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Comparative efficacy of modified versus standard deproteinized bovine bone mineral for compromised socket preservation: a randomized controlled trial

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Abstract

Background Socket preservation with deproteinized bovine bone mineral (DBBM) is standard practice following tooth extraction, yet outcomes in compromised sockets with damaged buccal walls due to severe periodontitis remain unpredictable, with excessive fibrous tissue formation limiting bone regeneration. This randomized controlled trial evaluated the histomorphometric efficacy of a novel DBBM (DB1) compared to standard DBBM (DB2) in compromised sockets, with primary focus on new bone formation and tissue composition, supplemented by clinical and radiographic assessments.

Materials and methods This randomized, controlled, single-blind clinical trial randomized 34 patients (31 completed per-protocol analysis) requiring single tooth extraction due to severe periodontitis or combined endodontic-periodontal lesions. Participants were randomly allocated to test (DB1, $n=17$) or control (DB2, $n=17$) groups, with all sites covered by collagen membrane. Bone biopsies were harvested at 16 weeks during implant placement for histomorphometric analysis using digital pathology software. Primary outcome was percentage of newly formed bone. Non-inferiority was assessed at three stringency levels (Δ = -7%, -5%, -3.5%): DB1 was considered non-inferior to DB2 if the lower bound of the 95% confidence interval for the difference (DB1-DB2) exceeded each threshold. Secondary outcomes included residual graft material, bone marrow and fibrous tissue, bone remodeling efficiency, implant stability quotient changes, and radiographic density changes measured by cone-beam computed tomography.

Results New bone formation in the test group (17.7 ± 9.8% vs. 10.8 ± 9.6%) demonstrated non-inferiority, with the 95% CI lower bound (-0.19%) exceeding all three predefined margins (mean difference + 6.95%, $p<0.001$). Bone remodeling efficiency similarly demonstrated non-inferiority (0.23 ± 0.15 vs. 0.13 ± 0.14; $p<0.001$). The test group showed significantly lower bone marrow and fibrous tissue content (47.4 ± 17.0% vs. 62.8 ± 19.8%; $p=0.028$) with higher residual graft retention (34.8 ± 12.2% vs. 26.5 ± 11.5%; $p=0.059$). No significant differences were observed in implant stability or radiographic density changes.

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Conclusions DB1 demonstrated non-inferiority to DB2 for compromised socket preservation, exhibiting distinct tissue composition patterns with reduced fibrous tissue formation and enhanced volume maintenance capacity.

Trial registration This randomized clinical trial has been retrospectively registered at Clinical Research Information Service (CRIS) with identification number KCT0011262 on December 5, 2025.

Keywords Socket preservation, Bone substitutes, Dental implants, Xenografts, Deproteinized bovine bone mineral

Introduction

Tooth extraction due to severe periodontitis or combined endodontic-periodontal lesions inevitably initiates a cascade of physiological changes that result in significant alveolar bone remodeling, with studies demonstrating substantial horizontal and vertical ridge reduction that is more pronounced in compromised sites compared to pristine extraction sockets [1, 2]. The presence of pre-existing bone wall defects and inflammatory tissue further complicate the natural healing process, often resulting in unpredictable outcomes with excessive fibrous tissue formation rather than bone regeneration, posing considerable challenges for optimal implant placement and often necessitating complex augmentation procedures [2, 3]. The preservation of alveolar dimensions in compromised extraction sites has therefore become a fundamental consideration in contemporary implant dentistry, particularly given the strong correlation between ridge morphology and successful implant outcomes [4].

Socket preservation techniques have emerged as effective interventions to minimize post-extraction bone loss, with xenografts demonstrating consistent clinical efficacy [5, 6]. Deproteinized bovine bone minerals (DBBM), in particular, have shown remarkable osteoconductive properties, with histological analyses revealing new bone formation in direct contact with graft particles [7, 8]. The combination of xenografts with collagen membranes has further enhanced clinical outcomes [9], with studies demonstrating favorable outcomes in posterior extraction sites [10] and long-term stability over 10 years [11], although systematic reviews indicate substantial variability in histomorphometric outcomes across different preservation techniques [12]. Outcomes in compromised sockets remain unpredictable, with considerable interindividual variability in tissue composition patterns [13].

Recent advances in manufacturing processes have led to modified DBBM formulations with enhanced deproteinization efficiency and improved particle porosity. One such material (designated DB1) underwent quality enhancements in 2022, yet the most recent randomized controlled trial evaluating this formulation [14] predated these improvements and focused on guided bone regeneration rather than socket preservation. This gap necessitates rigorous evaluation specifically in compromised socket scenarios.

Therefore, this randomized controlled trial compared a novel DBBM with enhanced processing (DB1) to the reference standard (DB2) in extraction sockets with damaged buccal walls due to severe periodontitis. Non-inferiority was assessed using histomorphometric analysis of new bone formation and tissue composition as primary outcomes, with clinical (implant stability) and radiographic (bone density) evaluations as secondary outcomes.

Methods

Study design

This prospective, randomized, controlled, single-blind clinical trial was conducted at the Department of Oral and Maxillofacial Surgery, Yonsei University Dental Hospital. The study protocol was designed to compare the efficacy of two deproteinized bovine bone minerals in compromised socket preservation following tooth extraction due to severe periodontitis or combined endodontic-periodontal lesions: A-Oss® (Osstem Implant, Seoul, Korea), designated as DB1 (test material), and Bio-Oss® (Geistlich Pharma, Wolhusen, Switzerland), designated as DB2 (control material). Both materials utilized the same particle size range of 0.25–1.0 mm to minimize potential confounding factors related to particle dimensions. This trial was retrospectively registered with the Clinical Research Information Service (CRIS), Republic of Korea, under identification number KCT0011262 on December 5, 2025. The experimental design adhered to the Declaration of Helsinki concerning human experimentation and Good Clinical Practice Guidelines. The study protocol was approved by the Institutional Review Board of Yonsei University Dental Hospital [2-2023-0016]. All participants provided written informed consent prior to enrollment. Quality assessment of the trial was carried out according to the randomized controlled trial (RCT) checklist of the CONSORT statement.

Sample size determination

The sample size for the present study was calculated based on effect size estimates derived from a previous randomized controlled clinical trial evaluating healing at molar extraction sites [15]. Using means and standard deviations reported in that study, an effect size (Cohen's *d*) of 0.8684 was determined. Sample size estimation was performed using G*Power software (version 3.1.9.2;

Heinrich-Heine-Universität Düsseldorf, Germany) [16]. A total of 30 participants (15 per group) was required to achieve a statistical power of 80% (1−β = 0.8) with a two-tailed α of 0.05. To account for an anticipated dropout rate of 20%, the planned enrollment target was increased to 40 participants. Ultimately, 34 participants were enrolled (17 in the DB1 group and 17 in the DB2 group), exceeding the minimum requirement for adequate statistical power. Of these, 31 participants (DB1: 16, DB2: 15) completed the per-protocol analysis after excluding 3 patients who experienced implant failure.

Patient selection

Inclusion criteria

- Age 20 years or older
- Requirement for single tooth extraction due to localized severe periodontitis or combined endodontic-periodontal lesion with presence of compromised extraction socket walls
- Good general health status
- Extraction site suitable for dental implant placement
- Adequate oral hygiene maintenance capability
- Signed informed consent

Exclusion criteria

- History of head and neck radiotherapy within the past year
- Chemotherapy treatment within the past year
- Antiresorptive treatment (bisphosphonates or denosumab) within the past year
- Metabolic bone diseases (Paget's disease, hyperparathyroidism, fibrous dysplasia)
- Requirement for extensive ridge augmentation procedures
- History of tumor resection in the head and neck region
- History of osteomyelitis
- Uncontrolled diabetes mellitus or hypertension
- Heavy smoking (> 20 cigarettes per day)
- Alcohol abuse
- Extensive caries
- Any medical condition deemed by the investigator to interfere with healing or study participation

Randomization and blinding

Eligible participants were randomly assigned to one of two treatment groups using a computer-generated randomization sequence: the test group received DB1, and the control group received DB2. Allocation concealment was maintained through sequentially numbered, opaque, sealed envelopes. Participants and the examining clinicians performing outcome assessments were blinded to the treatment allocation throughout the study period. The operating surgeon was not blinded due to the practical necessity of material handling during surgery, though both materials have similar physical characteristics (particle size 0.25–1.0 mm, granular morphology) that minimized potential identification bias.

Material characterization

Both DB1 and DB2 are deproteinized bovine bone minerals with particle size 0.25–1.0 mm. DB1 has undergone recent quality improvements in its manufacturing process since 2022, including enhanced particle porosity and improved deproteinization efficiency. Surface morphology and internal microstructure were characterized using scanning electron microscopy (SEM) and micro-computed tomography (micro-CT) analysis. Physical property data are provided in the supplementary materials.

Surgical procedures

Pre-surgical protocol

All participants underwent comprehensive medical and dental history review, clinical examination, and radiographic evaluation including periapical radiographs. Detailed oral hygiene instructions were provided, and professional prophylaxis was performed when indicated.

Socket preservation surgery

All surgical procedures were performed by experienced oral and maxillofacial surgeon under local anesthesia. Atraumatic tooth extraction was performed using periotomes and appropriate extraction forceps to minimize trauma to the surrounding alveolar bone. Following extraction, thorough debridement of the extraction socket was performed to remove all granulation tissue and debris, ensuring adequate bleeding from the socket walls.

Socket dimensions were measured using a periodontal probe: buccolingual width at the crest level, mesiodistal width at the crest level, and socket depth from the crest to the apical extent. The integrity of the buccal/labial and palatal/lingual bone walls was systematically assessed and classified according to the system described by Koo et al. [17]. According to the randomized allocation, either DB1 or DB2 was placed into the extraction socket. The grafting material was hydrated with sterile saline and the patient's blood before placement. A resorbable collagen membrane OssMem (Osstem Implant Co., Ltd., Seoul, Republic of Korea) was positioned to cover the graft material with adequate overlap onto the surrounding bone. Primary closure was achieved through careful tissue management and suturing techniques.

