilm adhesion and less inflammatory response. While being superior to titanium in terms of biological properties, just like all ceramics, it is a brittle material: even if thinner than 0.5 mm, it can still support load but it is not flexible and cannot be bent at all. In case a zirconia barrier misfits the recipient site, adapting it can be hard and time-consuming. Fixing these meshes with screws should be performed with care because an excessive tightening could lead to fracture, without any predictive sign of it, such as bending or spring-back. Even if all the produced barriers showed an excellent fitting with the receiving sites, performing an accurate CBCT segmentation is the first and the most important step in order to achieve a good and stable fitting. For this reason, patients having metal or zirconia restorations in the area to be treated should be carefully screened. The extent of bone augmentation and the obtained bone quality was more than satisfactory in all the cases without the occurrence of major complications. Even in case of wound dehiscence, zirconia, being smooth and biocompatible, allowed to overcome the limitations of non-resorbable PTFE membranes and titanium meshes: the patient was instructed to keep the exposed area clean and no infection was noticed. We are not claiming that a perfect bone regeneration can be obtained even if the zirconia barrier gets exposed: however, zirconia may be left in place for a longer period in comparison to PTFE or titanium, without contamination of the barrier before removing it [43]. It is apparently possible to obtain a greater bone augmentation than that reported in the literature in case of, both resorbable and non-resorbable membrane [43]. In the presented case of premature exposure, we should speculate that the exposure was due to a

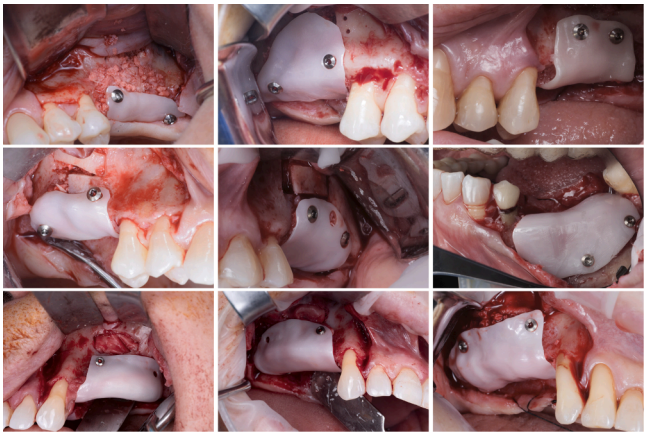

Fig. 4. Case series of the nine surgical sites treated with zirconia barriers.

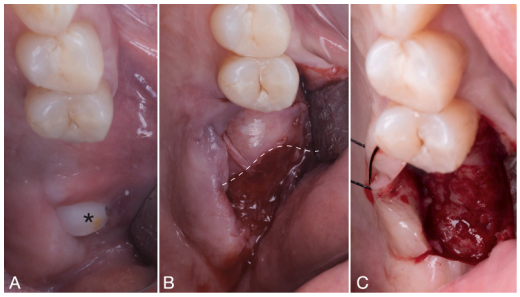

Fig. 5. (A) 1-month: soft tissue dehiscence and premature exposure of a zirconia barrier. (B) 4-month: barrier removal with no signs of infection. The mesial part of the grafted area showed an optimal appearance, while the distal part, under the exposed barrier, showed a less compact structure. The flap was sutured with primary intention. (C) 6-month: implant placement surgery with complete ossification of the grafted area.

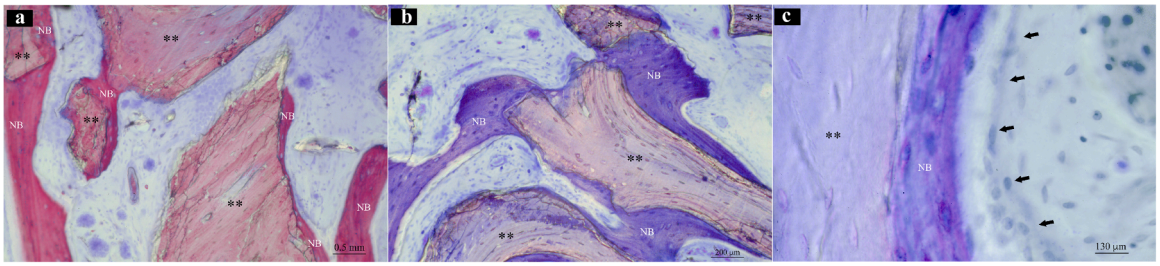

Fig. 6. Histological evaluation under a brightfield optical microscope of three bone biopsies collected during the placement of the implants. In a (x50 original magnification) the newly formed bone (NB) covers the biomaterial's particles (**); toluidine blue-fuchsin acid staining. In b (x100 original magnification) the newly formed bone (NB) appears to completely englobe the biomaterial's particles (**); toluidine blue -azure II staining. In c (x200 original magnification) a biomaterial particle (**) is wrapped by a layer of new mineralized bone (NB) covered by an active osteoblastic rim in osteoid matrix deposition stage (black arrows); toluidine blue -azure II staining (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

