

Digitally guided transcrestal sinus floor elevation using collagenated synthetic hydroxyapatite or collagenated xenograft: Histologic and volumetric comparison

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ABSTRACT

Objectives: This study evaluated clinical, radiographic, and histological outcomes after digitally guided transcrestal maxillary sinus floor elevation using two bone substitutes: a composite of cross-linked collagen with synthetic hydroxyapatite (test) and a collagen-enriched bovine-derived bone substitute (control).

Methods: In a prospective controlled trial, 26 patients with <5 mm residual bone height underwent digitally guided transcrestal sinus augmentation using test or control biomaterial, followed by staged implant placement after six months (T1). Bone cores were harvested during implant site preparation for histological analysis using a dedicated surgical guide. Radiographic volumetric and linear changes were evaluated on pre- and post-operative CBCT scans. Data were analyzed using Mann-Whitney U-test, Kruskal-Wallis, and Fisher's exact tests.

Results: At T1 both groups achieved significant graft volume gain with no intergroup difference. The test group showed a higher percentage of newly-formed bone ($31.6 \pm 21.6\%$ vs. $18.2 \pm 16.0\%$; $p = 0.004$) and lower residual graft ($2.2 \pm 6.3\%$ vs. $6.2 \pm 6.8\%$; $p = 0.003$). Inflammatory infiltration was lower in the test group ($p < 0.001$). Significant differences in residual graft distribution among biopsy regions were found only in the test group ($p = 0.03$).

Conclusions: The cross-linked collagen/synthetic hydroxyapatite scaffold promoted greater bone regeneration with lower graft remnants than the collagen-enriched xenograft. The digital workflow was used to standardize surgical planning, guide crestal access, biopsy harvesting, and implant placement, supporting procedural consistency in the histological assessment.

Clinical significance: Both biomaterials supported bone regeneration after staged transcrestal sinus floor elevation. The synthetic hydroxyapatite scaffold showed more newly-formed bone and a lower percentage of area occupied by residual graft material at 6 months, but the clinical significance of these preliminary findings requires confirmation in larger randomized studies with long-term follow-up.

1. Introduction

Tooth loss in the posterior maxilla is frequently followed by alveolar

ridge resorption and maxillary sinus pneumatization, both contributing to a progressive reduction in residual bone volume [1–4]. In this clinical setting, maxillary sinus augmentation has become a standard procedure

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for implant rehabilitation. The lateral approach has been shown to provide consistent, predictable results with high rates of long-term implant survival [5]. However, post-operative complications remain a concern, primarily due to the procedural morbidity associated with extensive flap elevation and the creation of a lateral osteotomy window [6–9].

Several alternative strategies have been proposed, including transcrestal sinus floor elevation, graftless sinus augmentation, and the use of short or tilted implants, as well as pterygoid and zygomatic implants [10].

Transcrestal sinus floor elevation (tSFE) is an established technique for vertical bone augmentation in the edentulous posterior maxilla, offering a less invasive alternative to the lateral approach [11]. While effective, also tSFE carries a risk of intra-operative and post-operative complications mainly due to the limited visual control inherent to its blind execution [12]. Nonetheless, its reduced surgical invasiveness, characterized by the absence of extensive flap elevation and lateral osteotomy, contributes to lower morbidity and improved patient acceptance compared with the conventional window approach [13]. Historically, the Sinus Consensus Conference held in Boston in 1996 recommended transcrestal sinus floor elevation in sites with 7–9 mm of residual bone height, based on the limited availability and poor prognosis of short implants at the time [14]. However, current evidence has shifted this paradigm: given the favorable clinical outcomes reported with short implants [15–17], both transcrestal and lateral sinus augmentation are now primarily indicated when residual bone height is less than 5 mm, where implant placement becomes unfeasible without grafting procedures. Recent studies and consensus papers clarified that the key factor in the algorithm for choosing between transcrestal or lateral approach lies primarily in the medio-buccal width of the sinus itself [10,18,19].

The transcrestal sinus elevation technique is particularly indicated in cases of narrow maxillary sinuses, where proper membrane elevation can be predictably achieved. In contrast, its application in wide sinus cavities is associated with an increased risk of Schneiderian membrane perforation, attributable to the larger surface area requiring detachment and the correspondingly greater mechanical forces involved, which may exceed the membrane's elastic capacity. This biomechanical limitation, corroborated by both clinical evidence and *in vitro* studies, suggests that a lateral window approach may be more appropriate in such anatomical scenarios to minimize the risk of membrane damage [20,21].

In transcrestal approach, the use of sinus elevators may reduce the risk of complications [22]. As in the lateral sinus floor elevation, once access to the Schneiderian membrane is achieved through the sinus floor, elevators can be also employed to favor initial membrane detachment from the floor. However, for this specific clinical situation, the use of modified sinus elevators is required.

At this stage, crestal membrane elevation can be completed through the direct insertion of granular, spongy or gel-form bone substitutes. These biomaterials, depending on their origin (autologous, allogeneic, xenogeneic, or synthetic), support bone regeneration in the newly-created sub-antral space through their osteoconductive properties and, where present, osteoinductive potential.

Among the various bone substitutes used in transcrestal sinus augmentation, one widely adopted option is the collagen-enriched bovine-derived bone substitute. This material is composed predominantly of deproteinized bovine bone granules combined with a minor fraction of highly purified porcine collagen. The addition of collagen improves the handling properties and moldability of the graft, facilitating its clinical application. The mineral phase serves as an osteoconductive scaffold, promoting new bone formation and supporting tissue integration over time [23]. Furthermore, its slow resorption rate contributes to the long-term maintenance of graft volume and structural stability throughout the healing and remodelling phases [24].

Among available grafting materials, composite scaffolds combining cross-linked collagen matrices with synthetic hydroxyapatite

microparticles have also been proposed for sinus augmentation procedures. These products present a porous, sponge-like architecture that not only supports osteogenesis but also enhances angiogenesis and cellular infiltration [25]. The sugar-based cross-linking of collagen enhances the mechanical integrity and longevity of the scaffold in the biological environment. Some studies have reported that such materials may result in a higher proportion of vital bone compared to traditional xenografts, potentially leading to improved integration with host tissue and more predictable regenerative outcomes [26].

The primary objective of the present prospective non-randomized comparative study was to compare the histomorphometric outcomes of regenerated bone following transcrestal sinus floor elevation using either a cross-linked collagen/synthetic hydroxyapatite scaffold or a collagen-enriched bovine-derived xenograft. The secondary objectives were to compare radiographic volumetric and linear changes, inflammatory response, and implant osseointegration between the two groups. The null hypothesis was that no significant differences would be observed between the two graft materials in terms of newly-formed bone, residual graft material, inflammatory score, radiographic bone gain, or graft volume at six months.

2. Materials and methods

2.1. Study design

This prospective non-randomized comparative clinical study was designed to evaluate, in transcrestal maxillary sinus floor elevation, the clinical performance of cross-linked collagen sponges incorporating synthetic hydroxyapatite microparticles (test group) compared with a collagen-enriched bovine-derived bone substitute (control group), and was conducted and reported in accordance with the STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The present study was carried out following the principles of the Helsinki Declaration, as revised in Fortaleza (2013) [27]. On 25th November 2022, the Ethics Committee Lazio 1 (Rome, Italy) authorized the protocol of the present clinical study (n. 933, protocol 1239–25/11/2022), which was recorded on a public database of clinical trials (www.clinicaltrials.gov - #NCT07041411).