Post-operative care

Standard post-operative instructions were provided, including analgesic and antibiotic protocols as indicated. Participants were scheduled for regular follow-up visits to monitor healing and assess for complications.

Socket classification system

Following tooth extraction, the extraction sockets were classified based on the integrity of the buccal/labial and palatal/lingual bone walls according to the classification system described by Koo et al. [15]. The sockets were categorized into six subgroups (A-F) and then grouped into three severity levels:

Severe defects (Groups A, B):

- Group A: Complete absence of both buccal/labial and palatal/lingual walls
- Group B: Complete absence of one wall and partial destruction of the other wall

Moderate defects (Groups C, D):

- Group C: Partial destruction of both buccal/labial and palatal/lingual walls
- Group D: Complete absence of one wall with the other wall intact

Mild defects (Groups E, F):

- Group E: Partial destruction of one wall with the other wall intact
- Group F: Both buccal/labial and palatal/lingual walls intact

The defect classification was performed immediately after tooth extraction by the operating surgeon, and the distribution of defect types was recorded for subsequent analysis of healing outcomes relative to initial socket morphology.

Clinical follow-up protocol

Clinical follow-up examinations were performed at 2-, 4-, and 12-weeks post-grafting, at implant placement (16 weeks), and at second-stage surgery, for a total of 7 scheduled visits. At each visit, clinical signs of infection, wound healing status, and any adverse events were systematically recorded and documented.

Implant placement and biopsy harvest

Dental implant placement was performed at 16 weeks post-extraction. Prior to implant site preparation, a bone biopsy was harvested from the center of the grafted extraction site using a trephine bur (diameter 3.0 mm). The harvested bone core was immediately processed for histological analysis. Implant placement was completed in the same surgical session following standard protocols.

Implant stability assessment

Resonance frequency analysis (RFA) was performed to evaluate implant stability at two time points: immediately after implant placement (baseline) and at 12 weeks during the second-stage surgery. Implant stability quotient (ISQ) values were recorded using an Osstell device (Osstell AB, Gothenburg, Sweden) in accordance with the manufacturer's instructions. Measurements were taken in two perpendicular directions, and the mean value was calculated for analysis.

Histological and histomorphometric analysis

Bone biopsy samples were obtained from the implant installation site using a trephine bur (diameter 3.0 mm) at 16 weeks post-grafting, performed during implant placement. To evaluate the representativeness of the biopsy specimens and minimize potential sampling bias, the volume occupied by the retrieved tissue specimen was recorded and expressed as a proportion of the total trephine capacity. This harvesting portion, representing the percentage of the trephine's internal volume successfully filled with biopsy tissue, provided a standardized metric for comparing biopsy yield between groups and ensuring adequate tissue representation across all samples.

The harvested bone cores were immediately processed for histological evaluation. All retrieved biopsy samples were immediately fixed in 4% paraformaldehyde solution for two days. Following fixation, specimens were decalcified using Calci-Clear Rapid (National Diagnostics) and subsequently embedded in paraffin blocks. Two central sections, each 5 μm thick, were cut from the embedded paraffin blocks using a microtome (Model RM2235; Leica).

The serial sections were stained with Masson's trichrome to facilitate microscopic examination and optimal differentiation of tissue components. This staining protocol allows clear visualization of newly formed bone (blue), residual graft material (red), and soft tissue components (red/pink). Histological slides were digitally scanned using high-resolution whole slide imaging systems to capture complete section morphology. The scanned images were processed and prepared for digital pathology analysis.

Histomorphometric analysis was performed using QuPath software [18], an open-source platform designed for comprehensive digital pathology image analysis, providing robust image viewing capabilities with advanced algorithms and scripting functionalities for quantitative tissue analysis. Multi-slide projects were created within QuPath to manage and analyze all histological

specimens systematically, and only the grafted area was analyzed, with native trabecular bone and marrow outside the grafted region excluded from measurements. Areas of interest were manually annotated by a single blinded examiner using QuPath's interactive drawing tools, and QuPath's object-based data model was utilized to quantify tissue components within annotated regions. The standardized harvesting portion calculation enabled normalization across all samples, ensuring that histomorphometric measurements were representative of the grafted tissue composition regardless of minor variations in biopsy yield.

Tissue components were identified using trained region-based annotation with distinct color coding: newly formed bone (NewBone, blue), representing areas of mature mineralized tissue formed de novo within the grafted site; residual graft material (Graft, pink), indicating remaining xenograft particles visible within the tissue section; and bone marrow and fibrous tissue (BM & Fb, light blue), encompassing soft tissue components including bone marrow spaces and fibrous connective tissue. This standardized annotation approach allowed for consistent, reproducible quantification of tissue composition across all samples. (Fig. 1).

All histomorphometric measurements were performed by a single experienced examiner blinded to treatment allocation and independent of the surgical procedures to ensure consistency and eliminate inter-examiner variability. To ensure measurement consistency, all analyses were performed by a single experienced examiner following standardized protocols. Intra-observer reliability was assessed by re-analyzing 20% of randomly selected specimens with a 2-week interval, demonstrating excellent reproducibility (ICC > 0.90) The QuPath software's batch processing capabilities enabled standardized analysis protocols across all specimens, enhancing reproducibility and reducing potential bias. All histomorphometric parameters were expressed as percentages of the total grafted tissue area. Bone Remodeling Efficiency (BRE) was calculated as NewBone / (NewBone + Graft), representing the efficiency of graft remodeling into new bone tissue.

Radiographic analysis

CBCT imaging protocol

Cone-beam computed tomography (CBCT) scans were obtained at baseline (immediately post-grafting) and at 3 months post-operatively using the Alphard 3030 system (Asahi Roentgen Ind. Co., Tokyo, Japan). Imaging parameters were standardized as follows: 80 kVp, 8 mA, 17-second exposure time, 15.4 × 15.4 cm^2 field of view, and 0.3 mm voxel resolution.

Hounsfield unit analysis

Baseline (immediately post-graft) and 4-month postoperative CBCT scans were analyzed for each extraction site. To ensure identical anatomical positioning, DICOM datasets from both time points were imported into 3D Slicer software (version 5.2.2; Harvard Medical School, Boston, MA, USA), and rigid registration was performed using stable adjacent anatomical landmarks (e.g., neighboring tooth roots, cortical bone contours) as reference points. This superimposition process allowed the alignment of both scans in three dimensions.

Following registration, sagittal slices passing through the mesio-distal center of the extraction socket were selected in both scans. ROI selection was then performed

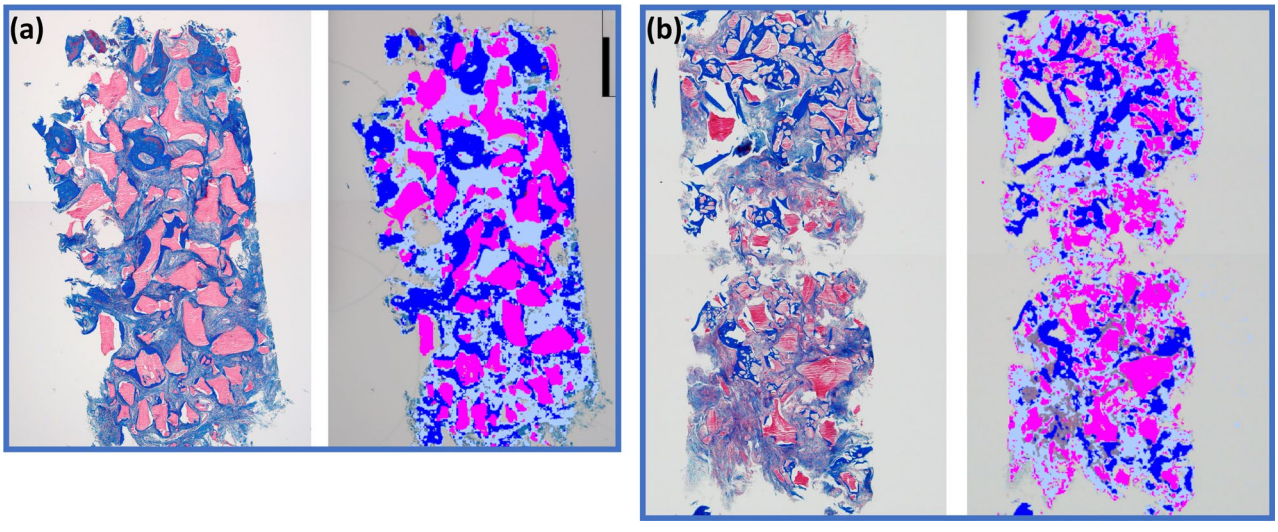

Fig. 1 Representative histologic sections and corresponding digital pathology annotations of grafted sites at 16 weeks post-grafting. **a** DB1 (test material) group and (**b**) DB2 (control material) group. Tissue components were identified using QuPath software with distinct color coding: newly formed bone (blue), residual graft material (pink), and bone marrow/fibrous tissue (light blue)

to ensure that the measurement areas corresponded to the same anatomical location at both time points.

For analysis, the ROI was defined within the central portion of the grafted socket, excluding native surrounding bone. A circular ROI with a consistent diameter of 3 mm was placed in the grafted area, and an identical-sized ROI was positioned in the adjacent basal bone on the same slice, serving as the reference tissue (Fig. 2).

Relative Hounsfield units (relative HU) were calculated as the grayscale value of the grafted ROI divided by the grayscale value of the basal bone ROI. The change in relative HU (ΔHU) was defined as the difference between the 4-month and baseline relative HU values, representing bone density changes over the healing period.

