# Highly porous porcine xenograft utilized in bone augmentation procedures: case reports with clinical, histological and histomorphometrical evaluation

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**ABSTRACT**

Purpose: The aim of this report was to evaluate clinically, histologically and histomorphometrically a new highly porous porcine cancellous xenograft.

Case reports: A porcine xenograft (Zcore™) was used to treat 3 patients requiring the use of a bone graft: patient A required a horizontal GBR with a simultaneous sinus lift, patient B required a socket preservation after lower canine extraction, patient C required a mandibular horizontal GBR for the first molar implant rehabilitation. Healing was uneventful for all the interventions and, after bone graft maturation, re-entry was scheduled after 8, 3 and 7 months for patient A, B and C respectively. At implant insertion, two specimens were harvested from patient A, and 1 specimen was taken either from patient B and C. All implants healed uneventfully. Histological sections showed xenograft particles integrated in newly formed bone. Histomorphometric analysis for patient A revealed a 60.2% of bone marrow/connective tissue and 39.8% of mineralized fraction in the first specimen, while the second specimen revealed a 58.1% of bone marrow/connective tissue and 41.9% of mineralized fraction. For patient B the specimen revealed a 61.4% of bone marrow/connective tissue and a 38.6% of mineralized fraction. For patient C the specimen revealed a 52.1% of bone marrow/connective tissue and a 47.9% of mineralized fraction.

Conclusions: The use of a highly porous porcine xenograft allowed greater empty space for new bone osseointegration. The values of histomorphometric analysis highlight a very good new bone formation for all the interventions.

**KEYWORDS**

Guided bone regeneration, histological evaluation, histomorphometrical evaluation, porcine xenograft, sinus lift, socket preservation

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## INTRODUCTION

Dental implants are nowadays a routine therapy in order to replace missing teeth. Long term stability of an implant requires the presence of an adequate volume of bone surrounding it.[1] As this volume is often unavailable due to bone resorption resulting from tooth loss, several techniques were proposed to gain bone regeneration. Among the different bone regenerative procedures, guided bone regeneration (GBR) using a bone graft covered by a barrier membrane is currently the regenerative approach most widely used and documented in literature.[2]

Relying on Melcher [3] and Nyman et al.[4] works on regeneration of periodontal tissue's, this technique is based on the employment of a barrier membrane in order to exclude soft tissues from the defect and to allow angiogenic and osteogenic cells to gain bone regeneration.[5]

Both resorbable and nonresorbable membranes have shown clinical effectiveness.

Collapse of the membrane into the bone defect, especially for what concerns resorbable membranes, can often lead to a compromised treatment result.[6]

With the purpose of avoiding this collapse, bone grafts are widely used in combination with the membrane due to their space-making capability.

Moreover, bone substitutes have several properties that contribute to bone regeneration promotion, as they can stimulate osteogenic cells from the recipient site, act as a scaffold supporting bone ingrowth, protect the augmented volume from its resorption and stabilize the blood clot. Considering that no single material can fulfill this wide range of purposes, they are often used in combination, and a strong effort is put into research to improve materials' characteristics.

Autogenous bone graft has been extensively used because of its osseoinductive, osseoconductive, and osteogenic properties.[7] High resorption rate and morbidity related to its harvesting are significant disadvantages of autogenous bone employment in a GBR treatment.[8] Consequently, other bone graft materials options, such as xenografts, human-derived allogenic bone (HALG), and synthetic biomaterials (alloplastic grafts), have been developed as alternative graft materials or used in combination with autogenous bone.

Allografts are derived from a donor of the same species and can either be fresh/frozen, freeze-dried or demineralized freeze-dried bone granules or blocks. Similarly to autografts, allografts can act not only as osteoconductive scaffolds, but may also have some osteoinductive potential, due to the presence of proteins such as bone morphogenetic proteins (BMP).[9] Resorption rate seems to be equal to the one showed by autografts.[10]

Alloplasts usually have only an osteoconductive function. The most employed alloplastic materials are Hydroxyapatite (HA) and tricalcium phosphates (β-TCP).

HA has composition and structure similar to natural bone, thus resulting in a strong bond with recipient site's tissue. HA grafts show slow and limited resorptive potential and generally are dependent on passive dissolution in tissue fluid and cell mediated processes.[11]

β-TCP, on the other hand, exhibits good biocompatibility, osteoconductivity and a fast resorption time allowing replacement with newly formed bone.[12]

Xenografts are graft tissues obtained by bovine, equine or porcine source and mainly characterized by osteoconductive properties. Organic immunogenic part of these bone substitutes is removed through a thermic and/or chemical procedure.

Thermic treatments lead to the sintering of the bone structure, increasing its crystallinity and resulting in a poorly resorbable material.[13]

The xenograft most employed in oral reconstructive surgery procedures is deproteinized bovine bone mineral (DBBM), whose application has been widely documented in literature with good clinical results.[14] Although the heat and chemical processing removes most of the osteogenic components from bone, it has been assessed that the potential risk of disease transmission from bovine species (bovine spongiform encephalopathy) cannot be excluded.[15]

Xenografts of equine source have also been introduced to clinical practice in the last years in various oral regenerative surgery applications.[16]

A new highly-porous porcine xenograft has been recently studied in alveolar ridge preservation treatment, showing a good behavior when compared to DBBM graft.[17]

This manuscript aims to clinically and histologically analyze the efficacy of a new porcine xenograft in different bone augmentation procedures.

## CASE REPORTS

A porcine xenograft (Zcore™, Osteogenics Biomedical, Lubbock, TX, USA) was used to treat 3 patients requiring the use of a bone graft. All participants signed an informed consent form for the intervention and to allow the harvesting of a bone specimen for histological/histomorphometric evaluation to analyze the maturation of the bone graft and determine the prosthetic loading time. Patient A (Figure 1a-l) required an horizontal GBR with a simultaneous sinus lift (SL), and was treated with the application of a long lasting collagen membrane (Cytoplast™ RTM, Osteogenics Biomedical) with a resorption time of 26-38 weeks, a graft of 100% of xenograft inside the sinus, a 1:1 ratio mixture of xenograft and autogenous bone, harvested with a disposable scraper (Safescraper® Twist, Meta, Italy) from the lateral bone wall where the entrance to the maxillary sinus was performed, to correct the horizontal ridge defect.