The study was conducted in a private dental clinic in Rome, Italy, where all surgical procedures were performed by two surgeons (LC and RM) between December 2022 and November 2024.

Written informed consent was obtained from all participants prior to enrollment, and all data were anonymized in accordance with ethical research standards.

2.2. Study population and group allocation

All patients requiring an implant-supported restoration of a single edentulism in the posterior maxilla were screened for possible enrollment in the present study. Inclusion criteria were the following: i) residual alveolar bone height <5 mm beneath the maxillary sinus floor; ii) healed bone crest (at least 12 weeks elapsed from tooth extraction); iii) age between 30 and 80 years; iv) ASA I or II status; v) periodontal health or treated periodontitis (PI<25%, BoP<10%); vi) willingness to sign informed consent and attend follow-up visits. Exclusion criteria were: i) smoking > 5 cigarettes/day; ii) pregnancy (confirmed by verbal inquiry); iii) chronic systemic pathologies (e.g. diabetes); iv) neoplasms of the oro-facial district; v) present or past treatment with antiresorptive or anti-angiogenic agents; vi) chronic systemic corticosteroid therapy; vii) chronic inflammatory diseases of the oral cavity; viii) autoimmune diseases; ix) documented hypersensitivity to any medication used in the study protocol; x) substance abusers; xi) history of malignant tumors of the maxillary sinus; xii) history of head/neck radiation therapy.

Patients were assigned to either the test group (treated with cross-linked collagen combined with synthetic hydroxyapatite) or the

control group (treated with a collagen-enriched, bovine-derived bone substitute) based on the chronological order of recruitment. The first series of sinus floor elevation procedures was performed using the test material, followed by subsequent cases treated with the control material.

2.3. Sample size calculation

An *a priori* power analysis was performed using G*Power version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) to estimate the minimum sample size for detecting between-group differences. The calculation used $\alpha = 0.05$, $\beta = 0.16$, a two-tailed test, a 1:1 allocation ratio, and an estimated effect size of $d = 1.25$ based on preliminary internal data. The required sample size was 13 participants per group. Because no directly comparable published data were available at the time of study planning, this calculation should be considered a feasibility estimate rather than a definitive power justification. Given the large assumed effect size and the limited sample size, the study should be regarded as preliminary and may be underpowered to detect smaller differences, particularly in regional histological analyses.

2.4. Experimental phase

2.4.1. Surgical procedures

All patients underwent a comprehensive pre-operative evaluation. This included a full periodontal examination, assessment of occlusal relationships, and evaluation of the prosthetic space. In addition, a cone-beam computed tomography (CBCT) scan and intraoral digital impressions of both arches were performed to support virtual case planning and surgical guide fabrication. The resulting Standard Tessellation Language (STL) and Digital Imaging and Communications in Medicine (DICOM) files were matched and integrated into a digital workflow for virtual planning using dedicated software (RealGUIDE, 3DIEMME, Cantù, Italy) (Fig. 1).

Following the administration of local anesthesia (2% mepivacaine HCl with 1:100,000 epinephrine), a minimally invasive full-thickness envelope flap was elevated to expose the surgical site. Access to the

sinus cavity was achieved via a crestal approach. The initial osteotomy was performed using a 2 mm drill through the surgical guide until contact with the cortical bone of the sinus floor was achieved. Subsequently, osteotomes of increasing diameters (typically 2.0, 2.7, 3.5, and 4.0 mm) were used to complete the crestal antrostomy. A preliminary detachment of the Schneiderian membrane was performed using specially designed microelevators (Dajelevators, Umberto Merighi, Valsamoggia, Italy). After membrane integrity was confirmed with the Valsalva maneuver, the selected bone substitute, pre-hydrated with the patient's blood, was inserted in small increments and gently compacted with a plugger to further elevate the Schneiderian membrane from the sinus floor and adjacent bony walls. Cross-linked collagen combined with synthetic hydroxyapatite (Ossix Bone, Dentsply Sirona, Charlotte, NC, USA) was inserted in test group, while a collagen-enriched, bovine-derived bone substitute (Bio-Oss Collagen, Geistlich, Wolhusen, Switzerland) was used in the control group. Once adequate elevation had been achieved, defined as a total height of at least 10 mm from the crestal bone level to the elevated membrane position as assessed on intra-operative periapical radiographs, the crestal access was sealed with a final increment of graft material.

The flap was then closed using resorbable 6–0 sutures (Monofast, Medipac, Kilkis, Greece), using either single interrupted stitches or the Sentineri technique [28]. Post-operative care included a 5-day antibiotic regimen (amoxicillin/clavulanate 1 g twice daily) and nonsteroidal anti-inflammatory medication (ketoprofen 80 mg as needed). Sutures were removed after 14 days, and healing was monitored on a monthly basis.

2.4.2. Dental implants installation and prosthetics

After a 6-month healing period, a CBCT scan was performed to assess the quality and maturation of the regenerated tissue. Subsequently, dental implants (PrimeTaper Implant System, Dentsply Sirona, Charlotte, NC, USA) were placed according to the pre-established surgical plan. Following local anesthesia and minimally invasive flap elevation, the osteotomy was performed through the surgical guide. A 4 mm external diameter trephine bur, mounted on a surgical motor (SA-310 Elcomed, W&H, Bürmoos, Austria), was used to harvest a bone core



Fig. 1. Illustrative case of virtual planning performed with dedicated software (RealGUIDE, 3DIEMME, Cantù, Italy), which matched and integrated STL and DICOM files from digital dental impression and CBCT scan, respectively.

from the planned implant site. The implant osteotomy was then completed, and the implant was inserted.

After an additional 4-month healing period, prosthetic rehabilitation was performed following standard clinical protocols.

2.4.3. Linear and tridimensional measurements analyses

To assess dimensional changes in the grafted area, pre-operative and 6-month post-operative CBCT scans were analyzed. Variations in the augmented region were evaluated in terms of bone height and graft volume. For linear measurements, the implant site was used as a reference, and assessments were performed along the ideal implant axis, previously determined using 3D planning software (RealGUIDE, 3DIE-MME, Cantù, Italy). Crestal bone height (CBH) was defined as the vertical distance between the alveolar crest and the sinus floor.

Sinus width was measured as the medio-buccal dimension at 10 mm from the crest. According to the classification proposed by Stacchi et al. [29], a threshold of 12 mm was used to define the sinus as either wide (>12 mm) or narrow (≤ 12 mm). For volumetric analysis, three-dimensional reconstructions of the grafted areas on 6-month CBCTs were obtained using a semi-automatic segmentation protocol performed using 3D Slicer (version 5.2.1), an open-source software platform for medical image analysis (www.slicer.org) [30]. Segmentation was carried out using a combination of threshold-based and manual refinement techniques (Fig. 2). For each site, a STL file of the grafted volume was generated. STL files were then processed using GOM Software 2022 Service Pack 2 (Carl Zeiss GOM Metrology, Göttingen, Germany) to calculate the total graft volume, expressed in cubic millimeters (mm^3) (Fig. 3).