Outcome measures

The primary outcome of this study was the percentage of newly formed bone (NewBone) within the biopsy specimen, assessed histomorphometrically. Secondary outcomes included the following:

- Implant stability change (ΔISQ): Measured using resonance frequency analysis at the time of implant placement and again at 12 weeks, with values

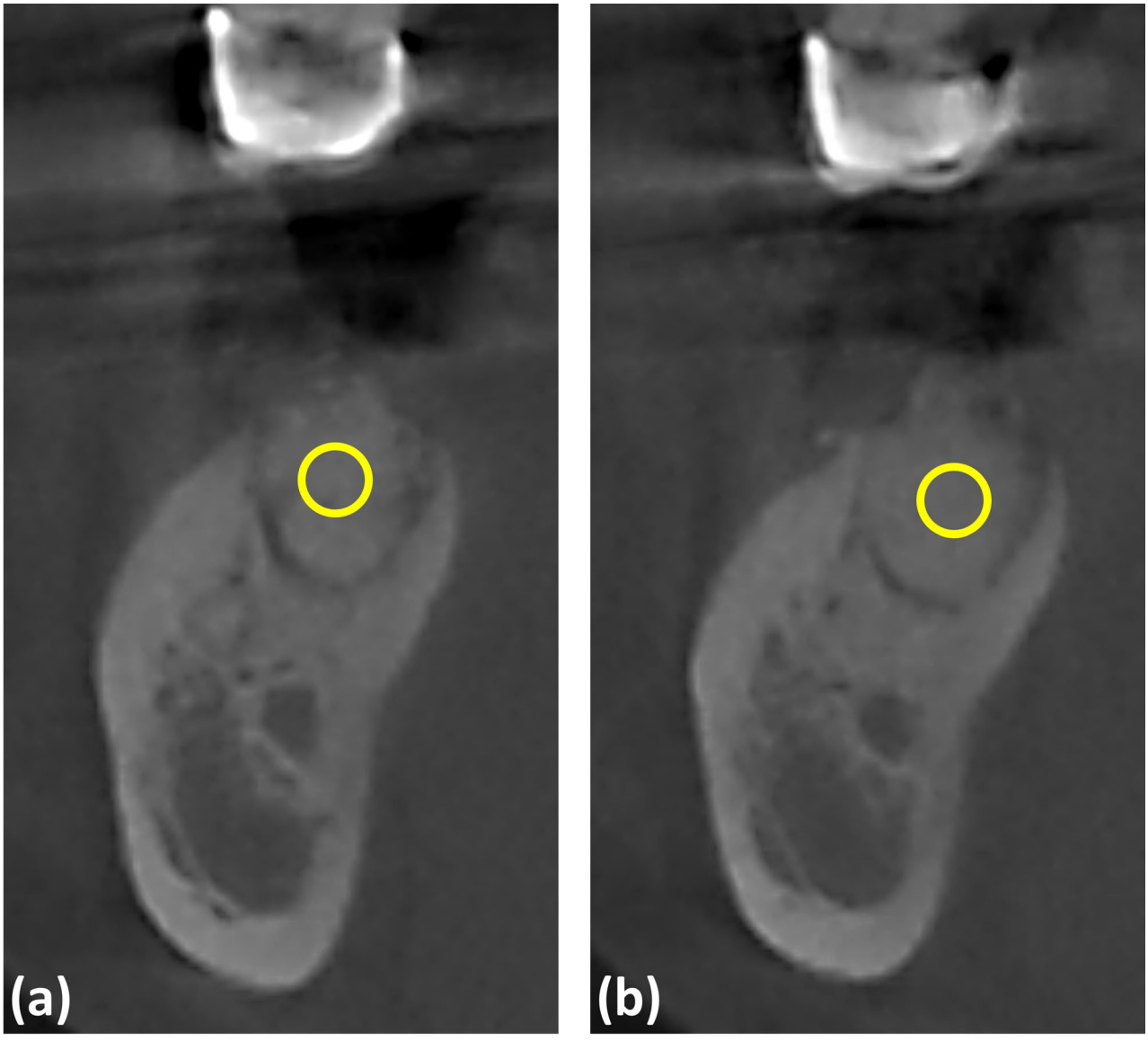

Fig. 2 Representative sagittal CBCT images showing the region of interest (ROI) placement. **a** Sagittal slice obtained immediately after tooth extraction and grafting, passing through the mesio-distal center of the extraction socket. **b** Corresponding sagittal slice at 4 months post–socket preservation. The yellow circle indicates the ROI, defined as a 3-mm-diameter circular area positioned in the central portion of the grafted socket, excluding native surrounding bone. Identical anatomical positioning of the ROI between time points was ensured by image registration, with the same slice used for both baseline and follow-up measurements

expressed as the difference between the two time points.

- Residual graft (Graft): The proportion of remaining graft particles within the histologic section, expressed as a percentage of the total area.
- Bone marrow and fibrous tissue (BM&Fb): The percentage of soft tissue components, including bone marrow and fibrous connective tissue, within the specimen.
- Bone Remodeling Efficiency (BRE): A calculated ratio defined as the amount of newly formed bone divided by the total mineralized component (i.e., NewBone / [NewBone + Graft]). This index was used to reflect the efficiency of bone turnover and remodeling within the grafted site.
- Relative Hounsfield Unit change (ΔHU): Cone-beam computed tomography (CBCT) grayscale values were measured within the grafted region and normalized to the adjacent basal bone to obtain relative HU. The change in relative HU (ΔHU) was defined as the difference between values obtained at baseline (post-graft) and at 16 weeks, and was used to assess changes in radiodensity within the grafted area over time.

Non-inferiority analysis

Non-inferiority was assessed using a fixed-margin approach, with margins determined from previously published histomorphometric data on DB2. Reported new bone formation values for DB2 ranged from 15.07% ± 10.52% [17] to 32.83% ± 14.72% [19], with other studies showing similar outcomes: 19.3% ± 22.6% [20] and 27.35% ± 12.39% [21]. Based on these distributions, clinically relevant non-inferiority margins (Δ) were set at – 7%, – 5%, and – 3.5% for new bone formation, and – 5% for bone remodeling efficiency (BRE). The primary outcome variables were the proportion of new bone formation (%) and BRE (%). For each outcome, the mean difference between groups (DB1 minus DB2) and its 95% confidence interval (CI) were calculated. Non-inferiority was concluded if the lower bound of the one-sided 95% CI exceeded the pre-specified Δ. This approach ensured that the observed differences were not only statistically non-inferior but also clinically within the range of variability previously reported for DB2.

Statistical analysis

Continuous variables were expressed as means ± standard deviations (SD), and categorical variables were presented as frequencies and percentages. Comparisons between DB1 and DB2 groups for continuous variables used independent-samples t-tests. For categorical variables, Pearson's chi-square tests or Fisher's exact tests were used. Between-group differences for single-time outcomes (new bone, graft, BM & Fb, BRE, and harvested portion) were assessed using two-sample t-tests. For outcomes measured repeatedly within subjects (ISQ and relative HU), linear mixed-effects models with a subject-specific random intercept were applied to account for intra-subject correlation. Linear regression was used to examine associations among outcome variables, and multiple linear regression was conducted to identify factors associated with new bone formation. For the non-inferiority comparison between DB1 and DB2, the null hypothesis assumed that DB1 was inferior to DB2 by more than the prespecified margin (H0: DB1 − DB2 ≤ Δ). The prespecified non-inferiority margins were – 7%, – 5%, and – 3.5% for new bone formation and – 5% for bone remodeling efficiency (BRE). Non-inferiority was assessed using the 95% confidence interval approach, corresponding to a one-sided significance level of 0.025. Non-inferiority was concluded if the lower bound of the two-sided 95% confidence interval for the mean difference (DB1 − DB2) exceeded the predefined margin (Δ). All statistical analyses were conducted using R software version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria), and a two-sided p-value < 0.05 was considered statistically significant.

Result

Participant characteristics and flow

A total of 34 patients were randomized, with 17 allocated to the DB1 group and 17 to the DB2 group. Three patients experienced implant failure at the 3-month follow-up and were consequently excluded from the per-protocol analysis. These failures were characterized by insufficient osseointegration and implant mobility despite the absence of overt infection. Accordingly, the final analytic cohort comprised 31 patients with 31 implants (DB1: 16, DB2: 15). Analyses were performed both on an intention-to-treat (ITT) basis, which included all randomized participants, and on a per-protocol (PP) basis, which excluded the three early failures. Because each patient received a single implant, the implant served as the unit of analysis, yielding 31 evaluable implants for histologic, radiographic, and clinical assessments. The demographic and baseline clinical characteristics of the study population are presented in Table 1, while the participant flow is depicted in Fig. 3 (CONSORT diagram). The mean age of participants was 60.9 ± 12.2 years, with no significant difference between groups (DB1: 60.3 ± 10.3 years; DB2: 61.5 ± 14.3 years; $p = 0.788$). Males accounted for 58.1% of the cohort, and sex distribution was balanced between groups ($p = 0.879$). Socket defect types (mild, moderate, severe) were similarly distributed ($p = 0.521$). The mean interval from graft placement to biopsy harvest was nearly identical in both groups (DB1: 127.1 ± 10.6 days; DB2: 127.2 ± 12.9 days; $p = 0.986$). The prevalence

Table 1 Demographic and baseline clinical characteristics of the study participants

Characteristic	Ovarall (*n* = 31)	DB1 (*n* = 16)	DB2 (*n* = 15)	*p*-value
Age	60.9 ± 12.2	60.3 ± 10.3	61.5 ± 14.3	0.788
Sex				0.879
F	13 (41.9)	6 (37.5)	7 (46.7)	
M	18 (58.1)	10 (62.5)	8 (53.3)	
Socket				0.521
Mild	18 (58.1)	10 (62.5)	8 (53.3)	
Moderate	9 (29.0)	5 (31.3)	4 (26.7)	
Severe	4 (12.9)	1 (6.3)	3 (20.0)	
Graft to Specimen days	127.2 ± 11.6	127.1 ± 10.6	127.2 ± 12.9	0.986
Smoking	5 (16.1)	3 (18.8)	2 (13.3)	1.000
Hypertension	5 (16.1)	3 (18.8)	2 (13.3)	1.000
Diabetus Mellitus	3 (9.7)	2 (12.5)	1 (6.7)	1.000
ISQ0M	70.2 ± 12.4	70.3 ± 13.7	70.1 ± 11.4	0.980
ISQ3M	80.2 ± 5.2	78.8 ± 5.3	81.8 ± 4.7	0.116
Relative HU 0 M	0.82 ± 0.21	0.83 ± 0.24	0.80 ± 0.18	0.768
Relative HU 4 M	0.92 ± 0.19	0.90 ± 0.23	0.94 ± 0.15	0.591

DB1 test deproteinized bovine bone mineral, *DB2* control deproteinized bovine bone mineral, *ISQ* implant stability quotient, *HU* Hounsfield unit

of smoking, hypertension, and diabetes mellitus was low and comparable between groups (all $p = 1.000$). Baseline implant stability (ISQ0M) and 3-month stability (ISQ3M) did not differ significantly between groups ($p = 0.980$ and $p = 0.116$, respectively). Similarly, relative Hounsfield unit (HU) values at baseline (Relative HU 0 M) and at 4 months (Relative HU 4 M) showed no significant differences ($p = 0.768$ and $p = 0.591$). Importantly, all 31 implants retained after the 3-month evaluation have remained clinically stable to date, with no additional failures or retreatments observed.

