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Maxillary sinus floor augmentation using sponge- and cotton-like graft materials in a rabbit model

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ABSTRACT

Objectives: Bone graft materials commonly used for maxillary sinus floor augmentation (MSFA), including hydroxyapatite (HAp) and β-tricalcium phosphate (β-TCP), are mostly granular and have poor handleability. HAp/collagen composite material (HAp/Col) and β-tricalcium phosphate (β-TCP)/poly(L-lactide-co-glycolide) (PLGA) have shown promise but their application in MSFA as bone graft materials remains unclear. Here, we investigated the bone-forming behavior of HAp/Col and β-TCP/PLGA in an MSFA rabbit model.
Methods: Male Japanese white rabbits were used. HAP/Col or β-TCP/PLGA was randomly applied to the MSFA model. The specimens were harvested at 4 weeks (W), 8W, 16W, and 24W after surgery, and the augmented regions were evaluated using micro-computed tomography and histological analyses.
Results: The graft materials were retained up to 16W in the HAp/Col group and 24W in the β-TCP/PLGA group. The augmented volume detected in the HAp/Col group at 4W was substantially reduced at subsequent time points. However, in the β-TCP/PLGA group, the volume observed at 4W was maintained up to 24W. In the HAp/Col group, the bone mineral content (BMC) at 4W was significantly lower than that at 8W ($p = 0.03716$), and this elevated BMC was significantly decreased at 16W ($p = 0.00185$) and 24W ($p = 0.00236$). In the β-TCP/PLGA group, the BMC tended to increase from 4W to 16W and then decreased.
Conclusions: Both HAp/Col and β-TCP/PLGA are useful for MSFA because of their ability to form new bone and good handleability. The appropriate graft material should be selected depending on the application needs while understanding the properties of the newly formed bone.

1. Introduction

Maxillary sinus floor augmentation (MSFA) using the lateral window approach is a popular dentistry procedure used to increase bone volume in the maxillary molar region when alveolar bone height is insufficient for successful implant placement [1]. Various bone graft materials are used for MSFA, most of which are calcium phosphate-based such as β-tricalcium phosphate (β-TCP) and hydroxyapatite (HAp). They are typically available in a granular form and may be biodegradable or non-biodegradable [1]. Although their granular form enables these

Abbreviations: 4W, 4 weeks; BMC, bone mineral content; BV, bone volume; GBR, guided bone regeneration; H&E, hematoxylin and eosin; HAp/Col, hydroxyapatite/collagen-l; micro-CT, micro-computed tomography; MSFA, maxillary sinus floor augmentation; MT, Masson's trichrome; β-TCP/PLGA, β-tricalcium phosphate/poly(L-lactide-co-glycolide).

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materials to fill narrow and complicated spaces, they often have poor handleability and require a covering membrane to prevent them from spreading out. If they migrate to submucosal layers, the treatment time could be prolonged or non-infectious inflammation could develop. Recently, new materials combining calcium phosphate and organic materials have been designed to improve handleability. However, there is a lack of data for evaluating the efficacy of these materials for MSFA, and the best bone graft material for MSFA remains debatable [2].

We previously reported that a sponge-like bone graft material composited with nanosized HAp and porcine collagen (Col) can remarkably induce bone formation on mouse calvarium [3]. The clinical applications of HAp/Col in alveolar bone preservation at tooth extraction sites [4] and in MSFA [5] have also been demonstrated. However, HAp/Col does not induce satisfactory outcomes in all cases. Moreover, biomedical materials have several limitations; for example, they can transmit unknown infections, and homogenizing their properties is challenging.

In recent years, biodegradable materials based on poly(L-lactide-co-glycolide) (PLGA) polymers have garnered substantial interest and have been utilized as osteosynthetic materials in fracture treatment [6] and reconstructive surgeries [7] for the head and neck regions. Additionally, materials composed of PLGA have been used as guided bone regeneration (GBR) membranes since the 1990s, and PLGA has been warranted to be safe for use in humans [8]. PLGA has also been combined with HAp as a barrier membrane for GBR [9]. However, there are no reports on its use as a bone graft material.

β-TCP/PLGA is a new cotton-like biodegradable bone graft material, which is completely artificial and easy to handle [10]. It is fabricated by dissolving 1.0–5.0 μm osteoconductive β-TCP particles in PLGA via electrospinning, forming a fibrous morphology of 40–320 μm [11]. This unique shape makes it a suitable graft material to fill complex bone defects and large bone cavities with a narrow window. Although there are no reports on the use of β-TCP/PLGA in MSFA, it is considered suitable for MSFA owing to its cotton-like form without sharp edges. This structure ensures that the material does not damage the surrounding fragile soft tissues including maxillary sinus membrane. The present study elucidates the bone-forming behavior of HAp/Col and β-TCP/PLGA in a rabbit MSFA model and discusses the effective applications of these materials.