All linear and volumetric measurements were performed by an

independent, blinded examiner (A.T.), after calibration against a reference examiner (L.C.) using ten randomly selected linear and volumetric assessments. Intra- and inter-examiner agreement for linear measurements within ± 0.1 mm was 96.4% and 92.6%, respectively, with corresponding intraclass correlation coefficients (ICC) of 0.96 and 0.93, indicating excellent reliability. For volumetric measurements within ± 5 mm^3 , intra- and inter-examiner agreement was 95.1% and 89.7%, respectively, with ICC values of 0.95 and 0.90, confirming the high reproducibility of the measurement protocol.

2.4.4. Histological analysis

Histological analysis was performed by one blinded independent assessor (P.S.). Bone samples were fixed in 10% buffered formalin (Carlo Erba Reagents, Cornaredo, Italy) immediately after harvesting to minimize tissue alterations. Fixation was carried out for 72 h, followed by a thorough rinse in water to remove residual formalin. Samples were then decalcified in 17% EDTA, pH 10 (Carlo Erba Reagents, Cornaredo, Italy) using a microwave-assisted protocol, as previously described [31]. The endpoint of decalcification was determined using the ammonium oxalate chemical test [32]. After decalcification, specimens underwent dehydration in a graded ethanol series (70% to 100%), xylene clarification, and paraffin embedding [33]. Histological section 4 μm thick were obtained using a rotary microtome (RM2245, Leica Biosystems, Nussloch, Germany). Only sections derived from the central portion of each biopsy, thereby avoiding areas potentially affected by friction from the trephine bur, were included in the analysis. Residual native crestal bone was excluded from histomorphometric analysis: the region of interest was limited to the regenerated sub-antral compartment, identified according to the baseline sinus floor position and the orientation of the harvested core. Sections were mounted on silanized glass slides (VWR International, Radnor, PA, USA) and stained with hematoxylin and eosin (Carlo Erba Reagents, Cornaredo, Italy) to enable identification and quantification of newly-formed bone and residual biomaterial, as well as qualitative assessment of soft tissue morphology, cellular composition, and inflammatory response.

Images were acquired using a transmitted light microscope (CX43, Olympus Corporation, Tokyo, Japan) equipped with an Olympus LC30 camera and processed with LCmicro software (version 2.2) (Olympus Corporation, Tokyo, Japan). For each sample, three representative sections were analyzed. Multiple high-resolution micrographs were taken per section and digitally stitched into a single panoramic image using AutoStitch software (version 1.0) (University of British Columbia, Vancouver, Canada; www.cs.ubc.ca/~mbrown/autostitch/autostitch.html) [34]. These composite images were used for histomorphometric analysis to quantify the areas of newly-formed bone and residual biomaterial, expressed as a percentage of the total section area. Measurements were performed on all three sections, and the arithmetic mean was calculated. Image analysis was carried out using ImageJ software (National Institutes of Health, Bethesda, MD, USA; <https://imagej.nih.gov/ij/>). The same images were also used for qualitative evaluation.

For standardized analysis, each bone core was divided into 2.5 mm-long segments, to avoid comparing areas with different regenerative patterns within the same plane, and to reduce potential bias caused by core fractures during harvesting or processing. Although efforts were made to obtain cores of uniform length (7–8 mm), intact samples were not always retrievable due to mechanical fragility during trephine extraction or decalcification. For this reason, the segmental analysis approach was adopted as the methodological standard: poorly mineralized samples, in which only a limited segment could be evaluated, were thus not weighted equally to longer, structurally intact specimens. Non-regenerated portions were excluded from analysis when their mechanical integrity was compromised.

In addition, hematoxylin and eosin (H&E) staining was used for a semi-quantitative assessment of inflammatory infiltrates, based on a previously validated scoring system [35]. Inflammatory response was

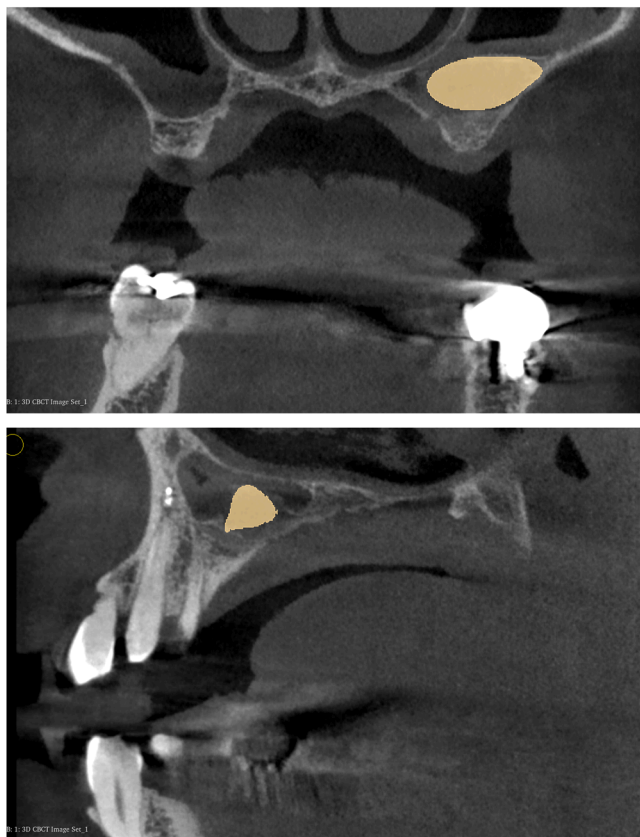


Fig. 2. Three-dimensional reconstruction of the grafted sinus area obtained through semi-automatic segmentation in 3D Slicer (version 5.2.1). Segmentation was performed using a combination of threshold-based and manual refinement tools, and the resulting model was exported as an STL file for volumetric analysis.

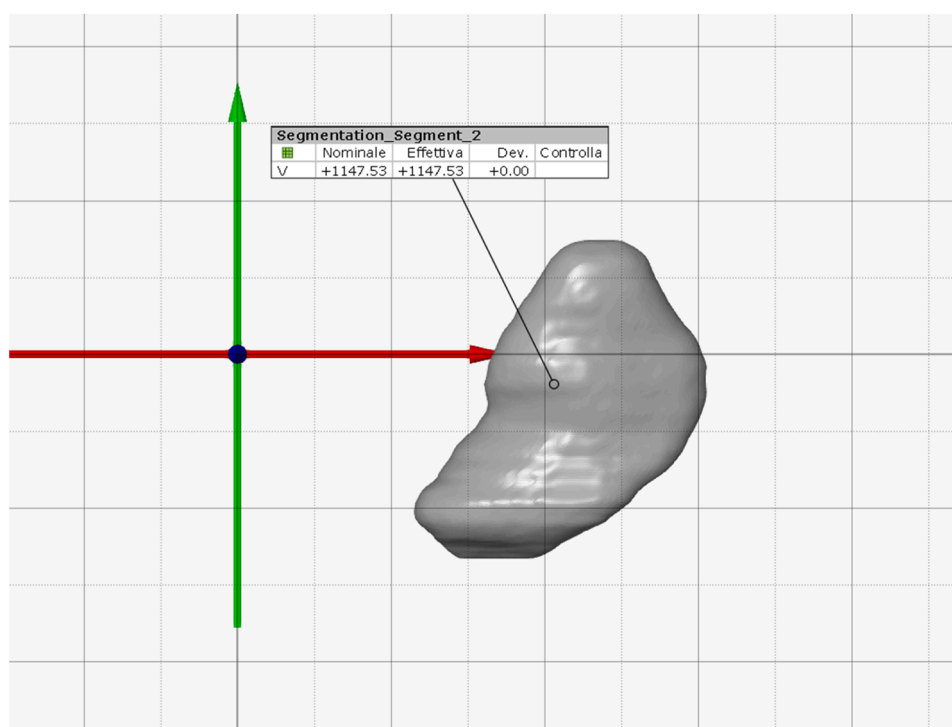


Fig. 3. Volumetric analysis of the segmented graft using GOM Software 2022 Service Pack 2 (Carl Zeiss GOM Metrology, Göttingen, Germany). STL files generated from the segmented models were processed to compute the total volume of the grafted area, expressed in cubic millimeters (mm^3).