Histologic analysis

Histological examination of the 31 specimens revealed favorable healing patterns in both groups without evidence of significant inflammatory reactions or foreign-body responses. Biomaterial particles were readily identifiable by their characteristic morphology and pale eosinophilic staining with empty lacunae, contrasting with newly formed bone tissue that exhibited intense eosinophilic staining and viable osteocytes within lacunae. DB1 specimens demonstrated notably higher quantities of residual graft particles compared to DB2 specimens, with materials showing good integration into the surrounding tissue matrix. Both xenografts displayed evidence of osteoconductive properties, with new bone formation primarily occurring at the biomaterial-bone interface. A distinctive finding was the reduced proportion of soft tissue components, including bone marrow and fibrous connective tissue, in DB1 specimens compared to DB2 specimens. The DB1 group showed more compact tissue architecture with less fibrous tissue infiltration, suggesting enhanced tissue maturation. New bone formation in both groups showed preferential localization in the apical and middle portions of the biopsy specimens, areas that presumably received enhanced vascular supply during the healing process. The coronal regions typically contained higher proportions of connective tissue, while the apical areas demonstrated more mature trabecular bone formation with clearly distinguishable osteocytes. Newly formed bone tissue exhibited typical trabecular architecture across both groups, with well-defined osteocytes indicating tissue vitality. The remaining tissue comprised primarily connective tissue with fibroblasts, collagen fibers, and small capillaries. Notable differences in tissue composition were observed between the two groups, with DB1 specimens showing reduced fibrous tissue content compared to DB2 specimens, as confirmed by quantitative histomorphometric analysis (Fig. 4).

Histomorphometric analysis

The histomorphometric outcomes are presented in Table 2. The proportion of bone marrow and fibrous tissue (BM & Fb) was significantly lower in the DB1 group (47.4 ± 17.0%) compared to the DB2 group (62.8 ± 19.8%) ($p = 0.028$). No statistically significant differences were observed in the amount of newly formed bone (17.7 ± 9.8% vs. 10.8 ± 9.6%; $p = 0.056$), residual graft material (34.8 ± 12.2% vs. 26.5 ± 11.5%; $p = 0.059$), or bone remodeling efficiency (0.23 ± 0.15 vs. 0.13 ± 14; $p = 0.074$) between the DB1 and DB2 groups. The harvested portion, defined as the proportion of obtainable tissue relative to the trephine core volume, did not differ significantly between DB1 (59.9 ± 18.1%) and DB2 (62.0 ± 21.4%) ($p = 0.773$).

Radiographic analysis

Radiographic outcomes, including CBCT-derived Hounsfield unit changes, did not differ significantly between groups. The change in relative Hounsfield unit values (ΔHU) between baseline and 3 months showed no significant difference (0.08 ± 0.25 vs. 0.14 ± 0.11; $p = 0.501$) (Table 2).

Clinical analysis

The change in implant stability quotient (ΔISQ) from implant placement to 3 months was 8.6 ± 13.7 in the DB1 group and 11.8 ± 11.3 in the DB2 group, showing no significant difference ($p = 0.501$) (Table 2).

Subgroup analyses

Subgroup analyses were performed according to tooth type (maxillary and mandibular), smoking status, and defect morphology (mild, moderate, severe) (Table 3).

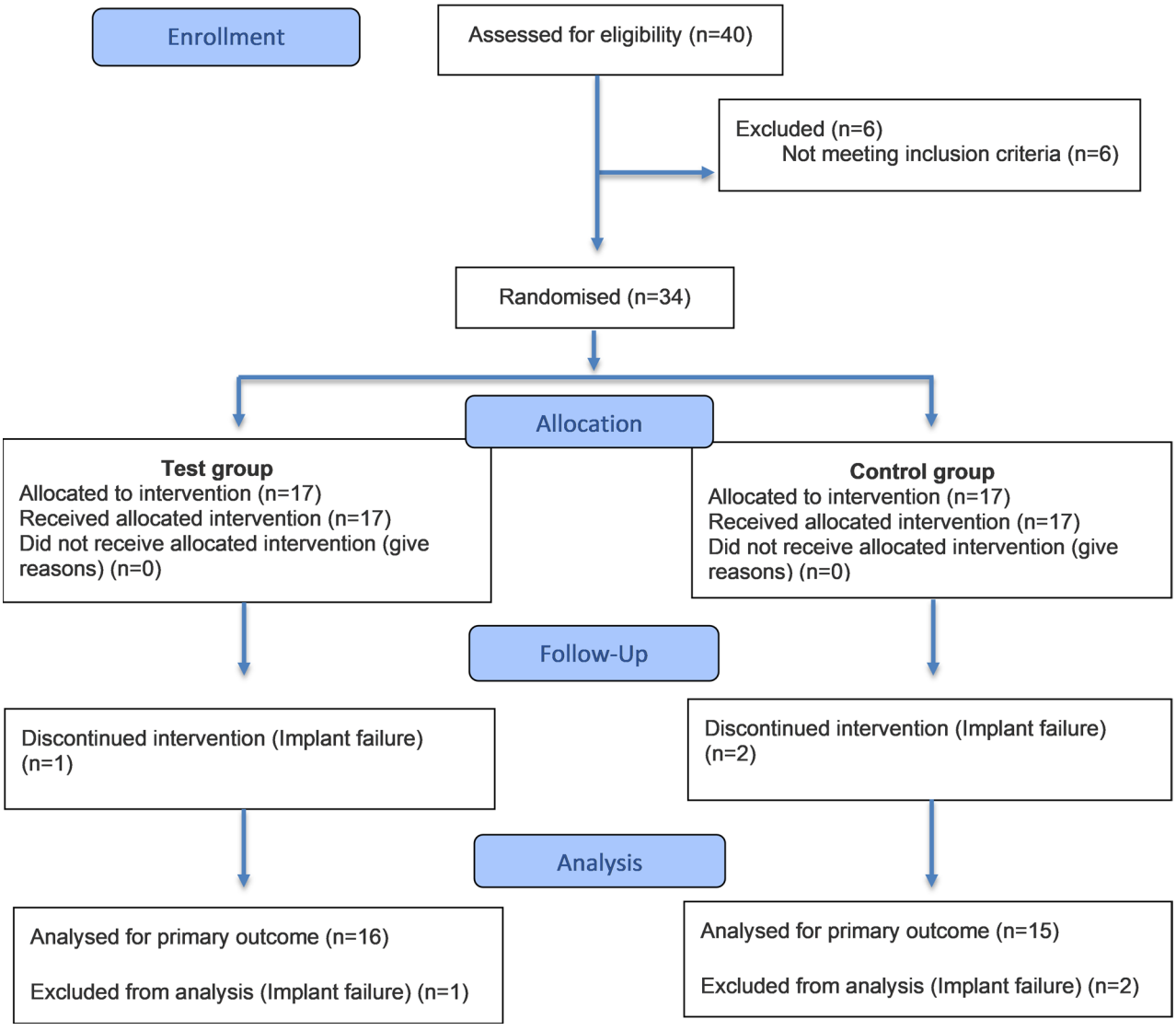

Fig. 3 CONSORT flow diagram of this study

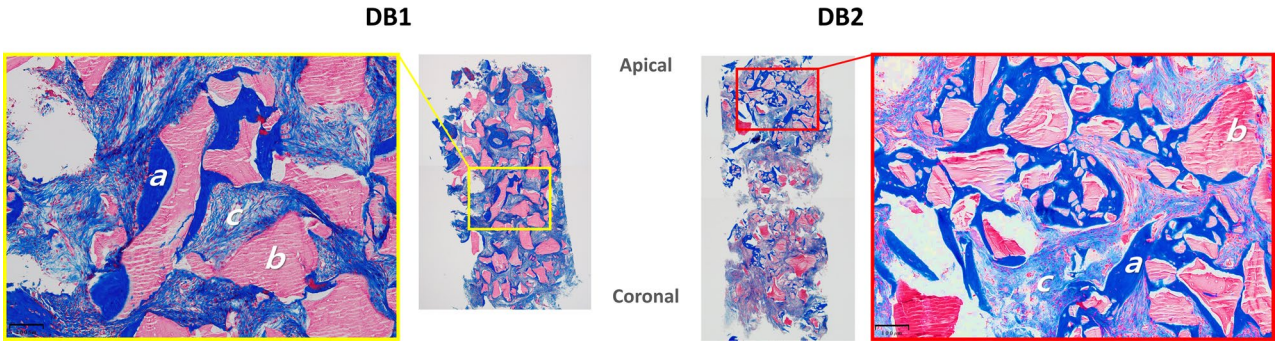

Fig. 4 Representative photomicrographs of histologic specimens from DB1 and DB2 groups. Magnified views (boxed areas) were from the central region of each specimen. **a** Mineralized new bone; **b** Residual bone graft material; (**c**) Bone marrow and fibrous tissue. Masson's trichrome staining