Patient B (Figure 2a-h) required a socket preservation after lower canine extraction. Only the xenograft filled the alveolar cavity that was closed with the application of a collagen fleece (Medicipio®C, Medichema, Germany) as a cap. Patient C (Figure 3a-l) required a mandibular horizontal GBR for the first left molar implant rehabilitation and was treated with the application of a long-lasting collagen membrane (Cytoplast™ RTM, Osteogenics Biomedical) and a 1:1 ratio mixture of xenograft and autogenous bone, harvested locally with a scraper. Healing was uneventful for all the interventions and, after bone graft maturation, re-entry was scheduled after 8, 3 and 7 months for patient A, B and C, respectively. Patient A received 2 implants in upper second premolar and first molar position (INNO Sub 3,5x12 and 4,5x12 respectively, Cowellmedi, Korea). Two specimens were harvested during implant site preparations. Patient B and patient C received 1 implant each (TSIII 3,5x10, Osstem, Korea, and INNO Sub 4,5x12, Cowellmedi, Korea, respectively), and 1 specimen was taken during implant site preparation from each patient. The biopsies were defatted in Xylene, infiltrated, embedded and polymerized in Technovit® 9100. Samples were cut in 500 µm sections using a low-speed rotary diamond saw. Sections were mounted onto opaque acrylic-slides and grounded to a final thickness of approximately 60 µm. Specimens were subsequently stained with azure II and pararosaniline. Newly formed bone mineral and Zcore™ are stained dark magenta, older bone / autogenous bone light magenta and soft tissue blue. Labeling for histomorphometric purpose of Zcore™ granules light blue, newly formed bone red and autogenous bone yellow.