2. Materials and methods

HAp/Col (ReFit®) and β-TCP/PLGA (ReBOSSIS-J®) were provided by HOYA Technosurgical Corporation (Tokyo, Japan) and ORTHReBIRTH (Kanagawa, Japan), respectively.

2.1. Establishing an MSFA rabbit model

Male Japanese white rabbits (3.0 ± 0.2 kg) were obtained from Oriental Yeast (Tokyo, Japan). The rabbits were administered an intramuscular injection of a three-in-one admixture solution (medetomidine hydrochloride: 0.15 mg/kg, midazolam: 2.0 mg/kg, and butorphanol: 2.5 mg/kg) as an anesthetic. After shaving and disinfecting the target site, local anesthesia (2% lidocaine containing 1/80,000 epinephrine) was injected into the region between the forehead and nasal cavity. Subsequently, a 20–25-mm incision was made in the skin, and the flap was elevated to expose the bone. A bone window was created using a trephine bar with an 8.0-mm outer diameter to approach both sides of the sinus. The sinus membrane was carefully elevated, and each cavity was randomly filled with either HAp/Col or β-TCP/PLGA (250 mm^3) (Fig. 1). The periosteum, muscle, and skin were sutured layer-by-layer to close the wound. Subsequently, an antibiotic (enrofloxacin, 1 mg/kg) and pain killer (carprofen, 4 mg/kg) were administered via intramuscular injection. The rabbits were euthanized using CO_2, and the specimens were harvested at 4 weeks (4W), 8W, 16W, and 24W after surgery. Four samples were used for each time course.

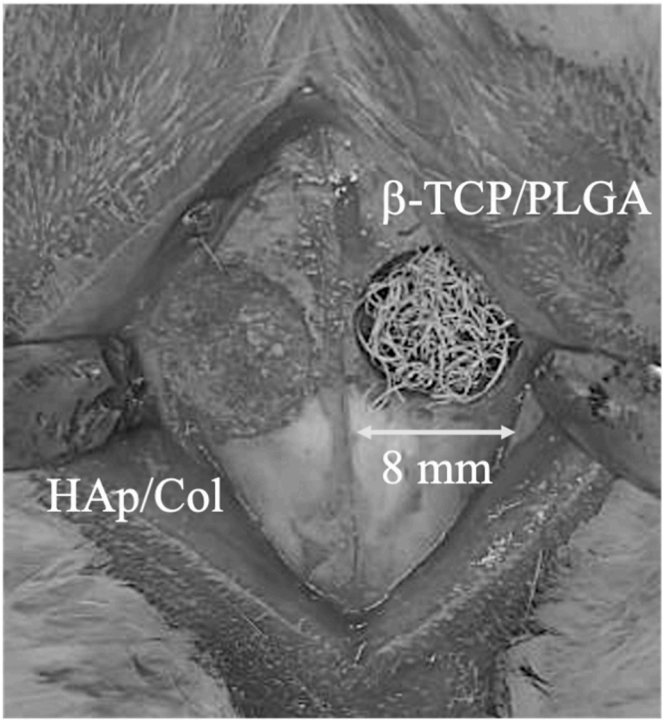

Fig. 1. Transplantation of graft materials.
The diameter of the bone window was 8 mm, created for approaching the sinus cavity. The bone graft materials, hydroxyapatite (HAp)/collagen (Col) and β-tricalcium phosphate (β-TCP)/poly(L-lactide-*co*-glycolide) (PLGA), were randomly transplanted into each side of the cavity.

2.2. Micro-computed imaging

New bone formation in each specimen was evaluated using micro-computed tomography (micro-CT) (Rigaku_mCT; Rigaku, Tokyo, Japan) at 100 mA and 90 kV. Bone volume (BV) and bone mineral content (BMC) were evaluated using a 3D image analysis software (TRI/3D-BON®; RATOC, Tokyo, Japan).

2.3. Histological evaluation

The specimens were fixed in 10% formalin solution for 5–7 days after micro-CT. Subsequently, they were sliced into approximately 3 mm coronal sections using a diamond saw. The sliced specimens were demineralized using ethylenediaminetetraacetic acid and then embedded in paraffin. Finally, the sections were spliced into 5-mm pieces using a rotary microtome (Leica RM2235 Manual Rotary; Leica Biosystems, Tokyo, Japan).