graded according to the density and distribution of inflammatory cells, as follows:

- Score 0: No inflammatory infiltrate
- Score 1: Occasional isolated mononuclear cells
- Score 2: Focal mononuclear infiltrate with limited distribution
- Score 3: Diffuse mononuclear infiltrate of moderate intensity
- Score 4: Extensive infiltrate with cellular aggregates and/or granulocytic components

2.4.5. Outcomes and predictor variables

The primary outcome of the present study was the percentage of newly-formed bone within the regenerated sinus area after 6 months of healing, assessed by histomorphometric analysis of bone core biopsies harvested at implant placement. Secondary outcomes included: (1) the percentage of residual graft material, also determined histomorphometrically; (2) the degree of inflammatory cell infiltration in the grafted area, evaluated through histological grading; and (3) radiographic parameters obtained from CBCT, including linear bone height gain and volumetric changes in the grafted region between baseline (pre-operative) and 6 months post-operatively.

Predictor variables were selected based on their potential influence on bone regeneration and included: type of grafting material (cross-linked collagen/synthetic hydroxyapatite composite vs. collagen-enriched xenograft), patient age, gender, baseline residual bone height, medio-buccal sinus width, smoking status, and occurrence of Schneiderian membrane perforation during surgery.

All histomorphometric measurements were expressed as mean percentage $\pm$ standard deviation for each biopsy segment (coronal, middle, and apical thirds, as well as the entire core), while radiographic changes were expressed in millimeters (linear) and cubic millimeters (volumetric).

2.4.6. Statistical analysis

Statistical analysis and data visualization were performed using GraphPad Prism (version 8.0.1 for Windows; GraphPad Software,

Boston, MA, USA). All variables in the dataset were first tested for normality using the Shapiro–Wilk test. Data were then summarized using mean and standard deviation for normally distributed variables, or median and interquartile range (IQR) for non-normally distributed variables.

Differences between the test and control groups in terms of age, residual crestal bone height, sinus medio-buccal dimension, total mineralized tissue, newly-formed bone, residual graft, and mesh volume (mm^3) were assessed using either the unpaired *t*-test or the Mann-Whitney U test, depending on the normality of distribution. Differences in categorical variables (gender, smoking habits, history of periodontitis, presence of membrane perforation) were assessed using the Fisher's exact test. Intergroup differences in the mean ranks of newly-formed bone and residual graft across the three defined regions of the bone core were analyzed using the Kruskal-Wallis test.

For all statistical analyses, a *p*-value ≤ 0.05 was considered statistically significant. The null hypothesis in each case stated that there was no difference between groups for the parameter being tested.

3. Results

3.1. Patient enrollment, characteristics, and follow-up

Out of 46 consecutively enrolled patients, 28 met the inclusion criteria, while 17 were excluded, and 1 patient withdrew prior to surgery. The first 14 eligible patients were allocated to the test group, and the subsequent 14 to the control group. Two patients (one from each group) dropped out before implant placement. Finally, 13 patients per group were included in the final analysis (6 males, 20 females; mean age: 61.2 years, SD: 8.2). The study flow is summarized in Fig. 4.

No significant differences were observed between the two groups in terms of age (*t*-test: *p* = 0.55), gender (Fisher's exact test: *p* = 1.00), smoking habits (Fisher's exact test: *p* = 1.00), and history of periodontitis (Fisher's exact test: *p* = 0.69). Detailed demographic and clinical characteristics are reported in Table 1.

After transcrestal antrostomy, three minor Schneiderian membrane

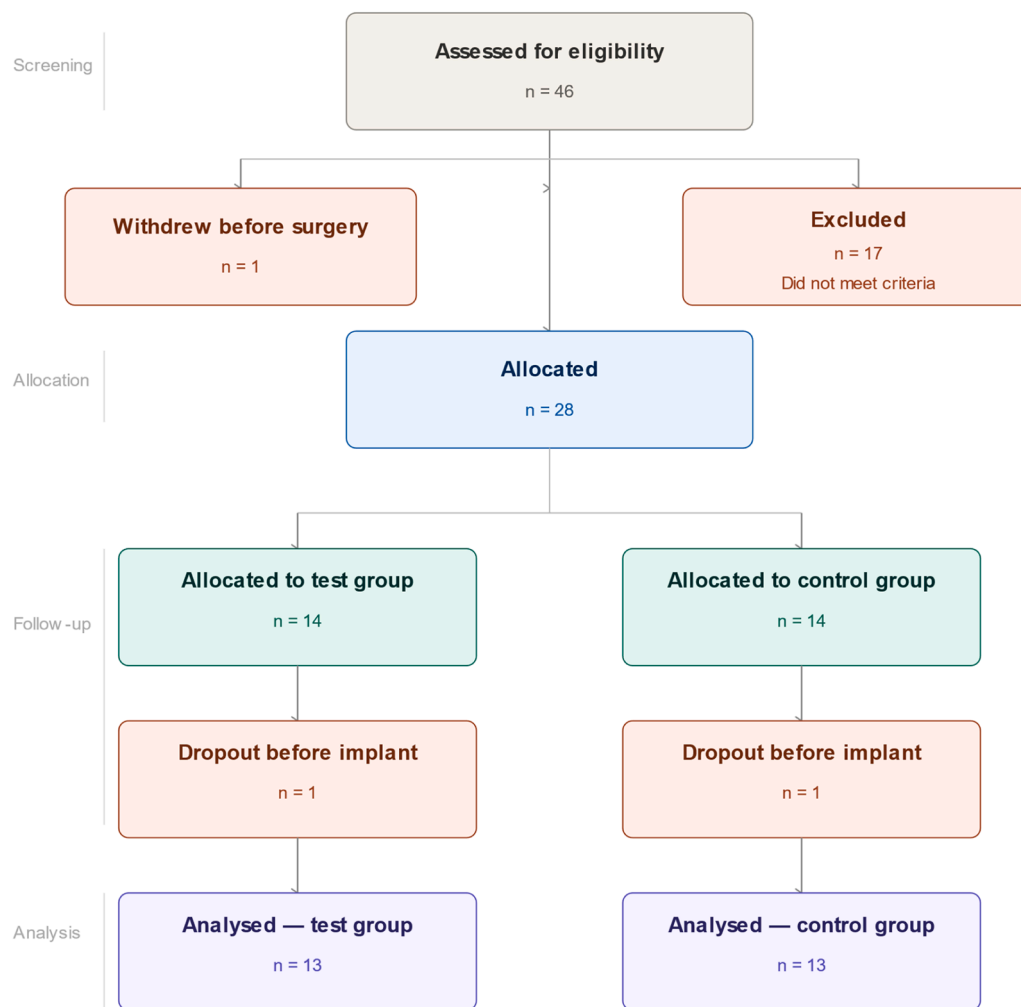


Fig. 4. Summary of the screening, exclusion, allocation, follow-up, and analysis process.