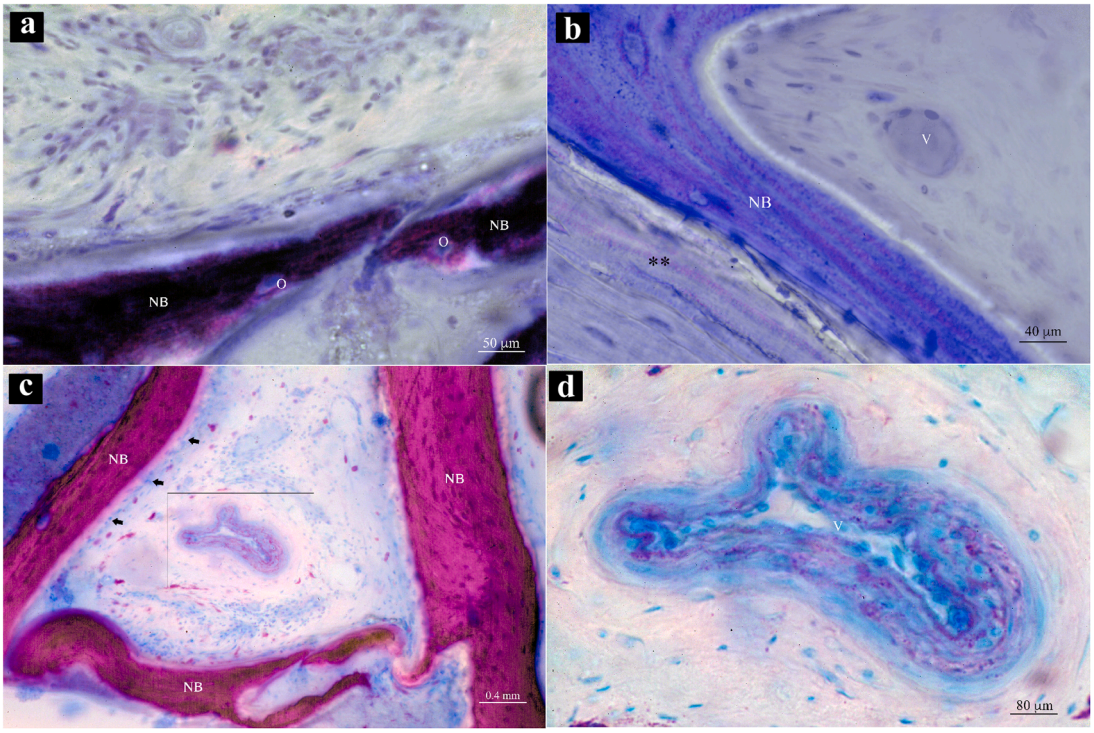

Fig. 7. Histological assessments at higher magnification of areas with a high cellularity associated with both presence of some vessels and bone deposition. In a (x200 original magnification) the newly formed bone (NB) presents some osteocytes (o) embedded inside the mineralized matrix; toluidine blue-fuchsin acid staining. In b (x200 original magnification) a biomaterial's particle (**) is covered by newly formed lamellar bone (NB) with a vessel (v) near the osteoblastic rim; toluidine blue -azure II staining. In c (x50 original magnification) of new mineralized bone (NB) covered by an extensive osteoblastic rim (black arrows) inside the square a big vessel; toluidine blue -fuchsin acid staining. In d (x400 higher magnification of square rectangle in c) there is evident a small artery (v) present inside the marrow space; toluidine blue -fuchsin acid staining (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

suboptimal design, with sharp edges beneath thin soft tissues.

Histological results of the presented cases series were interesting because they are different from other similar regenerative conditions, where the use of waterproof barriers, such as zirconia, was lacking. The reason for this histological evidence might be, in fact, the use of an extremely rigid, thin barrier composed of a biocompatible material with a large affinity for soft tissues. On the other end, the development of new vessels starts from the periosteum layer or from the connective tissue above the periosteal layer. This allows for the development of a denser vascular network within the transient matrix first, and later on, in the medullary spaces. It also probably supports the observed increase in osteogenesis potential.

Other barrier materials are rough and they present microporosity. Once exposed, they represent a favorable substrate for oral microbiome colonization [43–45]

For reasons that are not completely clear yet, zirconia meshes showed a complete absence of integration and adhesion with the surrounding soft and hard tissues, allowing for a rapid removal at the time of the re-opening surgery, unlike other barrier materials, whose removal is often a delicate and time-consuming process.

All the zirconia barriers used in this case series were produced with milling because 3D printing, even if available and described in the literature, has shown inferior mechanical properties so far. Nevertheless, we believe that additive manufacturing has greater capabilities if compared to subtractive manufacturing because there are virtually no limitations in terms of shapes and profiles that can be created. For this reason, we believe 3D printing will probably be the best choice in the future.

This case series is in all respects a proof-of-concept that zirconia can be used with safety and predictability in the GBR procedure in humans. The possibility of using a perfectly biocompatible material, customizable, easy to use and not prone to microbial colonization opens new, important perspectives for GBR. However only seven patients were treated with this technique and by the same operator; it is clear that long-term prospective clinical studies, with more patients enrolled, are needed to confirm the predictability of zirconia barriers. Still, the starting points appear more than promising.

5. Conclusions

Within the limitations of the present case series study, the tested customized-3D zirconia barriers confirmed good clinical and histological performances, and, even in case of a premature exposure, they did not show any signs of infection. The preliminary results suggest they are effective devices for GBR procedures. Further research will be necessary with a larger sample size.

CRediT authorship contribution statement

Federico Mandelli: Conceptualization, Investigation, Writing – review & editing. **Tonino Traini:** Conceptualization, Investigation, Writing – review & editing. **Paolo Ghensi:** Conceptualization, Investigation, Writing – review & editing.

Declaration of Competing Interest

Dr. Federico Mandelli has no conflict of interest
Dr. Tonino Traini has no conflict of interest
Dr. Paolo Ghensi has no conflict of interest—
FM deposited an international patent request for zirconia barriers.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jdent.2021.103780.

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