Table 2 Comparison of major outcome measures between the DB1 and DB2 groups

Outcome	DB1 ($n=16$)	DB2 ($n=15$)	Difference (95% CI)	*p*-value
NewBone	17.7 ± 9.8	10.8 ± 9.6	6.95 (-0.19, 14.08)	0.056
ISQ change	8.6 ± 13.7	11.8 ± 11.3	-3.11 (-12.44, 6.22)	0.501
Graft	34.8 ± 12.2	26.5 ± 11.5	8.37 (-0.36, 17.09)	0.059
BM & Fb	47.4 ± 17.0	62.8 ± 19.8	-15.31 (-28.83, -1.80)	**0.028***
BRE	0.23 ± 0.15	0.13 ± 0.14	0.10 (-0.01, 0.21)	0.074
Relative HU change	0.08 ± 0.25	0.14 ± 0.11	-0.06 (-0.20, 0.08)	0.392
Harvested portion	59.9 ± 18.08	62.0 ± 21.4	-3.11 (-12.44, 6.22)	0.773

BM & Fb bone marrow and fibrous tissue, *BRE* bone remodeling efficiency, *HU* Hounsfield unit, *ISQ* implant stability quotient; *$p < 0.05$, statistically significant

When stratified by anatomical location (maxillary teeth [tooth type 1] vs. mandibular teeth [tooth type 2]), no statistically significant differences were observed between DB1 and DB2 groups in any measured outcomes, including new bone formation, change in implant stability quotient (ISQ change), residual graft, bone marrow and fibrous tissue (BM & Fb), and bone remodeling efficiency (BRE). Similarly, when stratified by smoking status, no significant differences were found between the two groups in any histomorphometric or radiographic parameters. When grouped by defect morphology, none of the comparisons reached statistical significance, although numerical variations were observed across categories. Overall, subgroup analysis did not identify any statistically significant differences in major outcomes

Table 3 Subgroup analyses comparing major outcome measures between the DB1 and DB2 groups

Subgroup	Outcome	DB1	DB2	Difference (95% CI)	*p*-value
Toot type 1	NewBone	18.1 ± 12.0	12.0 ± 11.4	6.09 (-12.80, 24.98)	0.478
	ISQ change	9.0 ± 8.3	6.0 ± 5.7	2.50 (-10.98, 15.99)	0.683
	Graft	39.1 ± 14.9	27.9 ± 8.5	11.14 (-10.44, 32.71)	0.268
	BM & Fb	42.8 ± 20.9	60.0 ± 19.3	-17.23 (-49.86, 15.41)	0.258
	BRE	0.25 ± 0.19	0.15 ± 0.15	0.10 (-0.20, 0.39)	0.469
Toot type 2	NewBone	17.4 ± 8.4	10.5 ± 9.7	6.95 (-1.52, 15.41)	0.102
	ISQ change	8.2 ± 17.3	12.8 ± 11.9	-4.53 (-17.85, 8.80)	0.486
	Graft	31.5 ± 9.2	26.1 ± 12.5	5.44 (-4.90, 15.78)	0.284
	BM & Fb	51.1 ± 13.5	63.4 ± 20.6	-12.39 (-28.98, 4.21)	0.135
	BRE	0.22 ± 0.13	0.13 ± 0.14	0.09 (-0.03, 0.22)	0.146
Smokers	NewBone	21.0 ± 13.0	5.2 ± 7.4	15.83 (-17.43, 49.09)	0.227
	ISQ change	21.3 ± 13.9	3.5 ± 2.1	17.83 (-15.26, 50.93)	0.185
	Graft	26.5 ± 10.2	15.5 ± 3.7	10.96 (-14.12, 36.04)	0.258
	BM & Fb	52.5 ± 23.2	79.3 ± 3.7	-26.79 (-82.22, 28.64)	0.222
	BRE	0.29 ± 0.20	0.06 ± 0.08	0.23 (-0.27, 0.73)	0.237
Non-Smokers	NewBone	17.0 ± 9.4	11.6 ± 9.9	5.32 (-2.47, 13.12)	0.172
	ISQ change	5.6 ± 12.3	13.2 ± 11.7	-7.41 (-17.20, 2.38)	0.131
	Graft	36.7 ± 12.1	28.1 ± 11.4	8.61 (-0.93, 18.15)	0.075
	BM & Fb	46.3 ± 16.3	60.2 ± 20.0	-13.93 (-28.71, 0.84)	0.063
	BRE	0.22 ± 0.15	0.15 ± 0.14	0.07 (-0.05, 0.19)	0.214
Bone detect = mild	NewBone	17.8 ± 11.1	14.3 ± 10.4	3.43 (-7.44, 14.31)	0.513
	ISQ change	9.3 ± 16.1	14.6 ± 14.3	-4.72 (-20.31, 10.87)	0.530
	Graft	34.3 ± 8.6	29.7 ± 12.8	4.63 (-6.08, 15.34)	0.373
	BM & Fb	47.9 ± 15.0	56.0 ± 21.3	-8.06 (-26.21, 10.09)	0.361
	BRE	0.24 ± 0.18	0.18 ± 0.16	0.05 (-0.12, 0.23)	0.519
Bone detect = moderate	NewBone	16.8 ± 8.6	9.5 ± 8.2	7.29 (-6.15, 20.72)	0.241
	ISQ change	8.8 ± 10.1	9.8 ± 7.1	-0.95 (-13.16, 11.26)	0.870
	Graft	38.9 ± 17.6	27.1 ± 8.3	11.81 (-11.00, 34.62)	0.260
	BM & Fb	44.4 ± 23.1	63.5 ± 15.2	-19.10 (-51.03, 12.84)	0.200
	BRE	0.21 ± 0.12	0.11 ± 0.10	0.10 (-0.08, 0.28)	0.234
Bone detect = severe	NewBone	22.2 ± NA	3.1 ± 4.9	19.11 (-5.00, 43.22)	0.076
	ISQ change	0.0 ± NA	8.0 ± 9.5	-8.00 (-55.39, 39.39)	0.543
	Graft	19.6 ± NA	17.0 ± 8.8	2.57 (-40.93, 46.07)	0.823
	BM & Fb	58.2 ± NA	79.9 ± 12.9	-21.69 (-85.68, 42.31)	0.282
	BRE	0.28 ± NA	0.03 ± 0.05	0.25 (-0.01, 0.52)	0.055

ISQ implant stability quotient, *BM & Fb* bone marrow and fibrous tissue, *BRE* bone remodeling efficiency, *NA* not applicable

between the DB1 and DB2 groups within any of the examined strata.

Multivariable analysis of new bone formation

Multivariable linear regression was conducted to identify factors associated with new bone formation. The variables included in the model were group (DB1 vs. DB2), age, sex, extraction socket morphology, graft-to-specimen interval, tooth type, smoking, hypertension, and diabetes mellitus (Table 4).

None of the variables reached statistical significance ($p > 0.05$). Although the DB1 group showed a higher mean new bone formation than the DB2 group (coefficient = 5.253), the difference was not statistically significant ($p = 0.194$; 95% CI: – 2.910 to 13.417).

Additionally, variable selection using both Lasso regression and stepwise regression consistently identified the Group variable (DB1 vs. DB2) as the only variable retained in the model, suggesting it has the strongest explanatory influence on new bone formation despite the lack of statistical significance in the full model.

Correlation analysis

Correlation between new bone formation and ISQ change

A linear regression analysis was performed to assess the relationship between new bone formation (%) and the change in implant stability quotient (ΔISQ) from baseline to 3 months.

Table 4 Multivariable linear regression analysis for predictors of new bone formation

Variable	Coefficient	Lower	Upper	*p*-value
Group				
DB1	5.253	-2.910	13.417	0.194
DB2	reference			
Age	0.196	-0.200	0.591	0.313
Sex				
F	reference			
M	-0.251	-9.049	8.546	0.953
Socket				
Mild	reference			
Moderate	-4.179	-14.178	5.821	0.393
Severe	-10.629	-24.933	3.675	0.136
Graft to Specimen days	0.142	-0.263	0.547	0.473
Tooth.type				
1	reference			
2	0.153	-0.232	0.538	0.416
Smoking				
No	reference			
Yes	0.420	-12.066	12.905	0.945
Hypertension				
No	reference			
Yes	1.881	-10.759	14.521	0.759
Diabetes Mellitus				
No	reference			
Yes	8.971	-5.566	23.508	0.212

CI confidence interval

In the overall sample, there was no significant correlation between the two variables ($R^2 = 0.02$, $p = 0.468$). The regression line showed a slightly negative slope ($\beta = -0.112$), suggesting a weak inverse relationship; however, this association was not statistically significant. When analyzed by group, similar patterns were observed. In DB1 group, the correlation was negligible ($R^2 < 0.01$, $p = 0.855$) with a slope of $\beta = -0.0356$. In DB2, the correlation was also not significant ($R^2 = 0.03$, $p = 0.578$) with a slope of $\beta = -0.135$. These results indicate that new bone formation and early changes in implant stability were not meaningfully associated in either group.

Correlation between relative HU change and histomorphometric parameters

Correlation analyses were performed to assess the relationship between relative Hounsfield Unit (HU) change and histomorphometric outcomes, including new bone formation, residual graft material, and bone remodeling efficiency (BRE). As illustrated in Fig. 5, relative HU change showed a statistically significant correlation with the proportion of residual graft material ($p < 0.05$). In contrast, no statistically significant associations were observed between relative HU change and new bone formation or BRE.

Correlation between relative HU change and residual graft by group

As illustrated in Fig. 6, a correlation analysis was performed between relative Hounsfield Unit (HU) change and the proportion of residual graft material, stratified by group (DB1 and DB2). In the DB1 group, a statistically significant positive correlation was observed between relative HU change and residual graft ($p < 0.05$). In contrast, no significant correlation was found in the DB2 group.

Correlation between relative HU change and bone marrow and fibrous tissue by group

As shown in Fig. 7, a correlation analysis was performed between relative Hounsfield Unit (HU) change and the proportion of bone marrow and fibrous tissue (BM & Fb), stratified by group. In the DB1 group, a statistically significant negative correlation was observed ($p < 0.05$). In contrast, no significant correlation was found in the DB2 group.