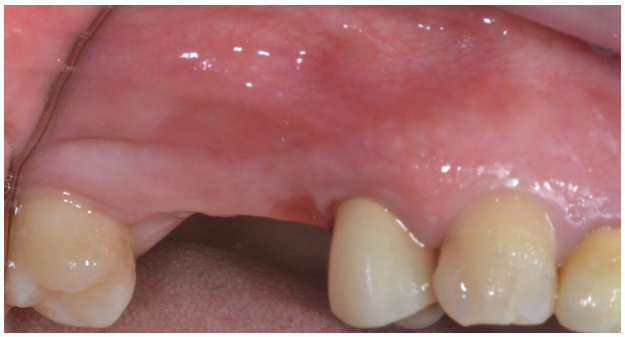


Figure 1a

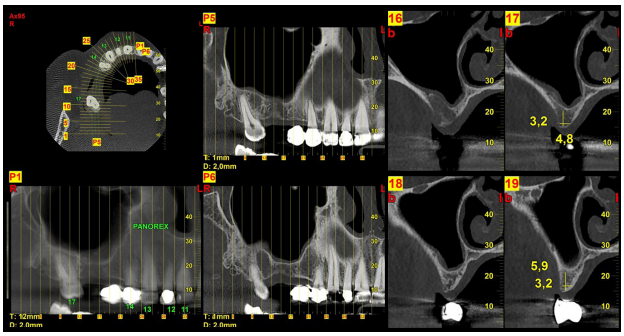



Figure 1b

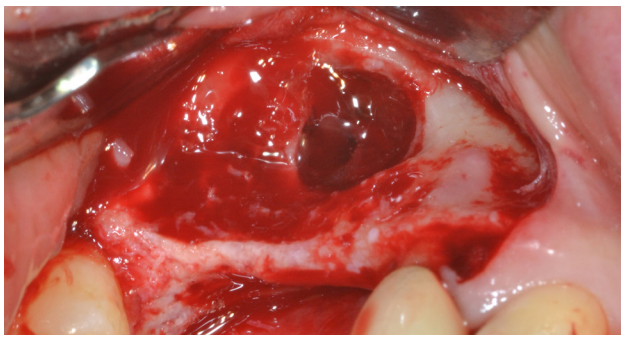


Figure 1c

Figure 1d

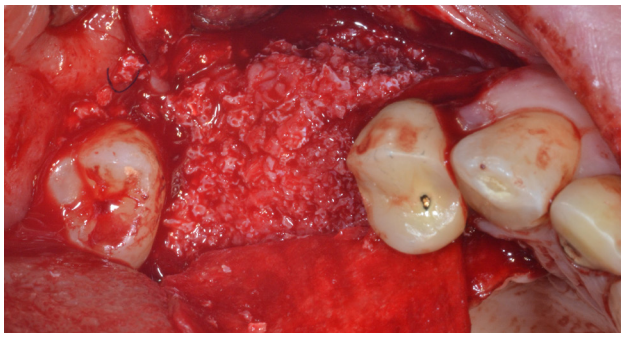


Figure 1e

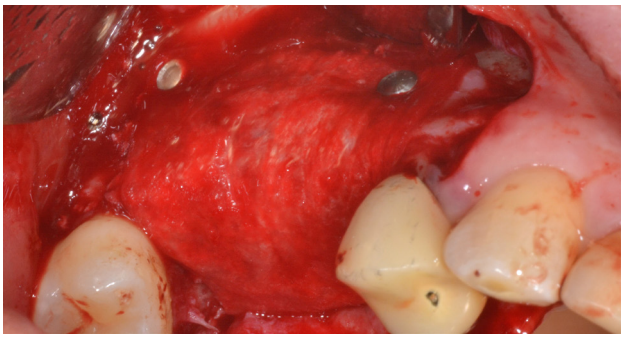


Figure 1f

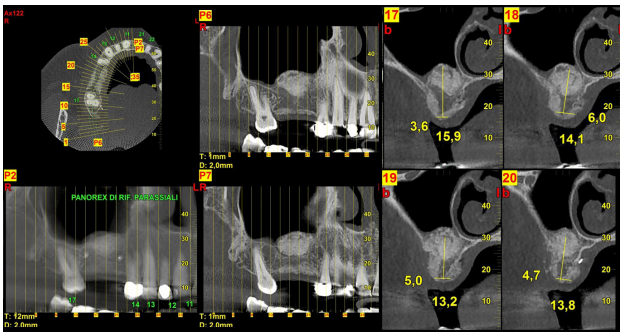



Figure 1g

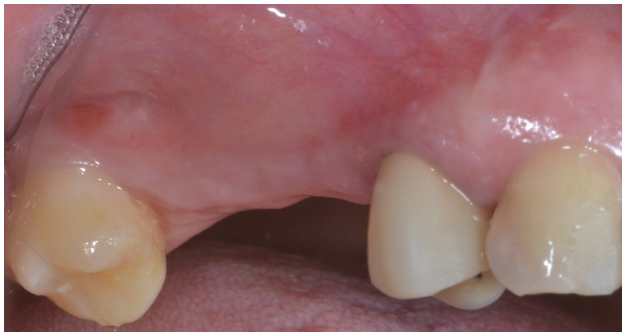


Figure 1h

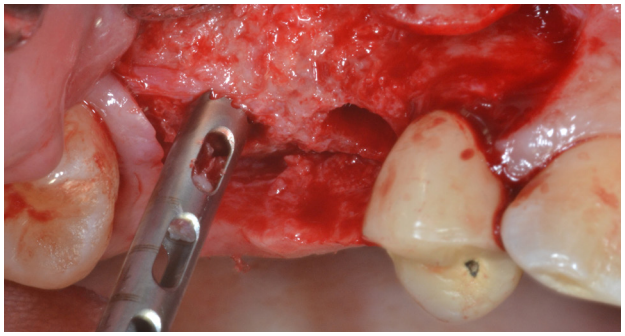
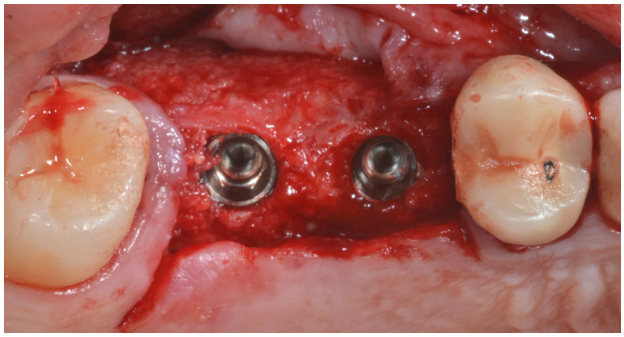


Figure 1i



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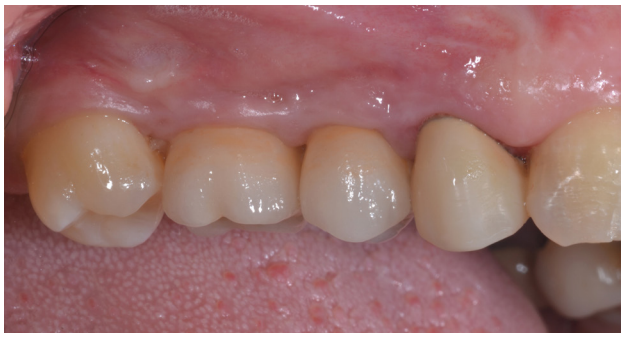


Figure 1k

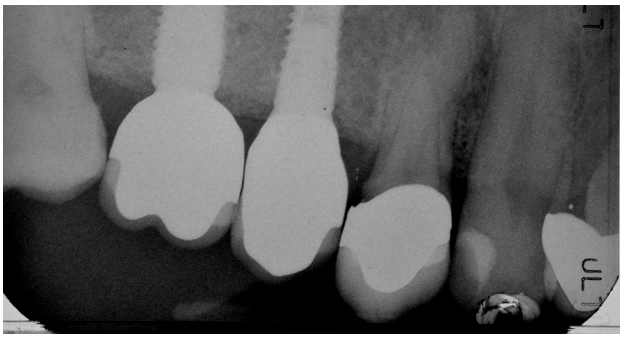


Figure 1l

**Figure 1.** Patient A requiring upper right second premolar and first molar rehabilitation (a); Cone Beam Computed Tomography (CBCT) scans show a reduced bone height and width (b); After a mucoperiosteal flap was raised, a lateral-approach sinus lift was performed (c); Autologous bone, harvested with the scraper during lateral sinus wall entry was mixed in a 1: 1 ratio with the xenograft (d), was used to correct the ridge defect (e), while only xenograft filled the sinus cavity; A cross-linked collagen membrane, stabilized with tacks both on buccal and lingual side, covered the graft (f); The 5-month CBCT scans (g) revealed excellent lateral and vertical bone augmentation; Re-entry was scheduled after a 8.month healing time (h); During implant sites preparation, two specimens were harvested (i) and two implants were inserted (j); The 3-year clinical (k) and radiographic (l) follow-up after prosthetic loading showed excellent hard and soft tissues maintenance