2.3.1. Hematoxylin and eosin staining

After hematoxylin and eosin (H&E) staining, the specimens were observed at low (× 20) and high (× 100) magnifications. To evaluate the extent of bone tissue formation in the augmented region, a 1 mm × 1 mm area (1 mm^2) at the center of the augmented region was detected, and the bone tissue ratio was evaluated using ImageJ (National Institutes of Health, Bethesda, MD, USA).

2.3.2. Masson's trichrome (MT) staining

MT staining was performed using a trichrome stain kit (Abcam, Cambridge, UK) and observed at a high (× 100) magnification.

2.4. Statistical analysis

The Friedman test was used to analyze the H&E staining results. The

Student's *t*-test was used to compare BV and BMC, determined by micro-CT examination, and bone tissue occupied ratio, determined using H&E staining, among different groups. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Macroscopic observations of the augmented regions

The augmented volume detected at 4W in the HAp/Col group considerably decreased from 8W onward. However, in the β-TCP/PLGA group, the volume observed at 4W remained unchanged and was almost maintained till 24W (Fig. 2).

3.2. Comparison of BV and BMC in the augmented regions over time

3.2.1. BV

A high-density area was observed over the entire augmented region at 4W in the HAp/Col group. BV was 67.56 ± 25.70 mm^3 at 4W, which was significantly higher than that at 8W (11.13 ± 1.10 mm^3), 16W (12.04 ± 14.16 mm^3), and 24W (12.55 ± 9.18 mm^3) ($p = 0.00472$, 0.00183, and 0.00152, respectively) (Fig. 3). There was no significant change in BV after 8W.

In the β-TCP/PLGA group, the entire augmented region showed low density at 4W. However, the density gradually increased, and the entire region had a uniformly high density at 24W while maintaining the volume of the augmented region. BV was 25.70 ± 8.05 mm^3 at 4W and was maintained at 47.58 ± 18.09, 62.92 ± 97.06, and 25.98 ± 8.76 mm^3 at 8W, 16W, and 24W, respectively, without any significant differences among the time points.

Further, BV exhibited a wide range at 16W in the β-TCP/PLGA group. BV in the HAp/Col group at 4W was significantly higher than that in the β-TCP/PLGA group at 4W ($p = 0.00566$) and 24W ($p = 0.00558$). However, at 8W, the β-TCP/PLGA group exhibited a higher BV than the HAp/Col group ($p = 0.02191$).

3.2.2. BMC

In the HAp/Col group, the BMC at 4W (30.85 ± 7.36 mg) was significantly lower than that at 8W (51.20 ± 1.29 mg) ($p = 0.03358$). This elevated BMC was significantly reduced at 16W (5.27 ± 5.70 mg) and 24W (5.12 ± 3.72 mg). In the β-TCP/PLGA group, BMC tended to increase from 4W (10.74 ± 3.58 mg) to 8W (23.68 ± 9.19 mg) and 16W (32.49 ± 52.97 mg) without significant differences. BMC had a wide range at 16W in the β-TCP/PLGA group. Comparing the two groups, HAp/Col showed significantly higher BMC than β-TCP/PLGA at 4W ($p = 0.00645$) and 8W ($p = 0.01182$).

3.3. New bone tissue formation and changes in the augmented regions over time, evaluated using H&E staining

According to the Friedman test, the area of bone tissue was significantly different among the groups ($p = 0.0033$). In the HAp/Col group, bone tissue was found to surround the graft material in the entire augmented region after 4W (Fig. 4). Bone and fat tissues were mainly observed, with a small amount of graft material at 8W and 16W. The augmented region was not clearly distinguished from the original mature bone, and no residual graft material was observed in the augmented region at 24W. However, the augmented BV decreased substantially.

In the β-TCP/PLGA group, little bone tissue was observed in the augmented region at 4W, and a small amount of bone tissue was observed around the graft material at 8W (Fig. 5). However, at 8W, abundant bone tissue was observed continuously from the original bone to the center of the augmented region, as well as farthest from the original bone in the augmented region. At 24W, bone tissue formation was observed throughout the augmented region. The cotton-like form of the graft material was maintained for up to 24W.

The 1-mm^2 region of bone tissue exhibited no significant difference between 4W (16.24 ± 1.71) and 8W (13.69 ± 2.59) in the HAp/Col group ($p = 0.15932$) (Fig. 6). The volume of the augmented region substantially decreased after 8W of augmentation and was thus not large enough to detect a 1-mm^2 area after 16W. Hence, the bone tissue area was evaluated at 4W and 8W in the HAp/Col group. In the β-TCP/PLGA group, the bone tissue area at 4W (1.18 ± 1.88) was significantly smaller than that at 8W (5.98 ± 2.49, $p = 0.02378$), 16W (4.76 ± 0.97, $p = 0.02358$), and 24W (8.40 ± 3.77, $p = 0.02277$). The new bone area tended to increase gradually till 24W, although without any significant difference. When comparing the two groups, the bone area at 4W in the HAp/Col group was significantly larger than that at any time point in the β-TCP/PLGA group ($p < 0.00001$). The new bone area at 8W in the HAp/Col group was also significantly larger than that at 4W ($p = 0.00036$), 8W ($p = 0.00515$), and 16W ($p = 0.00345$), but not that at 24W ($p = 0.06555$), in the β-TCP/PLGA group.