Table 1

Characteristics of patients included in the final analysis.

	Test	Control
Number	13	13
Gender (M/F)	3/10	3/10
Mean age (years)	59.6 ± 9.21	62.0 ± 7.27
Smoking (<5 c/d)	4	5
ASA 1/2	4/9	2/11
History of periodontitis	4	6
Residual bone height (mm)	3.34 ± 0.98	2.26 ± 1.43
Bucco-palatal sinus width (mm)	15.6 ± 2.8	14.6 ± 2.4

M: male; F: female; c/d: cigarettes per day; ASA: American Society of Anesthesiologists classification; mm: millimeters.

perforations were observed (Type I_s, according to Tavelli et al. 2020) [36]. In each case, following careful membrane elevation with manual elevators, the perforation was managed by placing a collagen membrane before proceeding with graft placement. One perforation occurred in the test group and two in the control group, with no statistically significant difference between groups (Fisher's exact test, $p = 1.00$).

A total of 26 implants were placed six months after transcrestal sinus floor elevation (5 mm diameter; 8 or 10 mm length). The overall implant osseointegration rate at reentry, following four months of submerged healing, was 100%.

3.2. Radiographic analysis

The comparison between pre-operative and 6-month post-operative CBCT scans showed that the test group exhibited a mean volumetric gain of 676.2 mm³ (SD: 399.9 mm³). The mean available bone height at the implant site increased from 3.34 mm (SD: 0.98 mm) at T0 to 10.16 mm (SD: 2.45 mm) at T1. In the control group, the mean volumetric gain at T1 was 569.2 mm³ (SD: 428.1 mm³). The mean available bone height at the implant site increased from 2.26 mm (SD: 1.43 mm) at T0 to 10.7 mm (SD: 2.66 mm) at T1.

Although residual bone height at baseline was significantly greater in the test group compared to the control group (t -test: $p = 0.004$), no significant differences were observed between the two groups in terms of mean volume gain (Mann-Whitney U test: $p = 0.71$) and mean bone height (t -test: $p = 0.61$) after six months of healing.

The mean medio-buccal sinus width was 15.6 mm (SD: 2.8 mm) in the test group (2 narrow, 11 wide sinuses) and 14.6 mm (SD: 2.4 mm) in the control group (2 narrow, 11 wide sinuses), with no statistically significant difference between groups (t -test, $p = 0.38$).

3.3. Histological and histomorphometric analysis

All 26 biopsies, 13 in the test group and 13 in the control group, were included in the whole-core histomorphometric analysis. Bone cores retrieved from the test group were generally longer than those from the control group, although the difference did not reach statistical significance (Mann-Whitney U test, $p = 0.08$). The mean core lengths were

5.77 mm (SD: 0.83 mm) in the test group and 4.86 mm (SD: 1.46 mm) in the control group.

In the control group, the trabecular architecture of the regenerated area appeared irregular and fragmented, whereas the test group exhibited more continuous and organized trabeculae, although areas of ongoing bone maturation remained evident, particularly in proximity to residual graft. Distinct morphological differences between the two bone substitutes were observed. The test material demonstrated signs of replacement resorption, with residual particles gradually degraded and replaced by newly-formed bone. In contrast, the control material largely maintained its original structure over time, suggesting limited remodelling activity and slower resorption dynamics.

The intra-trabecular tissue also differed between groups. In the control samples, it often consisted of dense fibrous connective tissue with diffuse mononuclear inflammatory infiltrates. In contrast, test group specimens typically presented looser connective tissue, particularly in areas of complete graft resorption, and showed no significant inflammatory cell presence. Where residual graft was still present, the surrounding tissue exhibited increased cellularity and matrix density, consistent with active remodelling (Fig. 5A and 5B).

The semi-quantitative inflammatory score supported these findings. The control group exhibited a mean score of 2.39 (SD: 0.63), with values ranging from 1 to 3, and no samples entirely without inflammatory infiltrates. In contrast, the test group demonstrated a significantly lower mean score of 0.77 (SD: 0.72), ranging from 0 to 2, with four samples (31%) showing no detectable inflammation. This difference was statistically significant (Mann–Whitney U test, $p < 0.001$).

The percentage of newly-formed bone across the entire biopsy was compared between the test and control groups. The data distribution

was non-normal, as confirmed by the Shapiro–Wilk test ($W = 0.924$, $p = 0.00017$). Therefore, a non-parametric test was applied. The Mann–Whitney U test revealed a statistically significant difference between the two groups ($U = 1045.5$, $p = 0.0041$), with the test group showing a higher mean percentage of newly-formed bone (mean: 31.6%; SD: 21.6%) compared to the control group (mean: 18.2%; SD: 16.0%). The comparison of residual graft percentages in the entire biopsy between the test and control groups was also performed using the Mann–Whitney U test. The test group showed significantly lower percentages of residual graft material (mean: 2.2%, SD: 6.3%) compared to the control group (mean: 6.2%, SD: 6.8%) ($U = 478.0$; $p = 0.003$).

For regional analysis, the coronal segment was evaluable in 13 test and 13 control samples. The middle segment was evaluable in 13 test and 10 control samples, while the apical segment was evaluable in 8 test and 4 control samples. Samples or portions of samples were excluded from regional analysis when fragmentation or poor structural integrity prevented reliable histomorphometric assessment. In the most coronal segment of the biopsy, defined as the 2.5 mm closest to the sinus floor, the mean percentage of newly-formed bone was 40.6% (SD: 20.0%) in the test group and 28.0% (SD: 11.8%) in the control group. Although a trend toward greater new bone formation was observed in the test group, the difference did not reach statistical significance (Mann–Whitney U test, $p = 0.065$). In the same segment of the biopsy, residual graft material was significantly less represented in the test group (mean: 5.1%, SD: 10.4%) compared to the control group (mean: 8.7%, SD: 4.9%). This difference was statistically significant, as determined by the Mann–Whitney U test ($p = 0.005$).