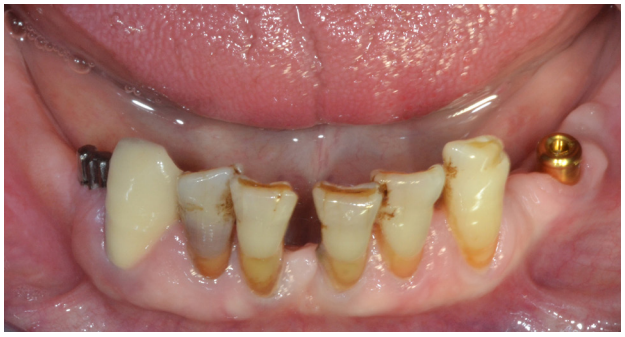
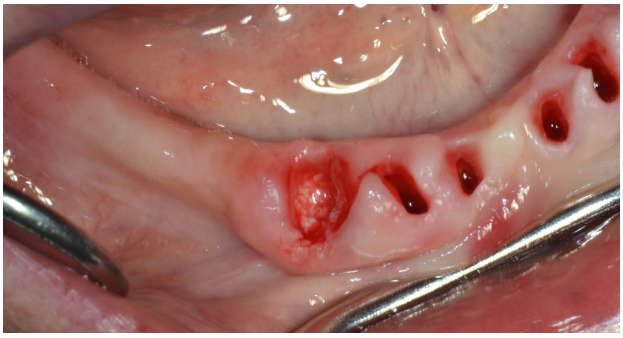


Figure 2a



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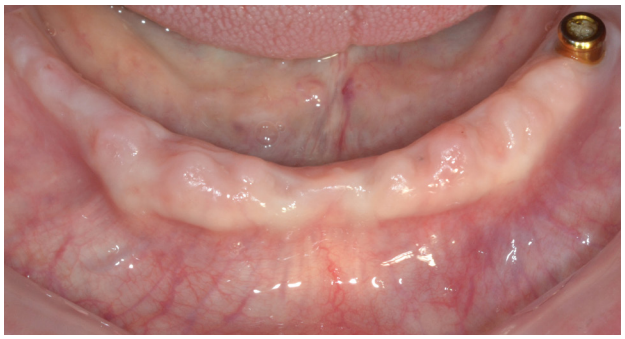

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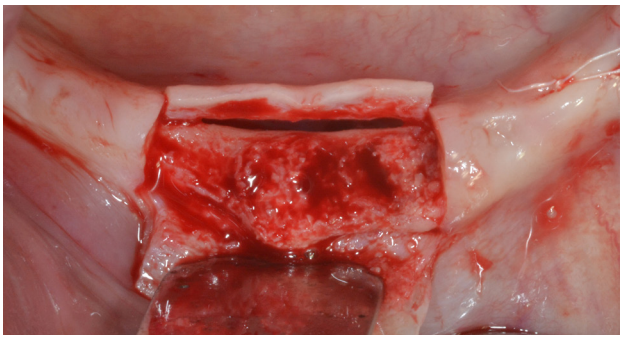

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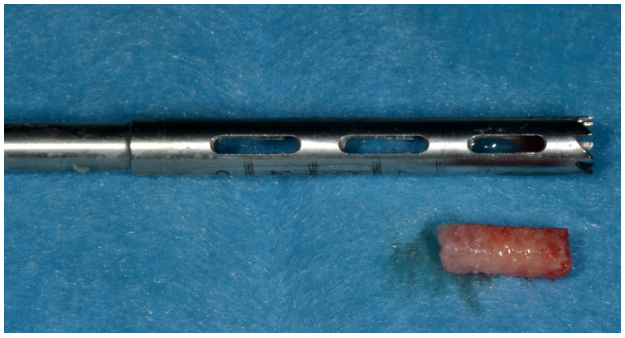

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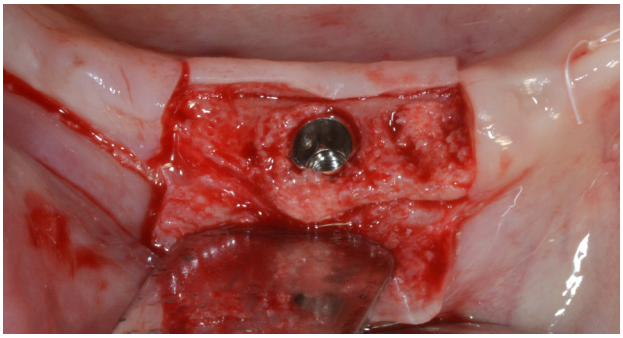

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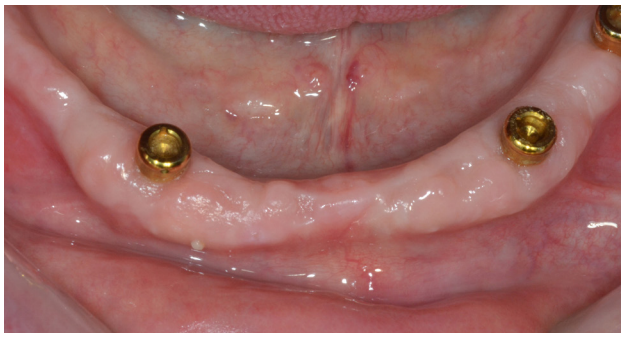


Figure 2g

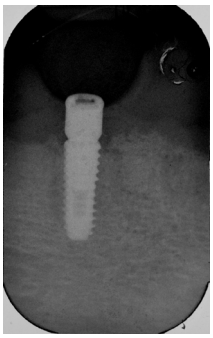


Figure 2h

**Figure 2.** Patient B requiring lower arch rehabilitation (a); After the extraction of all remaining periodontal teeth, a xenograft filled the socket of the right canine (b); After a 3-month healing period (c), a mucoperiosteal flap was raised (d) and a bone specimen was retrieved (e) during implant bed preparation. The implant was inserted in the canine position (f) and a Locator abutment (g) was connected to it two months later (h)