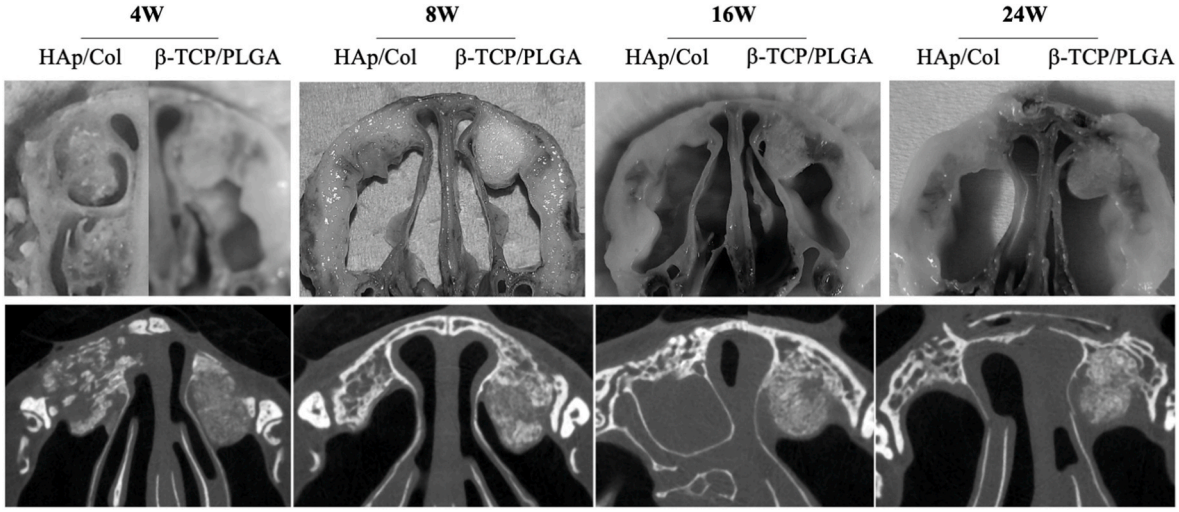

Fig. 2. Macroscopic findings on the specimen.
The augmented regions in the HAp/Col and β-TCP/PLGA groups had an equal volume at 4 weeks (4W). In the HAp/Col group, this volume considerably decreased after 8W; however, in the β-TCP/PLGA group, the volume remained unchanged till 24W.