In the middle third of the biopsy (defined as the segment between 2.5 mm and 5 mm from the sinus floor), the mean percentage of newly-

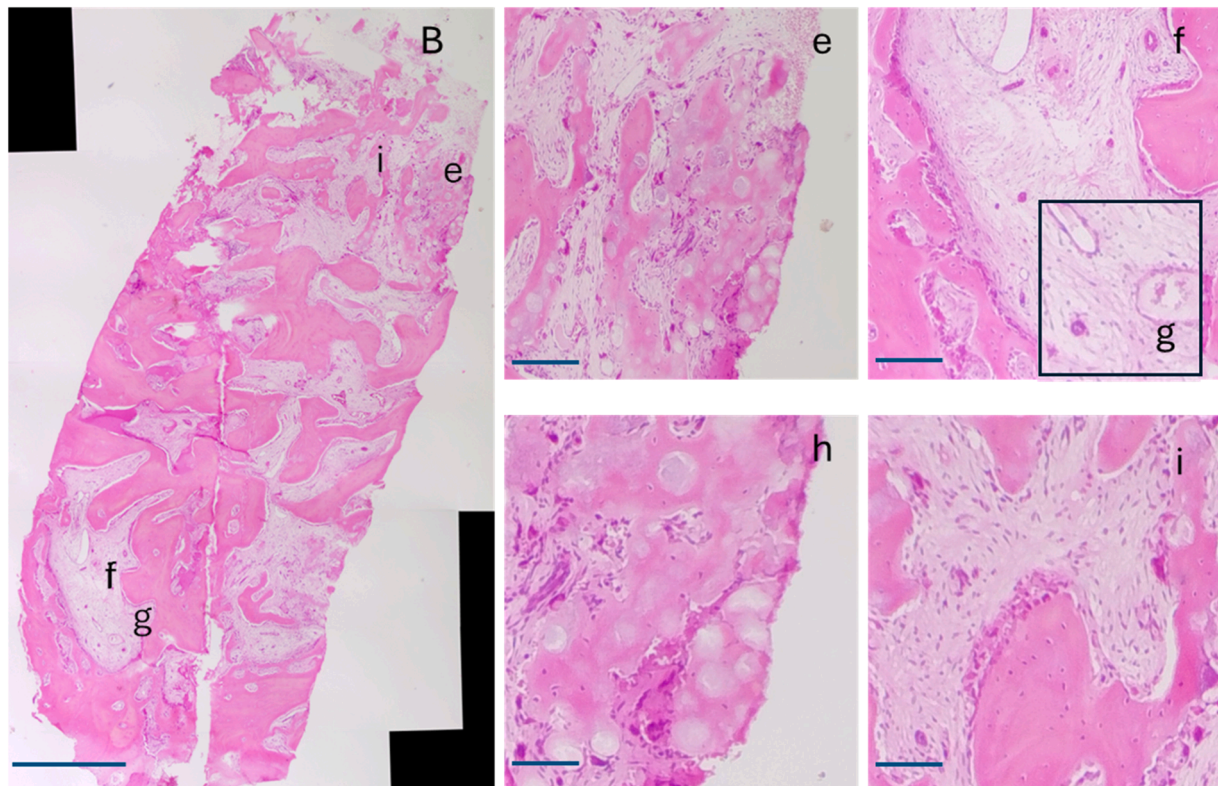


Fig. 5A. Histological section of regenerated tissue after grafting with hydroxyapatite-based cross-linked collagen sponge stained with hematoxylin and eosin; scale bar: 1 mm. A relatively thick trabecular architecture is visible, gradually thinning toward the apical portion of the core, where residual graft material remains detectable. In images e and h (e: magnification 100 $\times$, scale bar: 200 μ m; h: cropped detail, scale bar: 400 μ m), the remaining bone substitute appears globular in morphology and is embedded within the newly-formed bone matrix. It exhibits lower density than the surrounding bone, as indicated by its lighter eosin staining. In regions where residual graft is still present, the intratrabecular connective tissue appears fibrous and compact. Conversely, in areas of more advanced bone regeneration (image f: magnification 100 $\times$, scale bar: 200 μ m; image g: detail of f), the connective tissue is looser and less dense. No relevant signs of inflammation were observed across the sample. Several osteoblasts are visible lining the trabecular surfaces (image i: magnification 100 $\times$, scale bar: 200 μ m).

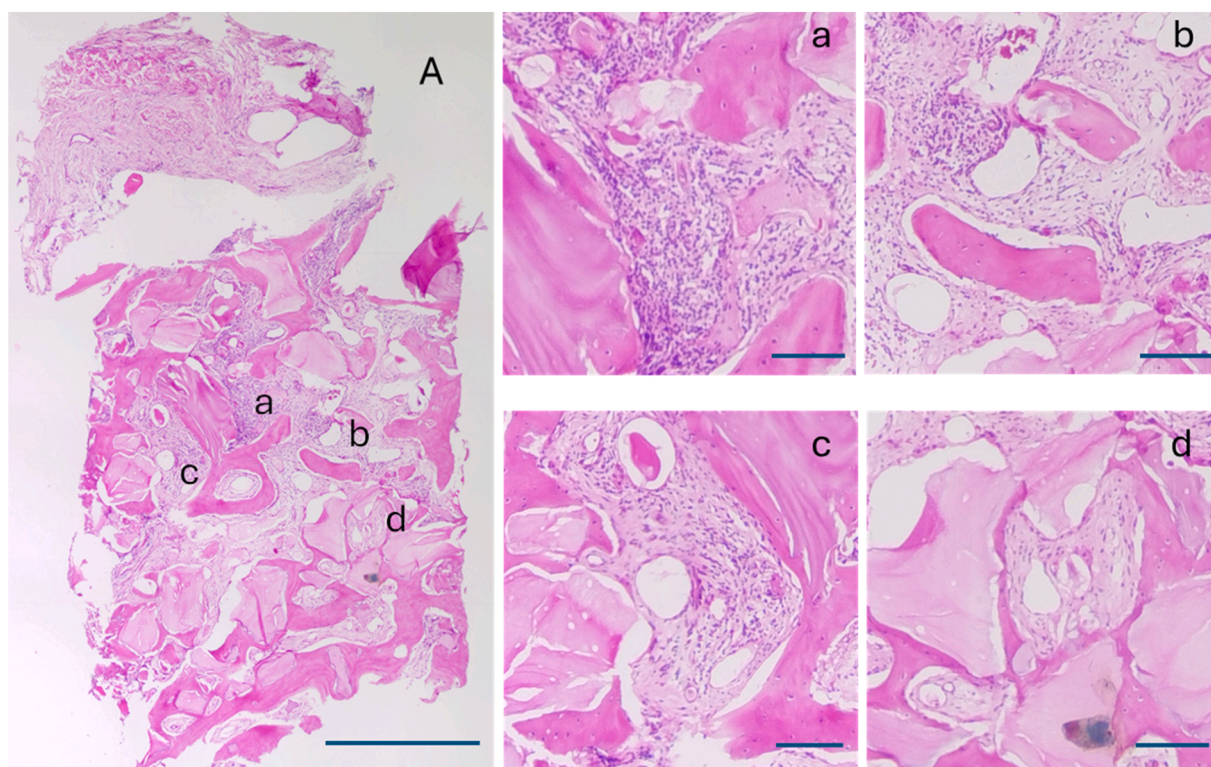


Fig. 5b. Histological section of regenerated tissue after grafting with collagen-enriched bovine-derived graft stained with hematoxylin and eosin; scale bar: 1 mm. A moderate amount of newly-formed bone is present, although its distribution is uneven. Residual graft granules remain clearly identifiable, as seen in image d (magnification 100 $\times$, scale bar: 200 μ m); they are partially surrounded by new bone, but areas of incomplete integration are evident, with visible gaps both within and around the granules. A diffuse inflammatory infiltrate is observed throughout the sample, particularly evident in images a and b. In the latter, a cluster of inflammatory cells is seen adjacent to a blood vessel (magnification 100 $\times$, scale bar: 200 μ m). The intratrabecular tissue is predominantly fibrous connective tissue, as illustrated in image c (magnification 100 $\times$, scale bar: 200 μ m); it appears compact, with no marked signs of fibrosis in the examined section.

formed bone was higher in the test group (39.2%, SD: 15.1%) compared to the control group (27.4%, SD: 12.0%), but without reaching statistical significance (Mann-Whitney U test, $p = 0.09$). In this area, the mean percentage of residual graft was significantly lower in the test group (1.6%, SD: 1.6%) than in the control group (10.6%, SD: 8.6%) (Mann-Whitney U test, $p = 0.001$).