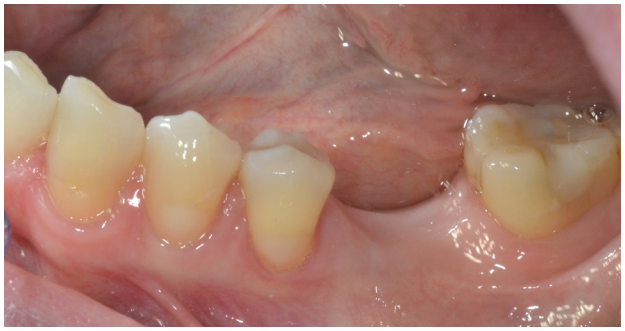
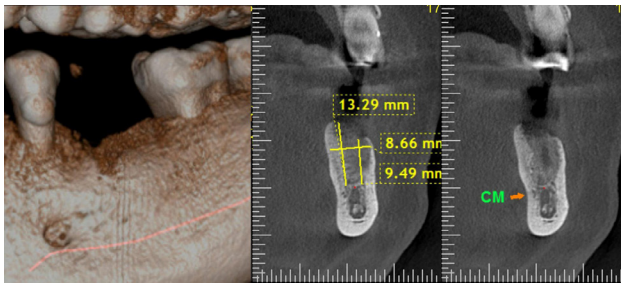


Figure 3a

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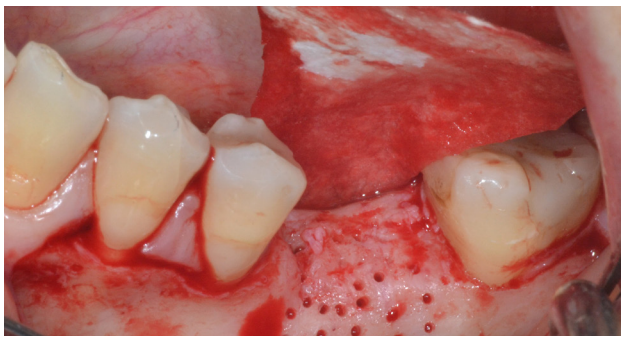

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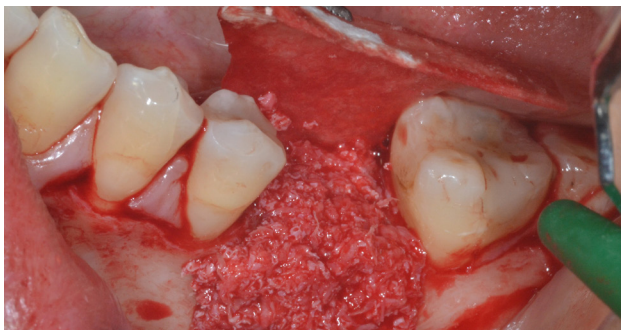

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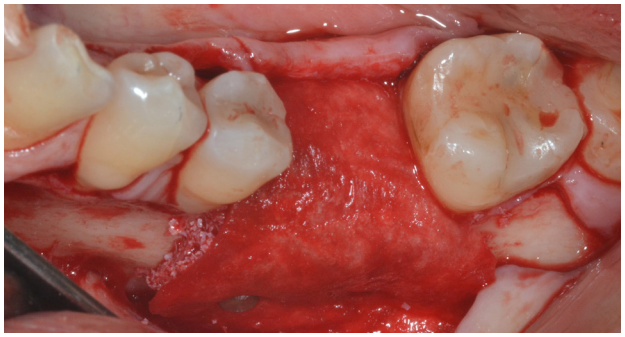

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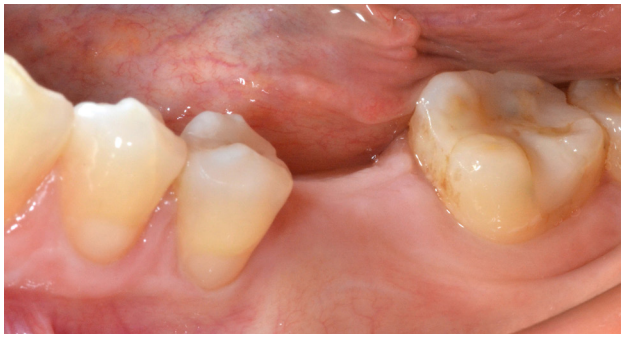

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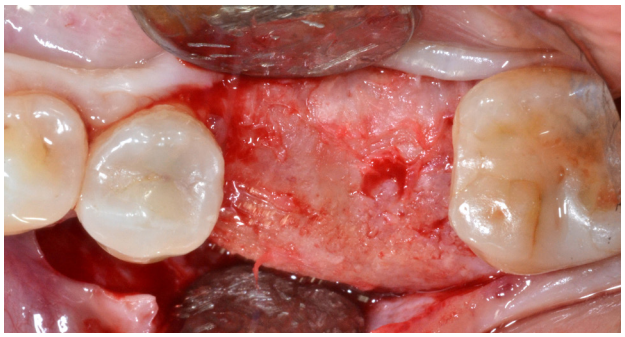