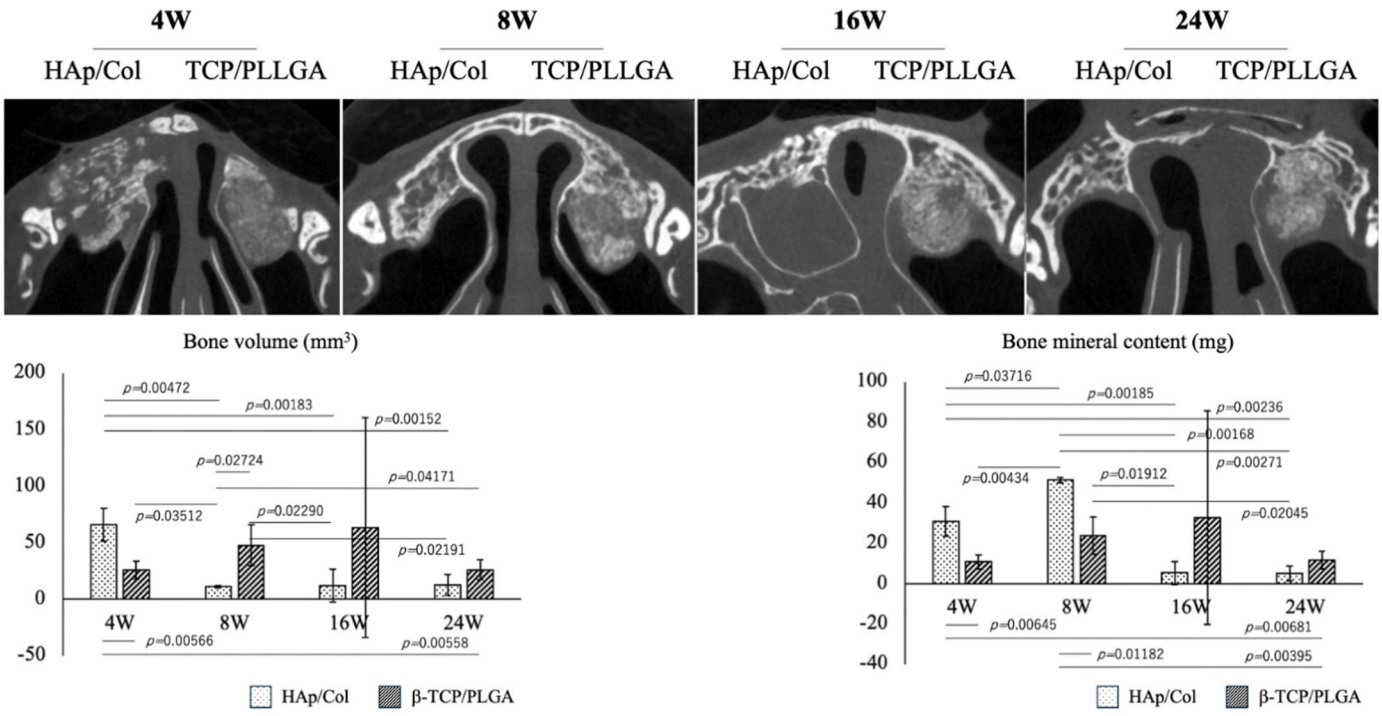

Fig. 3. Micro-computed tomography (micro-CT) findings and the volume of the newly formed bone at each time point.
The density in the augmented region was almost the same after 8W in the β-TCP/PLGA group. In the HAp/Col group, the bone volume (BV) showed a peak at 4W and thereafter substantially decreased. In the β-TCP/PLGA group, the BV did not show a remarkable change up to 24W. The bone mineral content (BMC) decreased after 16W in the HAp/Col group.

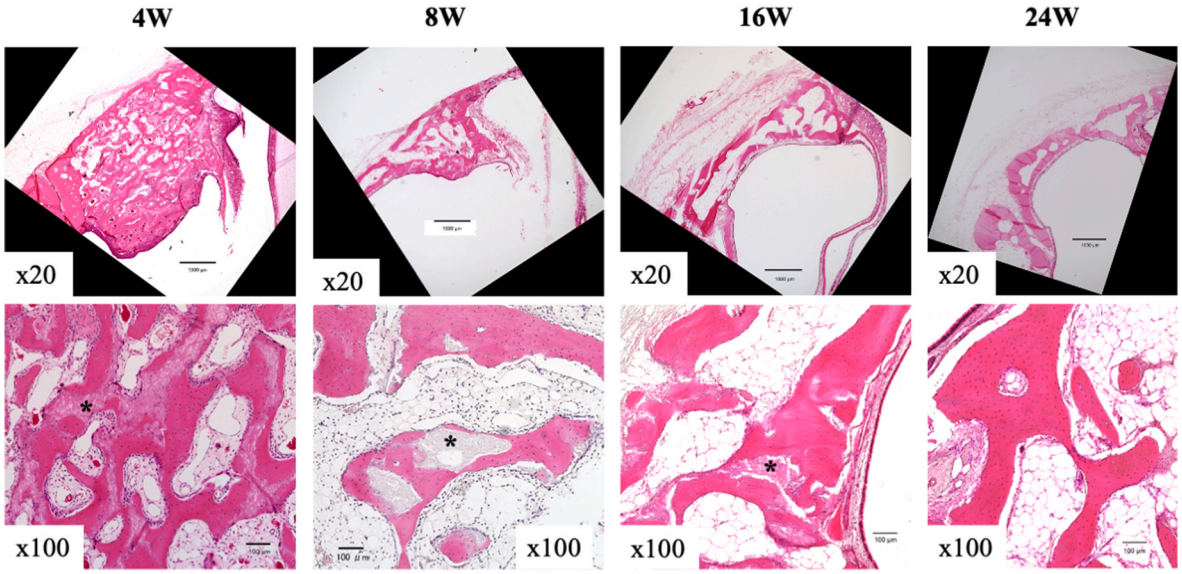

Fig. 4. Hematoxylin and eosin (H&E) staining of the HAp/Col group.
The bone tissue was observed surrounding the material (*) at 4W. There were a few remnants of the material remaining up to 16W.

3.4. New bone tissue formation in the augmented regions over time, evaluated using MT staining

In the HAp/Col group, MT staining revealed a mixture of blue-stained (collagen and immature bone tissues) and red-stained (mature bone tissue) areas around the material at 4W, which remained in a similar state even after 8W without retaining the graft materials (Fig. 7).