Correlation between ISQ change and relative HU change by group

The relationship between changes in implant stability quotient (ISQ) and relative Hounsfield Unit (HU) change was evaluated separately for the DB1 and DB2 groups. As shown in Figs. 1 and 8, no statistically significant

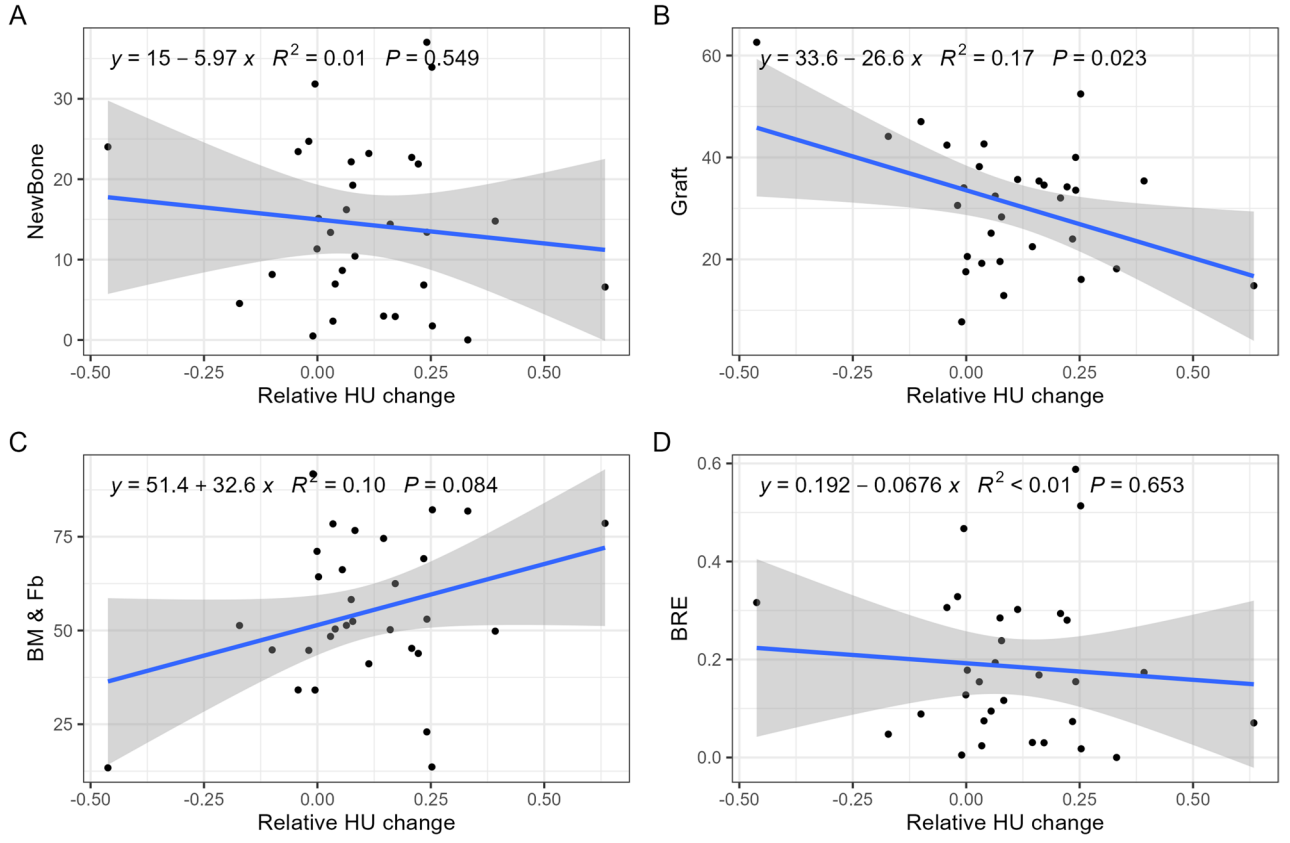

Fig. 5 Correlation between relative HU change and histomorphometric outcomes. Scatterplots with linear regression lines and 95% confidence intervals (CIs) show associations between relative HU change and (**A**) new bone formation, (**B**) residual graft material, (**C**) bone marrow/fibrous tissue, and (**D**) bone remodeling efficiency (BRE). Relative HU change correlated with residual graft ($p < 0.05$); associations with other outcomes were not significant

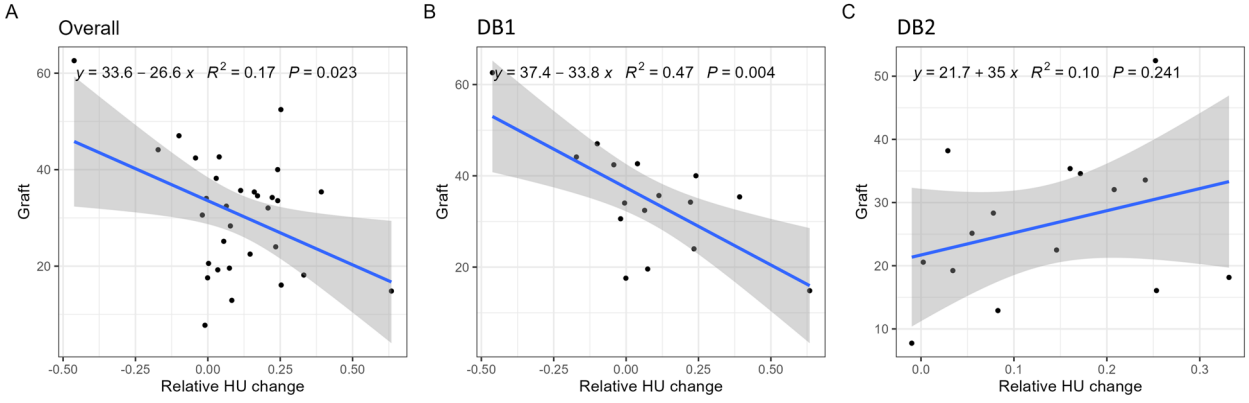

Fig. 6 Correlation between relative HU change and residual graft material. Scatterplots with linear regression lines and 95% confidence intervals (CIs) illustrate the relationship between relative HU change and residual graft material in (**A**) the overall cohort, (**B**) the DB1 group, and (**C**) the DB2 group. Relative HU change was inversely correlated with residual graft material in the overall cohort and DB1 ($p < 0.05$), whereas no significant correlation was observed in DB2

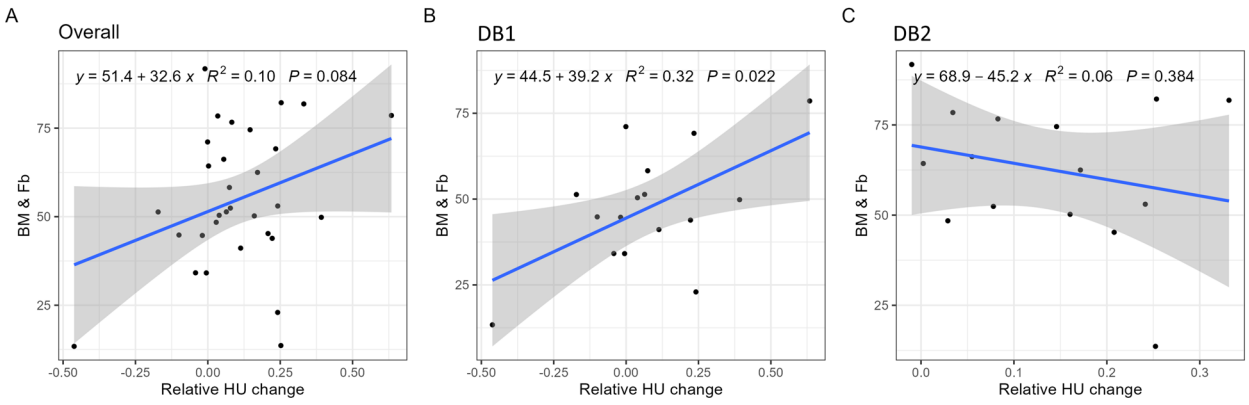

Fig. 7 Correlation between relative HU change and bone marrow/fibrous tissue. Scatterplots with linear regression lines and 95% confidence intervals (CIs) depict the relationship between relative HU change and marrow/fibrous tissue in (**A**) the overall cohort, (**B**) the DB1 group, and (**C**) the DB2 group. Relative HU change was positively correlated with marrow/fibrous tissue in DB1 ($p < 0.05$), whereas no significant association was observed in DB2. HU, Hounsfield unit

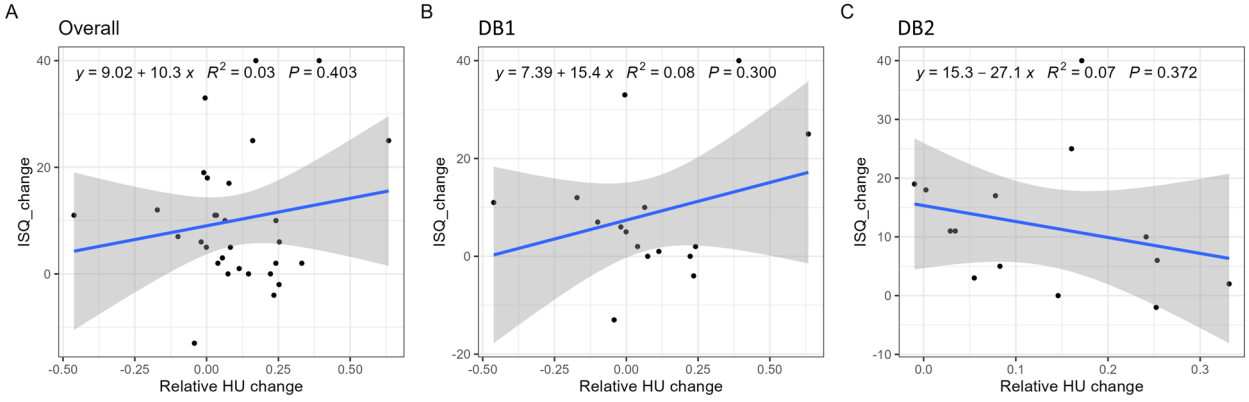

Fig. 8 Correlation between relative HU change and ISQ change. Scatterplots with linear regression lines and 95% confidence intervals (CIs) illustrate the association between relative HU change and implant stability (ΔISQ) in (**A**) the overall cohort, (**B**) the DB1 group, and (**C**) the DB2 group. No statistically significant correlations were observed in the overall cohort or either subgroup (all $p > 0.05$). HU, Hounsfield unit; ISQ, implant stability quotient

correlation was found in either group. Although a weak positive trend was noted in the DB1 group, this relationship did not reach statistical significance.