In the apical third of the biopsy (defined as the portion between 5 mm and 7.5 mm from the sinus floor), the test group showed a mean percentage of newly-formed bone of 24.5% (SD: 20.9%), while the control group had a mean of 17.5% (SD: 15.1%). The difference between groups was not statistically significant (Mann-Whitney U test, $p = 0.68$). Regarding residual graft material, the test group exhibited a minimal mean percentage of 0.05% (SD: 0.1%), compared to 6.0% (SD: 5.4%) in the control group. This difference was also not statistically significant ($p = 0.07$). Descriptive statistics for all variables, categorized by treatment group and biopsy core segment are listed in Table 2.

Intragroup comparisons were performed to evaluate the distribution

of newly-formed bone and residual graft across the three predefined regions of the biopsy core (coronal, middle, and apical thirds). In the test group, the percentage of newly-formed bone did not differ significantly among regions (Kruskal-Wallis, $p = 0.18$). However, a significant difference was found for the percentage of residual graft among the three thirds (Kruskal-Wallis, $p = 0.03$). In the control group, no statistically significant intragroup differences were detected among regions for either newly-formed bone ($p = 0.51$) or residual graft ($p = 0.60$) (Fig. 6).

4. Discussion

The present study aimed to evaluate histological and radiographic outcomes following digitally guided tSFE using either a composite graft composed of cross-linked collagen integrated with synthetic hydroxyapatite (Ossix Bone, Dentsply Sirona, Charlotte, NC, USA) or a collagen-enriched, bovine-derived xenograft (Bio-Oss Collagen, Geistlich, Wolhusen, Switzerland). The null hypothesis of the study was partially

Table 2

Descriptive statistics for all variables, categorized by treatment group and biopsy core segment.

Group		SW (mm)	Mesh volume (mm ³)	coronal portion			middle portion			apical portion			entire biopsy		
				NFB (%)	RG (%)	MS (%)	NFB (%)	RG (%)	MS (%)	NFB (%)	RG (%)	MS (%)	NFB (%)	RG (%)	MS (%)
CONTROL	Mean	14.6	569.2	28.0	8.7	63.3	27.4	10.6	62.0	17.5	6.0	76.5	18.2	6.2	75.6
	SD	2.4	428.1	11.8	4.9	13.2	12.0	8.6	13.2	15.1	5.4	20.6	16.0	6.8	13.1
TEST	Mean	15.6	676.2	40.6	5.1	54.3	39.2	1.6	59.2	24.5	0.05	75.4	31.6	2.2	66.1
	SD	2.8	399.9	20.0	10.4	10.9	15.1	1.6	15.2	20.9	0.1	20.9	21.6	6.3	22.3
Diff.	p-value	0.38	0.71	0.065	0.005*	0.88	0.09	0.001*	0.71	0.68	0.07	0.79	0.004*	0.003*	0.78

SW: medio-buccal sinus width; NFB: newly-formed bone; RG: residual graft; MS: marrow spaces; SD: standard deviation; Diff: difference; *: statistically significant.

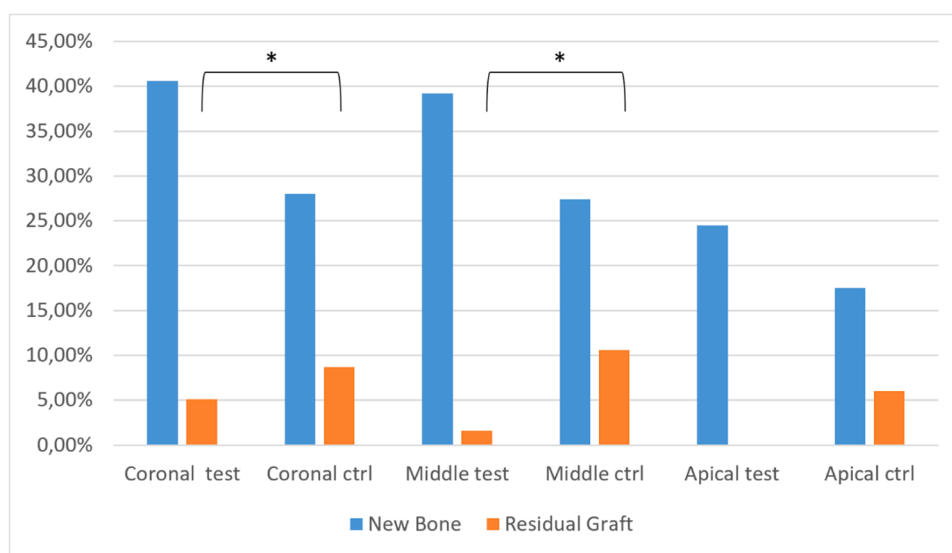


Fig. 6. Comparison of new bone and residual graft percentages between test and control (ctrl) groups in coronal, middle, and apical biopsy sections. *: statistically significant difference.

rejected. Significant differences were observed between groups for whole-core newly-formed bone, residual graft material, and inflammatory score, whereas no significant differences were detected for radiographic volume gain or post-operative bone height.

Clinical indications for tSFE have broadened in recent years [10], primarily due to its minimally invasive nature compared to the lateral window technique. Over the past decade, its application has also extended to cases with residual bone height less than 5 mm [19,37–40]. However, this indication should be approached with caution, as clinical outcomes are strongly influenced by sinus morphology. In particular, the medio-buccal width affects the mechanical stress exerted on the Schneiderian membrane during its indirect elevation by the graft material, thereby increasing the risk of perforation [20,21]. Moreover, in wide sinus configurations, predictable membrane elevation extending to the lateral and medial bony walls is often unachievable, thereby limiting the extent of membrane displacement and reducing the regenerative potential of the augmented space [29,41,42]. In the present study, no significant differences in sinus width were observed between test and control groups, thereby strengthening the clinical relevance of the findings by minimizing the influence of anatomical variability as a potential confounding factor. Moreover, the use of specially designed micro-elevators to facilitate the initial detachment of the Schneiderian membrane from the sinus floor, prior to graft insertion, may have contributed to a smoother and more controlled membrane elevation. Three small Schneiderian membrane perforations occurred across 26 procedures (11.5%), with no significant difference between the test and control groups. This incidence aligns with rates reported in the current literature [21,43,44].

Radiographically, hydroxyapatite-based cross-linked collagen sponge and collagen-enriched bovine-derived graft produced a similar vertical bone gain after 6 months, with no significant differences in graft volume or post-regeneration bone height. This suggests that, despite their differing compositions, both graft materials provided sufficient volumetric stability in the sub-antral space throughout the healing period. Therefore, they may be both considered as suitable options for staged transcrestal sinus floor elevation procedures, when simultaneous implant placement is not feasible.