Figure 3g

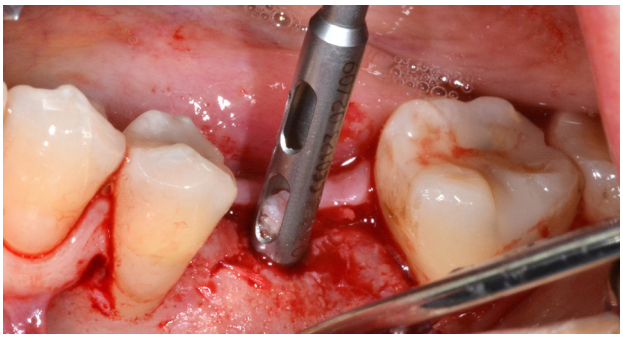


Figure 3h

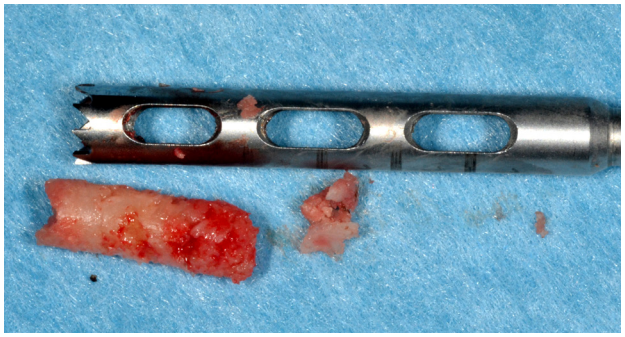


Figure 3i

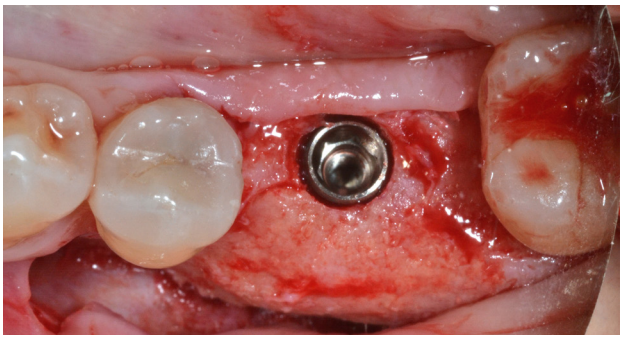
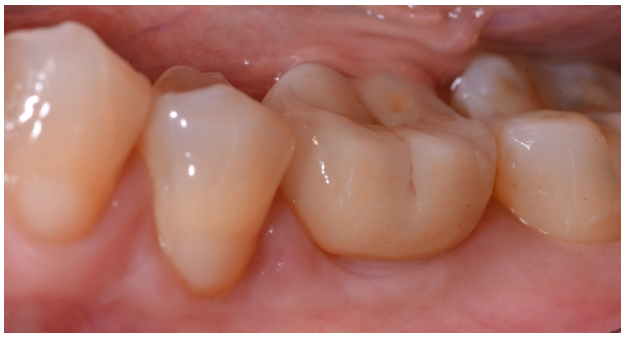


Figure 3j



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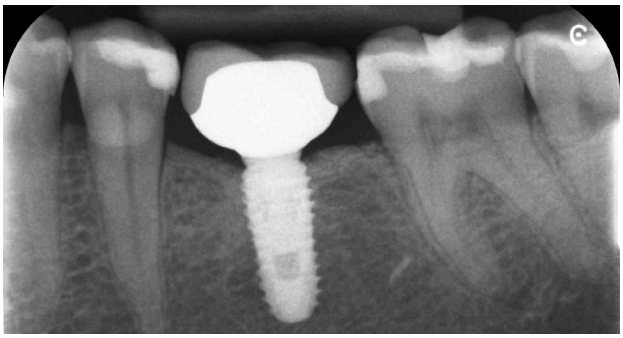

Figure 3l

**Figure 3.** Patient C requiring left lower first molar rehabilitation (a); Cone Beam Computed Tomography (CBCT) scans show a reduced bone width (b); After mucoperiosteal flap elevation and cortical perforations, a cross-linked collagen membrane was stabilized to the lingual side with tacks (c); a mixture of autogenous bone and xenograft in a 1:1 ratio was applied to correct the bone defect (d), then the collagen membrane was secured with tacks on the buccal side (e) to cover the bone graft; After a 7-month healing time (f), a mucoperiosteal flap was raised (g) and, during the implant bed preparation (h), a bone specimen was retrieved (i); An implant was inserted in the lower left first molar position (j); The 1-year clinical (k) and radiographic (l) follow-up after prosthetic loading showed excellent hard and soft tissues maintenance..

All implants healed uneventfully and received their prosthesis after a period of 4, 3 and 4 months for patient A, B, and C respectively. Histological sections showed xenograft particles integrated in newly formed bone, active osteoblasts producing osteoid, demonstrating ongoing bone formation, and a bone marrow with well vascularized, uninflamed, loose connective tissue. Histomorphometric analysis was carried out on two sections per each specimen and the mean values are reported. For patient A, the first specimen (Figure 4) investigated the regeneration inside the sinus (Table 1) and revealed a 60.2% of bone marrow/connective tissue and 39.8% of mineralized fraction (23.2% of Zcore™ 16.6% of new bone mineral); the second specimen of patient A (Figure 5) investigated the ridge regeneration (Table 2) and revealed a 58.1% of bone marrow/connective tissue and 41.9% of mineralized fraction (5.7% of avital autogenous bone, 22.0% of Zcore™, 14.2% of new bone mineral). For patient B (Figure 6) the specimen (Table 3) revealed a 61,4% of bone marrow/connective tissue and a 38.6% of mineralized fraction(27.8% of Zcore™, 10.8% new bone mineral). For patient C (Figure 7) the specimen (Table 4) revealed a 52.1% of bone marrow/connective tissue and a 47.9% of mineralized fraction (1,1 of avital autogenous bone, 26.6% of Zcore™, 20.2% of new bone mineral).

## DISCUSSION

All the cases treated in this series showed a good clinical result, as well as a good response from the histomorphometric analysis. Porosity is a key characteristic for bone substitutes, allowing for neoangiogenesis, diffusion of nutrients and new vital bone deposition.[18] The presence of channels interconnecting pores of 200-350 µm or wider offers an optimal scaffold for both new vessels and new bone tissue ingrowths, maximizing the osteoconductive capability of a bone substitute.[19]

The porcine xenograft employed in the present case series shows void spaces for 88%-95% of its volume (data provided by the Producer), thus offering an ideal porosity to reach the regeneration of a bone defect.