Non-inferiority analysis

For new bone formation, the mean difference between the DB1 and DB2 groups was +6.95% (95% one-sided CI lower bound: −0.19%, $p < 0.001$ for non-inferiority). The lower limit of the CI exceeded all predefined non-inferiority margins (Δ = −7%, − 5%, and − 3.5%), confirming the non-inferiority of DB1 even under the strictest criterion. For BRE, expressed in percentage points, the mean difference was +10.0% (95% one-sided CI lower bound: −1.0%, $p < 0.001$ for non-inferiority). The lower limit of the CI was greater than the non-inferiority margin (Δ = −5%), indicating that DB1 was non-inferior to DB2 with respect to bone remodeling efficiency. Overall, both histomorphometric parameters demonstrated that DB1 achieved bone regeneration outcomes that were statistically non-inferior, and in mean values, numerically superior, to those of DB2 (Fig. 9).

Discussion

This randomized controlled trial demonstrated non-inferiority of DB1 compared to DB2 in compromised socket preservation across all predefined margins (-7%, -5%, -3.5%). A notable finding was DB1 specimens showing reduced bone marrow and fibrous tissue content combined with higher residual graft material, indicating different tissue composition patterns with greater volume-sustaining capacity.

These findings align with comparative xenograft studies reporting variable histomorphometric outcomes. Cook and Mealey [19] established clinical frameworks with standard deproteinized bovine bone mineral achieving 32.83% ± 14.72% new bone formation, while Calasans-Maia et al. [20] reported 19.3% ± 22.6% with experimental xenografts, comparable to our DB1 outcomes. De Risi

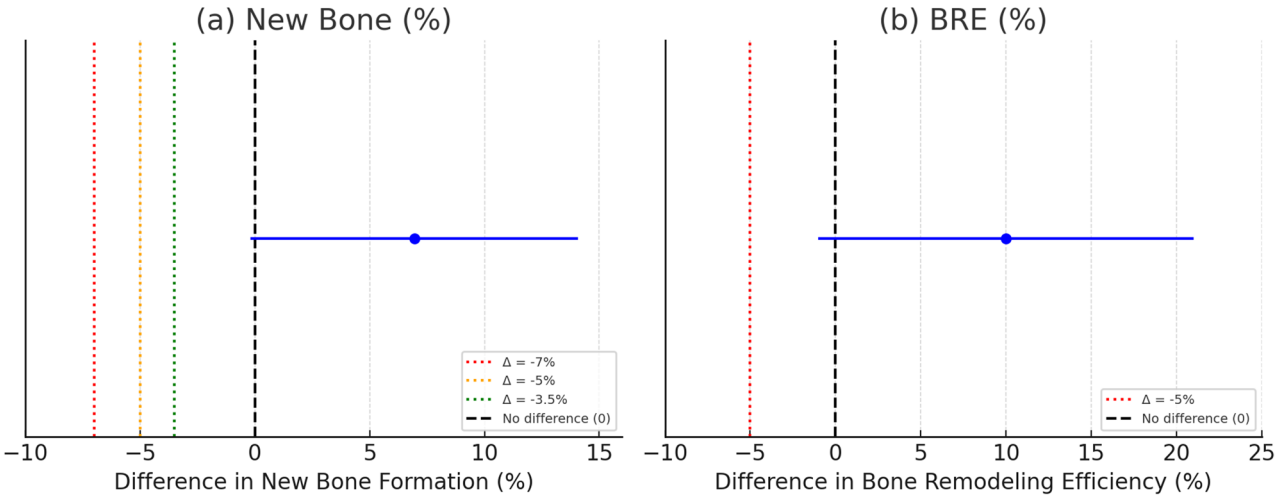

Fig. 9 Non-inferiority analyses for new bone formation and bone remodeling efficiency. Panels display mean differences (DB1 − DB2; dots) with 95% confidence intervals (horizontal bars). **a** New bone formation (NBF, %): non-inferiority margins Δ = −7, − 5, −3.5; the 95% CI lies entirely above all margins, meeting non-inferiority. **b** Bone remodeling efficiency (BRE, percentage points): margin Δ = −5; the 95% CI lies above the margin, meeting non-inferiority

et al. [13] documented bovine xenograft new bone formation ranging from 15 to 30% in socket preservation, encompassing both materials in our study. The preferential spatial distribution of new bone formation in apical and middle regions reflects vascular supply influence, consistent with socket morphology studies by Koo et al. [17] and Artzi et al. [22].

However, contrasting evidence exists. Mardas et al. [6] and Gholami et al. [21] demonstrated different outcomes for synthetic materials compared to bovine xenografts, with new bone formation of 21.7-28.46% versus 16.7–22.60% respectively. These studies highlight the complexity of material selection and the importance of direct comparative evaluations between specific products.

The differential tissue composition observed between DB1 and DB2 groups carries significant clinical implications for compromised socket preservation outcomes. The combination of higher residual graft retention with significantly reduced fibrous tissue formation in the DB1 group suggests enhanced volume maintenance capacity during the critical healing period. This finding aligns with previous studies demonstrating that residual graft material serves as a scaffold to resist dimensional changes while promoting bone formation, particularly important in compromised sockets with pre-existing bone wall defects [13]. The pattern observed with DB1 is consistent with reports by Calasans-Maia et al. [20], who found reduced connective tissue formation with enhanced bovine xenografts compared to standard formulations. Furthermore, the significant correlation between radiographic density changes and graft retention specifically in the DB1 group provides evidence that the superior graft stability translates into measurable clinical benefits, supporting enhanced resistance against bone resorption in challenging extraction scenarios where socket wall integrity is compromised.

The multivariable regression analysis revealed trends regarding socket morphology influence on bone formation. Despite limited statistical power due to sample size, negative coefficients for moderate (-4.179) and severe (-10.629) defects compared to mild defects suggest progressive decline in bone formation with increasing socket wall damage. These coefficient magnitudes indicate trends that warrant investigation in larger studies, emphasizing that socket wall classification influences regenerative outcomes.

Hounsfield unit (HU) measurements provided insights into bone quality changes during healing. HU values have demonstrated utility in predicting implant stability [23, 24], assessing graft quality [25, 26], and evaluating new bone formation in grafted defects [27, 28]. The correlation between relative HU changes and residual graft material, particularly in the DB1 group, supports the utility of CBCT-derived measurements for non-invasive assessment of socket preservation outcomes.

The quality improvements implemented in the test material since 2022 may explain the observed differences. The enhancement of particle porosity eliminated low-porosity particles that previously comprised a significant portion, while improved deproteinization efficiency resulted in lower residual protein content compared to the control material (which contains > 15% non-porous particles). These modifications potentially influenced osteoconductive properties and inflammatory responses.

This investigation addresses an evidence gap as the first clinical evaluation of the enhanced DBBM formulation in socket preservation. Previous studies by Lim et al. [14] evaluated pre-improvement formulations of similar

materials, while comparative studies largely focused on different material categories rather than head-to-head bovine xenograft evaluations. Our comprehensive histomorphometric, radiographic, and clinical approach provides more complete characterization than studies relying primarily on dimensional assessments.

Several methodological aspects enhance validity: randomized, single-blind design with predetermined non-inferiority margins, standardized socket assessment using the Koo classification system, and comprehensive outcome measures addressing quantitative and qualitative healing aspects. However, important limitations should be considered. The relatively modest sample size of 31 patients, while adequate for the primary outcome analysis (exceeding the calculated requirement of 30), limits generalizability and the ability to perform adequately powered subgroup analyses. The single-center design introduces potential selection bias. Additionally, the predominance of molar sites limits applicability to anterior extractions [29, 30]. Regarding the 16-week healing period, this timeframe aligns with widely adopted protocols for socket preservation [1, 17] and represents a critical evaluation point for xenograft-mediated bone regeneration as shown by systematic review [13]. While extended healing beyond 4 months may yield increased new bone formation [31], our protocol achieved clinically successful outcomes with all sites supporting implant placement without additional augmentation, suggesting this timeframe provides sufficient healing for the study objectives.

Future investigations should evaluate enhanced DBBM formulations across different clinical scenarios with extended follow-up periods to assess long-term tissue behavior, while multi-center trials would enhance generalizability [32–34]. Long-term clinical outcomes including implant survival, patient-reported measures, and cost-effectiveness analyses would strengthen clinical relevance.

Conclusions

In conclusion, DB1 demonstrates comparable efficacy to DB2 for compromised socket preservation, exhibiting significantly reduced fibrous tissue formation and higher residual graft retention.

Abbreviations

BM&Fb	Bone marrow and fibrous tissue
BRE	Bone remodeling efficiency
CBCT	Cone-beam computed tomography
CI	Confidence interval
DB1	Deproteinized bovine bone mineral (test material)
DB2	Deproteinized bovine bone mineral (control material)
DBBM	Deproteinized bovine bone minerals
DICOM	Digital Imaging and Communications in Medicine
HU	Hounsfield unit
ISQ	Implant stability quotient
RFA	Resonance frequency analysis
ROI	Region of interest
SD	Standard deviation
SEM	scanning electron microscopy
ΔHU	Relative Hounsfield Unit change

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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The authors have nothing to report.