In the β-TCP/PLGA group, blue-stained collagen fibers were observed without red-stained areas at 4W and blue-stained bone tissue was observed at 8W. At 16W, a mixture of blue- and red-stained bone tissues was observed, but blue-stained areas were predominant. At 24W, the red- and blue-stained areas appeared almost equal.

4. Discussion

Although mature bone formed early and the bone graft material degraded by 24W when MSFA with HAp/Col was performed in the rabbit model, the volume of the newly formed bone tissue decreased quickly. In contrast, after performing MSFA with β-TCP/PLGA, bone formation took longer, the bone graft material was retained, and the

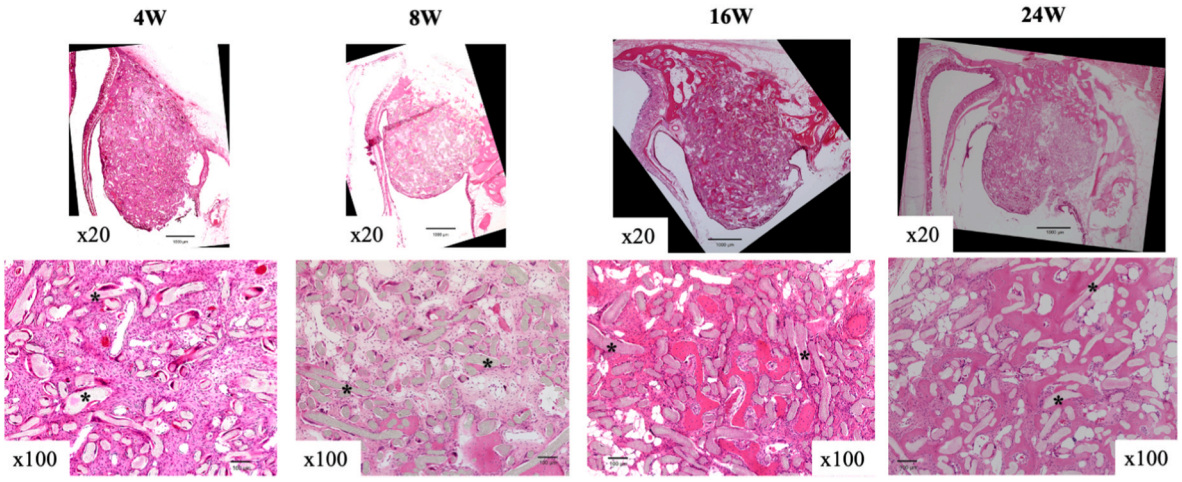

Fig. 5. H&E staining of the β-TCP/PLGA group.
Bone tissue was hardly found at 4W and little bone tissue appeared to surround the materials (*) at 8W. Bone tissue appeared to expand in the augmented region at 16W and 24W.

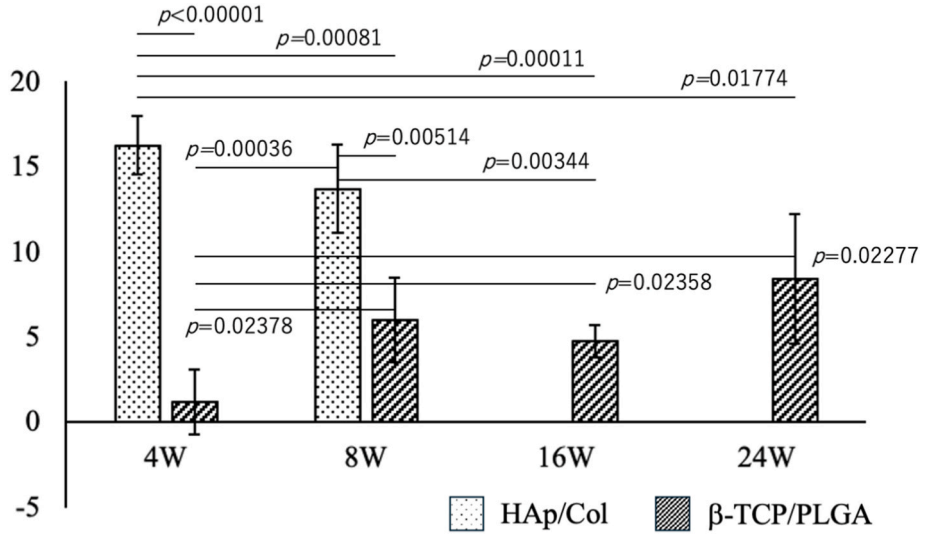

Fig. 6. New bone tissue formation.
The newly formed bone tissue in the HAp/Col group was larger than that in the β-TCP/PLGA group at 4W and 8W. In the β-TCP/PLGA group, bone tissue region at 4W was smaller than that at 8W, 16W, and 24W. The newly formed bone tissue remained unchanged after 8W in the β-TCP/PLGA group.
HAp/Col; hydroxyapatite/collagen-l, β-TCP/PLGA; β-tricalcium phosphate/poly($_L$-lactide-*co*-glycolide).