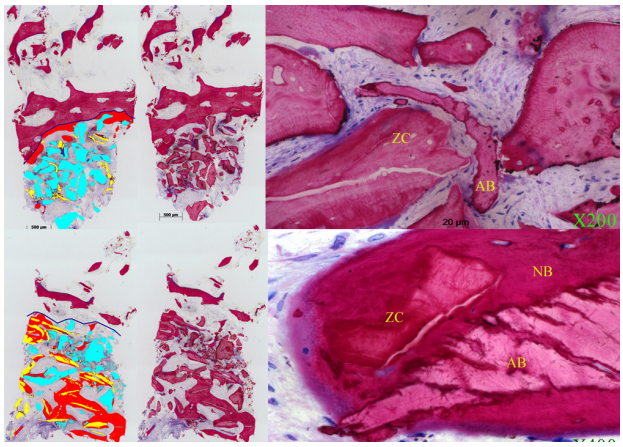


**Figure 4.** Sections show in the lower half a mixture of ZCORE (ZC) and autogenous bone (AB) partially embedded in newly formed bone (NB). Connective tissue is well vascularized and shows no signs of inflammation (azure II and pararosaniline stain, original magnification x200/x400).

This characteristic can maybe promote the integration between

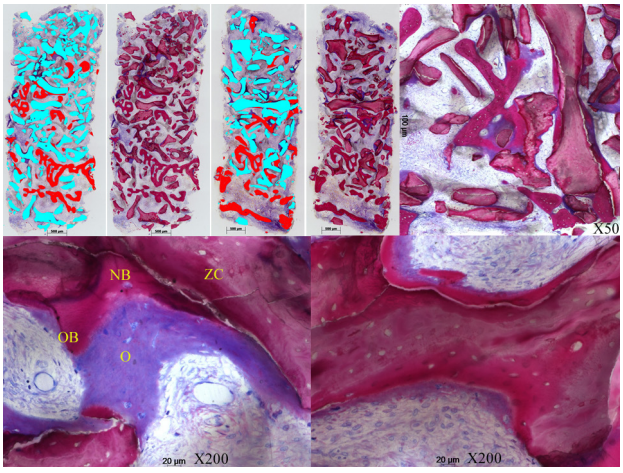


**Figure 6.** Porcine xenograft particles (ZC) integrated in newly formed bone (NB) or in well vascularized, uninflamed, loose connective tissue. Seams of active osteoblasts (OB) form dark blue stained osteoid (O) and new bone (azure II and pararosaniline stain, original magnification x50/x200)

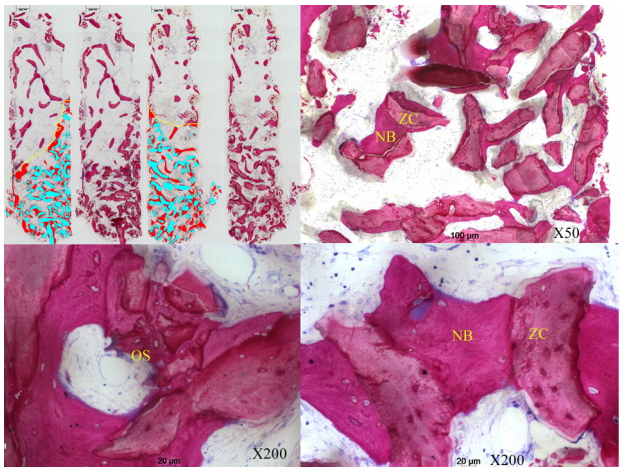


**Figure 5.** Sections show avital porcine xenograft particles (ZC) with appositions of newly formed bone (NB); bone substitute lacking osteocyte cell nuclei. Osteon formation (OS) by new bone with integrated ZCORE particles. Active osteoblasts producing osteoid demonstrate ongoing bone formation (azure II and pararosaniline stain, original magnification x50/x200).

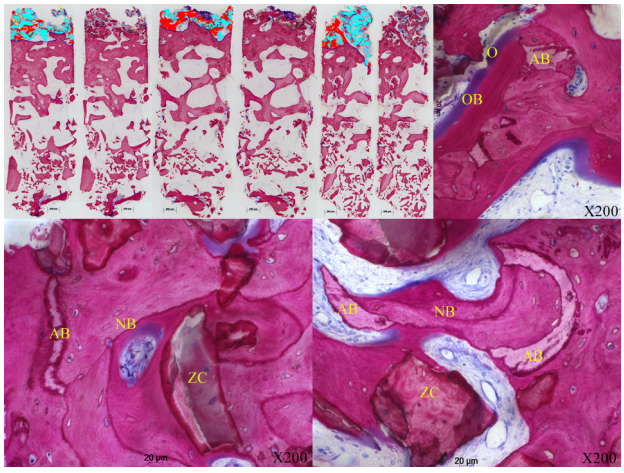


**Figure 7.** Sections show the augmented area, ZCORE particles (ZC) and avital autogenous bone chips (AB) embedded in newly formed bone (NB) can be seen. Osteoblasts (OB) form dark blue stained osteoid (O) and indicate ongoing bone formation (azure II and pararosaniline stain, original magnification x200)

**Table 1.** Histomorphometric data related to Patient A (specimen 1)

| Section | A | B | Mean |
|---|---|---|---|
| **Dimension (mm)** | 5.0 x 2.7 | 4.9 x 2.9 | |
| **Coverage (%)** | | | |
| **New bone mineral** | 7.8 | 20.5 | 14.2 |
| **Zcore** | 29.9 | 14.1 | 22.0 |
| **Autogenous bone** | 3.2 | 8.3 | 5.7 |
| **Mineralized fraction** | 40.9 | 42.9 | 41.9 |
| **Connective tissue, Bone marrow** | 59.1 | 57.1 | 58.1 |

**Table 2.** Histomorphometric data related to Patient A (specimen 2)

| Section | 15-1A | 15-1B | Mean |
|---|---|---|---|
| **Dimension (mm)** | 8.7 x 2.5 | 8.4 x 2.6 | |
| **Coverage (%)** | | | |
| **New bone mineral** | 16.7 | 16.4 | 16.6 |
| **Zcore** | 25.2 | 21.3 | 23.2 |
| **Mineralized fraction** | 41.9 | 37.7 | 39.8 |
| **Connective tissue, Bone marrow** | 58.1 | 62.3 | 60.2 |