Histological and histomorphometric analyses revealed significant differences in tissue quality, remodelling kinetics, and inflammatory response between the two bone substitutes. The test group showed significantly higher percentages of newly-formed bone and lower residual graft material compared to the control group. These differences

were consistent across the coronal, middle, and apical thirds of the biopsy cores, although statistical significance in deeper regions was limited by reduced sample availability. In fact, although all 26 biopsies were included in the whole-core histomorphometric analysis, regional analysis was limited by fragmentation and loss of structural integrity in some specimens, particularly in the deeper portions of the cores. However, fragmentation has not to be interpreted solely as a technical artifact, since poor core integrity may also reflect limited mineralization or incomplete consolidation of the regenerated tissue [45–47]. In the coronal and middle thirds, where sample integrity was highest, the test material demonstrated a clear advantage, suggesting more efficient remodelling and tissue turnover. Qualitative analysis also supported these findings: trabeculae in the test group appeared continuous and well-organized, while the control group often exhibited numerous unresorbed graft particles embedded within an irregular trabecular structure [48,49].

The inflammatory profile further distinguished the two materials. Nearly one-third of test samples exhibited no detectable inflammation, while all control samples showed at least mild inflammatory infiltrates, often associated with the presence of compact fibrous connective tissue. Inflammatory infiltrates associated with residual bovine-derived xenograft particles have occasionally been reported in literature [50,51]; however, these findings are not consistent across the literature and should not be considered a characteristic response to these materials. The high-temperature deproteinization process used in the production of these xenografts preserves biocompatibility but significantly alters the mineral structure, reducing resorbability and promoting long-term material persistence [52–55]. As a result, this bone substitute tends to remain integrated within the regenerated tissue for extended periods, contributing to volume stability but reducing the relative space available for newly-formed bone and marrow compartments at the evaluated healing time. In contrast, the test scaffold appears to degrade via a different mechanism. No signs of osteoclastic resorption, such as Howship's lacunae, were observed, suggesting an enzymatic resorption pathway through a creeping substitution process [56,57]. The spherical morphology of residual particles and their integration within newly-formed bone support this hypothesis [58]. This degradation profile allowed the development of a more regular trabecular pattern and a lower inflammatory infiltrate. Additionally, in sites where the biomaterial had been fully resorbed, the intratrabecular tissue often resembled loose connective or even adipose tissue, which is an indicator of advanced tissue maturation [59]. However, the observed histological

differences are likely multifactorial and should not be attributed exclusively to biomaterial resorption rate. Differences in scaffold architecture, porosity, collagen structure, particle morphology, wettability, and space-maintaining properties may have influenced cell migration, vascular ingrowth, and bone formation. In addition, patient-related biological variability and subtle differences in local sinus anatomy or surgical handling may have contributed to the observed outcomes.

A digital workflow was used to standardize prosthetically driven planning, surgical guide fabrication, crestal access, biopsy harvesting, and implant placement. Although no quantitative accuracy assessment was performed in the present study, the use of guided procedures was intended to improve spatial consistency between the planned implant position, the augmented area, and the biopsy site. Therefore, no conclusions can be drawn from this study regarding the accuracy of the digital workflow compared with freehand procedures.

The main strengths of the present investigation include its prospective design, the use of standardized surgical protocols and histological processing methods, and the combined evaluation of radiographic and histomorphometric parameters, allowing for a comprehensive assessment of regenerative outcomes. The segmentation of biopsy cores into defined coronal, middle, and apical thirds enabled a more precise evaluation of site-specific regeneration patterns.

Nevertheless, some limitations must be acknowledged. The relatively small sample size ($n = 26$) may have limited the statistical power of the study and increased the risk of type II errors. The high standard deviations observed for several histomorphometric parameters indicate substantial interindividual variability, which may have masked more subtle between-group differences. Although no significant differences were observed between groups for age, gender, smoking status, history of periodontitis, or medio-buccal sinus width, baseline residual bone height was significantly higher in the test group. Because of the limited sample size, multivariable adjustment for potential confounders was not performed, as it would have generated unstable estimates and increased the risk of overfitting. In addition, several statistical comparisons were performed across different outcomes and biopsy regions, and no formal adjustment for multiple testing was applied. This may have increased the risk of type I error, particularly for secondary and regional histological analyses. Although previous studies suggest that residual bone height has limited influence on new bone formation after sinus floor elevation [29,60–62], its potential confounding effect cannot be completely excluded; since no statistical adjustment for baseline residual bone height was performed, the observed histological differences cannot be considered fully independent of baseline anatomical conditions and should therefore be interpreted with caution.

Also the chronological allocation of patients represents a methodological limitation, as it may introduce selection or temporal bias. Although the procedures were performed by experienced operators using a standardized protocol, subtle changes related to procedural refinements over time cannot be completely excluded.

In addition, the follow-up was restricted to the early healing phase, and long-term clinical and radiographic outcomes remain to be assessed. Potential sampling bias related to tissue loss during harvesting and processing could have affected histological representation: moreover, although histological and radiographic measurements were performed by independent blinded assessors, blinding at the surgical level was not feasible because of the different handling characteristics of the two biomaterials. This represents an additional source of potential performance bias.

Regarding the histological analysis, incomplete or fragmented biopsy cores, particularly in deeper regions, reduced the number of evaluable middle and apical segments and may have introduced selection bias in regional comparisons. This limitation is especially relevant for the apical region, where only 8 test and 4 control samples were available. Since fragmentation may reflect poor mineralization or incomplete consolidation of the regenerated tissue, the exclusion of fragmented portions

may have led to an overestimation of the regenerative outcomes in those regions. Therefore, regional histological findings should be considered less robust than whole-core analyses and interpreted with caution. In addition, inflammatory infiltrate was assessed by a single blinded examiner using a predefined semi-quantitative scale, but without inter-observer reproducibility testing.

5. Conclusions

Both biomaterials supported transcresal sinus floor elevation and enabled implant placement after 6 months. The collagenated synthetic hydroxyapatite scaffold was associated with higher newly-formed bone, a lower percentage of residual graft material, and lower inflammatory scores in this preliminary cohort. However, because of the non-randomized design, baseline imbalance in residual bone height, absence of adjustment for potential confounders and multiple testing, limited sample size, and reduced number of evaluable samples in regional analyses, these findings should be interpreted cautiously. Randomized controlled studies with larger samples and long-term clinical outcomes are required to confirm whether these histological differences translate into clinically meaningful advantages.

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CRediT authorship contribution statement

Luigi Canullo: Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Paolo Savadori:** Writing – review & editing, Investigation. **Rossano Mura:** Writing – review & editing, Investigation. **Alessio Triestino:** Writing – review & editing, Data curation. **Francesca Bixio:** Writing – review & editing, Validation. **Valerio Massimo Sora:** Software, Formal analysis. **Ugo Consolo:** Writing – review & editing, Supervision. **Claudio Stacchi:** Writing – original draft, Methodology, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Luigi Canullo reports equipment, drugs, or supplies was provided by Dentsply Sirona. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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