Authors' contributions

HY: writing – original draft, investigation, data curation, funding acquisition, writing – review and editing. SChoi: data curation. data acquisition, review and editing. SJH: statistical analysis, review. EJ: data acquisition. DK: conceptualization, supervision, validation, data curation, data acquisition, funding acquisition, project administration.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in full accordance with the ethical principles of the Declaration of Helsinki and adhered to Good Clinical Practice Guidelines. The study protocol received approval from the Institutional Review Board of Yonsei University Dental Hospital (IRB No. 2-2023-0016). Written informed consent was obtained from all participants prior to enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Araújo M, da Silva JCC, de Mendonça AF, Lindhe J. Ridge alterations following grafting of fresh extraction sockets in man. A randomized clinical trial. Clin Oral Implants Res. 2015;26:407–12. https://doi.org/10.1111/clr.12366.
2. Iasella JM, Greenwell H, Miller RL, Hill M, Drisko C, Bohra AA, et al. Ridge preservation with freeze-dried bone allograft and a collagen membrane compared to extraction alone for implant site development: a clinical and histologic study in humans. J Periodontol. 2003;74:990–9. https://doi.org/10.1902/jop.2003.74.7.990.

3. Chen ST, Buser D. Esthetic outcomes following immediate and early implant placement in the anterior maxilla–a systematic review. Int J Oral Maxillofac Implants. 2014;29 Suppl:186–215. https://doi.org/10.11607/jomi.2014suppl.g.
4. Wang RE, Lang NP. Ridge preservation after tooth extraction. Clin Oral Implants Res. 2012;23:147–56. https://doi.org/10.1111/j.1600-0501.2012.02560.
5. Machtei EE, Mayer Y, Horwitz J, Zigdon-Giladi H. Prospective randomized controlled clinical trial to compare hard tissue changes following socket preservation using alloplasts, xenografts vs no grafting: clinical and histological findings. Clin Implant Dent Relat Res. 2018;20:685–93. https://doi.org/10.1111/cid.12707.
6. Mardas N, Chadha V, Donos N. Alveolar ridge preservation with guided bone regeneration and a synthetic bone substitute or a bovine-derived xenograft: a randomized, controlled clinical trial. Clin Oral Implants Res. 2010;21:1377–86. https://doi.org/10.1111/j.1600-0501.2010.01918.x.
7. Barone A, Todisco M, Ludovichetti M, Gualini F, Aggstaller H, Torres-Lagares D, et al. A prospective, randomized, controlled, multicenter evaluation of extraction socket preservation comparing two bovine xenografts: clinical and histologic outcomes. Int J Periodontics Restor Dent. 2013;33:795–802. https://doi.org/10.11607/prd.1690.
8. Cardaropoli D, Tamagnone L, Roffredo A, Gaveglio L, Cardaropoli G. Socket preservation using bovine bone mineral and collagen membrane: a randomized controlled clinical trial with histologic analysis. Int J Periodontics Restor Dent. 2012;32:421–30.
9. Iorio-Siciliano V, Blasi A, Nicolo M, Iorio-Siciliano A, Riccitiello F, Ramaglia L. Clinical outcomes of socket preservation using bovine-derived xenograft collagen and collagen membrane post-tooth extraction: a 6-month randomized controlled clinical trial. Int J Periodontics Restor Dent. 2017;37:141–50. https://doi.org/10.11607/prd.2474.
10. Araújo MG, Lindhe J. Ridge preservation with the use of Bio-Oss collagen: a 6-month study in the dog. Clin Oral Implants Res. 2009;20:433–40. https://doi.org/10.1111/j.1600-0501.2009.01705.x.
11. Roccuzzo M, Gaudioso L, Bunino M, Dalmasso P. Long-term stability of soft tissues following alveolar ridge preservation: 10-year results of a prospective study around nonsubmerged implants. Int J Periodontics Restor Dent. 2014;34:795–804.
12. Iorio-Siciliano V, Ramaglia L, Blasi A, Bucci P, Nuzzolo P, Riccitiello F, Nicolò M. Dimensional changes following alveolar ridge preservation in the posterior area using bovine-derived xenografts and collagen membrane compared to spontaneous healing: a 6-month randomized controlled clinical trial. Clin Oral Investig. 2020;24:1013–23. https://doi.org/10.1007/s00784-019-02979-w.
13. De Risi V, Clementini M, Vittorini G, Mannocci A, de Sanctis M. Alveolar ridge preservation techniques: a systematic review and meta-analysis of histological and histomorphometrical data. Clin Oral Implants Res. 2015;26:50–68. https://doi.org/10.1111/clr.12288.
14. Lim J, Jun SH, Tallarico M, Park JB, Park DH, Hwang KG, et al. A randomized controlled trial of guided bone regeneration for peri-implant dehiscence defects with two anorganic bovine bone materials covered by titanium meshes. Mater (Basel). 2022;15:5294. https://doi.org/10.3390/ma15155294.
15. Walker CJ, Prihoda TJ, Mealey BL, Lasho DJ, Noujeim M, Huynh-Ba G. Evaluation of healing at molar extraction sites with and without ridge preservation: a randomized controlled clinical trial. J Periodontol. 2017;88:241–9. https://doi.org/10.1902/jop.2016.160445.
16. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–91. https://doi.org/10.3758/BF03193146.
17. Koo TH, Song YW, Cha JK, Jung UW, Kim CS, Lee JS. Histologic analysis following grafting of damaged extraction sockets using deproteinized bovine or porcine bone mineral: a randomized clinical trial. Clin Oral Implants Res. 2019;30:1–10. https://doi.org/10.1111/clr.13557.
18. Bankhead P, Loughrey MB, Fernández JA, Dombrowski Y, McArt DG, Dunne PD, et al. QuPath: Open source software for digital pathology image analysis. Sci Rep. 2017;7:16878. https://doi.org/10.1038/s41598-017-17204-5.
19. Cook DC, Mealey BL. Histologic comparison of healing following tooth extraction with ridge preservation using two different xenograft protocols. J Periodontol. 2013;84:585–94. https://doi.org/10.1902/jop.2012.120219.
20. Calasans-Maia M, Resende R, Fernandes G, Calasans-Maia J, Alves AT, Granjeiro JM. A randomized controlled clinical trial to evaluate a new xenograft for alveolar socket preservation. Clin Oral Implants Res. 2014;25:1125–30. https://doi.org/10.1111/clr.12237.
21. Gholami GA, Najafi B, Mashhadiabbas F, Goetz W, Najafi S. Clinical, histologic and histomorphometric evaluation of socket preservation using a synthetic nanocrystalline hydroxyapatite in comparison with a bovine xenograft: a randomized clinical trial. Clin Oral Implants Res. 2012;23:1198–204. https://doi.org/10.1111/j.1600-0501.2011.02288.
22. Artzi Z, Tal H, Dayan D. Porous bovine bone mineral in healing of human extraction sockets. Part 1: Histomorphometric evaluations at 9 months. J Periodontol. 2000;71:1015–23. https://doi.org/10.1902/jop.2000.71.6.1015.
23. Turkyilmaz I, Ozan O, Yılmaz B, Ersoy A. Determination of bone quality of 372 implant recipient sites using Hounsfield unit from computerized tomography: a clinical study. Clin Implant Dent Relat Res. 2008;10:238–44. https://doi.org/10.1111/j.1708-8208.2008.00085.
24. Sogo M, Ikebe K, Yang TC, Wada M, Maeda Y. Assessment of bone density in the posterior maxilla based on Hounsfield units to enhance the initial stability of implants. Clin Implant Dent Relat Res. 2012;14:42–6. https://doi.org/10.1111/j.1708-8208.2011.00423.
25. Smolka W, Eggensperger N, Carollo V, Ozdoba C, Iizuka T. Changes in the volume and density of calvarial split bone grafts after alveolar ridge augmentation. Clin Oral Implants Res. 2006;17:149–55. https://doi.org/10.1111/j.1600-0501.2005.01182.
26. Loveless T, Kılınç Y, Altay M, Flores-Hidalgo A, Baur D, Quereshy F. Hounsfield unit comparison of grafted versus non-grafted extraction sockets. J Oral Sci. 2015;57:195–200. https://doi.org/10.2334/josnusd.57.195.
27. Bastami F, Shahab S, Parsa A, Abbas FM, Kooshki MHN, Namdari M, et al. Can gray values derived from CT and cone beam CT estimate new bone formation? An in vivo study. Oral Maxillofac Surg. 2018;22:427–34. https://doi.org/10.1007/s10006-017-0657-7.
28. Kaya S, Yavuz I, Uysal I, Akkuş Z. Measuring bone density in healing periapical lesions by using cone beam computed tomography: a clinical investigation. J Endod. 2012;38:28–31. https://doi.org/10.1016/j.joen.2011.09.032.
29. Caneva M, Botticelli D, Morelli F, Cesaretti G, Beolchini M, Lang NP. Alveolar process preservation at implants installed immediately into extraction sockets using deproteinized bovine bone mineral: an experimental study in dogs. Clin Oral Implants Res. 2012;23:789–96. https://doi.org/10.1111/j.1600-0501.2012.02511.
30. Clementini M, Agostinelli A, Castelluzzo W, Cugnata F, Vignoletti F, De Sanctis M. The effect of immediate implant placement on alveolar ridge preservation compared to spontaneous healing after tooth extraction: radiographic results of a randomized controlled clinical trial. J Clin Periodontol. 2019;46:776–86. https://doi.org/10.1111/jcpe.13125.
31. Vaia E, Petruzzi M, Marchi F, De Fazio R, Cortellini D, De Angelis N. The influence of different healing times on bone regeneration following tooth extraction and alveolar ridge preservation with bone substitutes: A randomized controlled clinical trial. Int J Periodontics Restor Dent. 2021;41(4):e171–80.
32. MacBeth N, Trullenque-Eriksson A, Donos N, Mardas N. Hard and soft tissue changes following alveolar ridge preservation: a systematic review. Clin Oral Implants Res. 2017;28:982–1004. https://doi.org/10.1111/clr.12911.
33. Avila-Ortiz G, Chambrone L, Vignoletti F. Effect of alveolar ridge preservation interventions following tooth extraction: a systematic review and meta-analysis. J Clin Periodontol. 2019;46:195–223. https://doi.org/10.1111/jcpe.13057.
34. Barone A, Toti P, Quaranta A, Alfonsi F, Cucchi A, Negri B, et al. Clinical and histological changes after ridge preservation with two xenografts: preliminary results from a multicentre randomized controlled clinical trial. J Clin Periodontol. 2017;44:204–14. https://doi.org/10.1111/jcpe.12655.

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