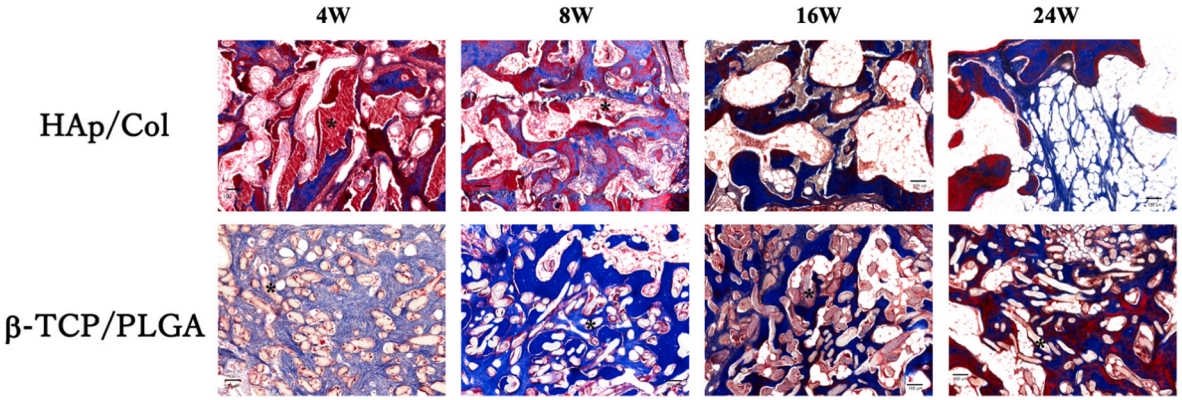

Fig. 7. Masson's trichrome (MT) staining (× 100).
Newly formed bone was stained blue and mature bone tissue was stained red. In the HAp/Col group, red regions were identified at 8W and gradually increased thereafter. In the β-TCP/PLGA group, a few red regions were confirmed at 16W but were clearly detected at 24W.

volume of the newly formed bone was maintained for up to 24W. Both materials were easy to handle and did not disperse during transplantation. Our results suggest that both materials are effective for MSFA, and bone graft material should be selected based on an understanding of the characteristics of the newly formed bone by each material.

Considering the biocompatibility, degradability, osteoconductivity, osteoinductivity, and osteogenic potential required for bone graft materials for bone augmentation, including MSFA [2,12,13], autologous bone grafts are still considered ideal [1,14–16]. However, autogenous bone grafts have several challenges, such as necessity of a donor site, expanded invasiveness and operative duration due to bone harvesting, and unpredictable augmented bone resorption after transplantation [1,17,18]. Therefore, an ideal bone graft material remains to be developed. Bone graft materials used for MSFA with dental implant placement should be completely degraded, considering the implant-to-bone contact ratio [19] and the risk of infection due to residual material [20]. In addition, it is desirable that the material used in GBR or MSFA cases is easy to manipulate. Calcium phosphate-based materials, mainly used as bone graft material, are not always easy to handle as they mostly come in a granular form. To improve their handleability, platelet-rich plasma and peripheral whole blood are often mixed with the granular materials; however, blood sampling is a highly invasive and expensive procedure [21].

HAp/Col is a useful bone graft material, which can be easily manipulated owing to its spongy nature under wet conditions [4]. Its structure is similar to that of biological bone, which contains 80% Col and 20% Hap. Additionally, HAp/Col exhibits high biocompatibility and excellent osteoconductivity [22], leading to competitive new bone formation in both basic and clinical applications [3,4]. The problem with many commercial HAp graft materials is that they are not completely degradable and persist for a long time, as HAp is usually cauterized in its production process [23]. However, HAp/Col, used in this study, was a freeze-dried gel of $Ca(OH)_2$ suspension and Col solution containing phosphoric acid and was prepared using the simultaneous dropping method without cauterization. In addition, the HAp component was nanosized in the material. Thus, HAp/Col is completely degraded even though it contains HAp [3,4]. This is advantageous with respect to the implant-to-bone contact ratio.