**Table 3.** Histomorphometric data related to Patient B

| Section | A | B | Mean |
|---|---|---|---|
| **Dimension (mm)** | 5.9 x 2.5 | 6.1 x 2.4 | |
| **Coverage (%)** | | | |
| **New bone mineral** | 10 | 11.5 | 10.8 |
| **Zcore** | 30.2 | 25.5 | 27.8 |
| **Mineralized fraction** | 40.2 | 37 | 38.6 |
| **Connective tissue, Bone marrow** | 59.8 | 63 | 61.4 |

**Table 4.** Histomorphometric data related to Patient C

| Section | A | | B | Mean |
|---|---|---|---|---|
| **Dimension (mm)** | 8.6 x 2.9 | 8.1 x 3.1 | 8.9 x 2.3 | |
| **Coverage (%)** | | | | |
| **New bone mineral** | 12.1 | 32.7 | 15.9 | 20.2 |
| **Zcore** | 31.1 | 17.6 | 31 | 26.6 |
| **Autogenous bone** | 2.4 | 0.4 | 0.4 | 1.1 |
| **Mineralized fraction** | 45.6 | 50.7 | 47.4 | 47.9 |
| **Connective tissue, Bone marrow** | 54.4 | 49.3 | 52.6 | 52.1 |

the graft and the new bone spreading from the walls of the recipient site, which is confirmed by the presence of newly formed bone on the surface of the graft's particles. In all the cases, in fact, particles of the Zcore™ enograft were not so evident at reentry and the bone resulted compact and didn't show not-integrated granules during the implant site preparation.

Dense vascularization and no signs of inflammation in the connective tissue surrounding the mineral component of the biopsies, together with active osteoblasts and osteoid substance that can be seen in the histologic pictures are proof of an ongoing ossification in the sites of grafting, especially for what concerns Patient B, where specimens were obtained in an early stage of hard tissue's maturation.

A recent study conducted on an animal model performed a histomorphometric analysis of calvarial defects treated by GBR with the use of deproteinized bovine bone mineral (DBBM) as bone substitute, presently the most used xenograft in oral surgery.[20] The authors found a medium percentage of 22.7% of new bone formation (NBF) and 30% of residual xenograft (RX) after 1 month of healing in sites treated with DBBM and covered by a collagen membrane (CM).

Although data from non-human studies are hardly comparable to the clinic situation, the findings of this paper are similar with the ones obtained in patient C of the present case series, who underwent a GBR treatment by means of a graft (1:1 autograft and porcine xenograft) covered by a resorbable membrane, that showed 20.2% and 26.6% of NBF and RX respectively. GBR was also performed in patient A of this study, showing a percentage of 14.2% of NBF and 22% of RX in the coronal portion of the specimen (while the apical one was treated with a sinus lift intervention).

Results of a histologic study on humans from Zitzmann et al [21] in which six patients received a GBR treatment with the use of DBBM and a collagen membrane are in line with those of this work too, getting a medium percentage of NBF and RX equal to 22.6% and 30.5% respectively at the end of the healing period.

Another histologic study carried out by Friedman et al. [22] and performed using DBBM and a long lasting resorbable membrane (similar to the Cytoplast® RTM collagen membrane employed for patient C) found a medium NBF of 39% and RX of 15%.

Patient B received a grafting of Zcore™ in a treatment of socket preservation and showed a NBF of 10.8% with a RX of 27.8%. The remaining 61.4% of soft tissue found in this specimen is probably due to the ealy stage of healing (the biopsy was obtained after only 3 months from grafting), but the high presence of osteoblasts and osteoid substance attests an ongoing bone maturation.

In a work by Machtei et al [23] thirty-three patients underwent socket preservation interventions with the employment of DBBM, showing a NBF of 21.5% after 4 months of healing, but with a higher percentage of RX (40%) and a lower of soft tissue (38.5%) that could show a reduced residual osteogenic potential of the site.

A recent randomized clinical trial by Lai et al.[17], which directly compared the grafting of DBBM and porcine xenograft in socket preservation procedures, didn't show any difference between the two materials from both a clinical and a histological point of view.

Histomorphometric results of the graft filling the lifted sinus in patient A showed a NBF equal to 16.6% with a RX of 23.2%. In a study carried out by Froum et al.[24], in which thirteen patients underwent sinus lift surgeries with the employment of DBBM, the NBF resulting from the histological analysis was 12.44% and RX was 33%, thus showing similar results with those of this case series.

Comparing the findings of this work with other studies investigating the histological outcomes of widely clinically employed bone substitutes, no significant differences can be found. With all the limits of the evidence provided by a case series, the positive outcome of this work lay the foundation for more studies, possibly in the form of RCTs, that can either support or not in an evidence-based perspective the employment of this new material.

## CONCLUSIONS

This work showed clinical success after the employment of a highly porous porcine xenograft as a grafting material in different interventions, with a good presentation of the sites at re-entry. Histological analysis of the specimens proved good conditions of the sites grafted, with the integration between the graft particles and newly formed vital bone and no signs of inflammation. Histomorphometrical results are in line with those of studies employing other bone substitutes. More studies are requested to empower the evidence about the use of Zcore™.

## DISCLOSURE STATEMENT

The authors report no conflicts of interest related to this study. No external funding, apart from the support of the authors' institution, was available for this study.

Requirement for Ethics Board Approval was not necessary since these case reports are a retrospective description of clinical findings in best proven interventions during the normal course of clinical treatment. Since there is no hypothesis testing, no systematic data collection beyond that which is part of routine clinical practice, and the work has already been done, Case Series do not usually qualify as “research” requiring approval from ethical boards designed to protect humans involved in clinical research. The collection of bone samples during the preparation of the implant bed for histological and histomorphometric analysis served to analyze the maturation of the bone graft and determine the prosthetic loading time. This procedure was part of the treatment and should not be considered excessive treatment, as that bone had to be removed and wasted anyway.

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