We previously found that HAp/Col suppresses alveolar bone resorption after tooth extraction by filling itself into the socket owing to its bone formation ability [4]. The present study demonstrated that HAp/Col induced mature bone formation relatively early following MSFA, as evidenced by the findings of H&E and MT staining. This is consistent with our previous findings that HAp/Col promotes early mature bone formation on mouse calvarium [3]. The micro-CT findings revealed that BMC in the HAp/Col group was higher than that in the β-TCP/PLGA group at 4W and 8W after surgery. Additionally, HAp/Col itself was degraded within 16W after MSFA. These outcomes indicate the effectiveness of HAp/Col for dental implant treatment in terms of implant-to-bone contact ratio. However, the augmented BV quickly decreased in the HAp/Col group. The possible reasons for this early resorption of the augmented bone following MSFA with HAp/Col may be that the newly formed bone could not tolerate the air pressure in the maxillary sinus owing to the early degradation of HAp/Col, or the newly formed bone showed disuse atrophy. Thus, performing MSFA with simultaneous implant placement would be a good indication for applying HAp/Col in MSFA. However, clinical reports on its application in MSFA are limited [5], warranting further investigations.

Only a few clinical studies have described Col/calcium phosphate hybrid materials [24] similar to HAp/Col [25]. Although these Col-based materials have shown good handleability and efficacy, there are several concerns regarding the use of Col as a biomaterial, including the difficulty of homogenizing the material, the possibility of variations in the degradation ratio *in vivo*, and the potential presence of unknown infections. Therefore, researchers have attempted to develop alloplastic bone graft materials.

PLGA and β-TCP are completely alloplastic materials, which can dispel the aforementioned concerns associated with the use of biological materials. The osteoconductivity of β-TCP has been reported to be comparable to that of HAp [23,26]; thus, β-TCP is commonly used in clinical practice as a bone graft material with favorable outcomes, similar to those of HAp. However, most β-TCP materials come in a granular form and have low handleability. β-TCP/PLGA used in this study had good handleability owing to its cotton-like form fabricated by the electrospinning method [27]. This cotton-like form also makes it useful as a bone graft material [28] for use in complex bone defects in regions with narrow spaces and wide or deep depths. Some studies have demonstrated the usefulness of nanofiber materials prepared using the electrospinning method as wound dressings and tissue engineering scaffolds [29]; however, *in vivo* studies on this topic are still limited, even though some studies have demonstrated bone healing by filling bone defects with β-TCP/PLGA [30].

The present study demonstrated that the augmented BV was maintained for up to 24W following MSFA with β-TCP/PLGA. Histological findings revealed the presence of bone tissue around the area starting at 8W after MSFA. We assumed that β-TCP was gradually exposed due to the slow hydrolysis of PLGA, facilitating osteogenesis while maintaining the augmented volume. Thus, β-TCP/PLGA may be effective for not only cases in which implants are placed simultaneously with MSFA but also cases in which implant placement is delayed until bone healing due to insufficient bone height, as the amount of augmented BV is maintained for a prolonged period.

New bone maturation was considered to have progressed based on our H&E and MT staining results. However, the newly formed bone area did not change remarkably in the central augmented region after 8W of surgery. Similarly, BMC showed no significant change after 8W according to our micro-CT findings. β-TCP/PLGA remained for up to 24W after MSFA, suggesting that the material itself may limit the area of osteogenesis or adipose degeneration over a long period. In addition, the wide range of BMC at 16W after surgery implied that the hydrolysis of PLGA was encouraged at around 16W after MSFA with β-TCP/PLGA. Osteogenesis was suppressed by local acidification caused by this prolonged hydrolysis of PLGA. β-TCP/PLGA could maintain the augmented volume because the material itself remains for a long period unlike HAp/Col in MSFA; thus, the decreased implant-to-bone contact ratio and postoperative infection need to be taken into account.

5. Conclusion

Both HAp/Col and β-TCP/PLGA are effective for MSFA because of their ability to form new bone and good handleability. As the characteristics of the newly formed bone with each bone graft material could be different, it is necessary to use them depending on their application while understanding the properties of the newly formed bone.

CRediT authorship contribution statement

Seigo Ohba: Conceptualization, Investigation, Writing – original draft. **Rena Shido:** Investigation. **Hideyuki Yamamoto:** Software. **Masahito Hara:** Investigation. **Yasutoshi Nishikawa:** Conceptualization. **Toshihiro Kasuga:** Conceptualization, Validation. **Tomohiro Yamada:** Writing – review & editing. **Yoshinori Sumita:** Validation. **Tatsuo Shirota:** Writing – review & editing.

Ethical approval

This study was approved by the Animal Experimental Committee of Nagasaki University (approval number: 2009171663).

Data availability statement

Data supporting the findings of this study are available on request from the corresponding author, subject to approval from the funding company (ORTHOReBIRTH).

Funding

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Declaration of competing interest

HAp/Col (ReFit®) and β-TCP/PLGA (ReBOSSIS-J®) were provided by HOYA Technosurgical Corporation and ORTHOReBIRTH, respectively.

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