An Organic Mineral Adhesive Bone Graft: A Preclinical Study

Joseph P. Fiorellini, DMD, DMSc[1]/Sean Mojaver, DDS[1]/George Kay, DMD, MMSc[2]/Yu Cheng Chang, DMD, MSOB[1]/Michael Brown, MS, MMSc[2]/Hector Sarmiento, DMD, MSOB[1,3]

Purpose: To evaluate four formulations of tetracalcium phosphate combined with phosphoserine (TTCP-PS) in comparison to the conventional grafting materials bioglass (BG) and deproteinized cancellous bovine bone with a bioresorbable collagen membrane in standardized defects created in the angle of the rat mandible. ***Materials and Methods:*** TTCP-PS is a synthetic, injectable, cohesive, self-setting, mineral-organic wet-field adhesive. Microcomputed tomography (microCT) and histomorphometry were used to evaluate bone replacement with each of these materials after in vivo residence of either 4 or 12 weeks. ***Results:*** Specific TTCP-PS formulations can form bone comparable to conventional materials in an osteopromotive mechanism but with the advantage of having cohesive and adhesive properties. ***Conclusions:*** This study showed the potential for TTCP-PS to be used as a viable candidate for bone grafting procedures. *Int J Oral Maxillofac Implants 2025;40:504–511. doi: 10.11607/jomi.11074*

Keywords: biocompatible biomaterials, bone adhesive, bone graft resorption, bone regeneration, bone-to-implant interface, calcium phosphate, cohesive bone graft, histomorphometry, injectable graft material, mineral-organic cement, mandibular defect model, microCT, osteopromotion, preclinical in vivo study, tetracalcium phosphate phosphoserine (TTCP-PS)

Dental implants have had a high survival rate and were considered the standard of care for many indications but anatomical limitations often complicate implant placement. Many patients required hard and soft tissue grafting due to ridge deficiency immediately at tooth extraction or in a healed site. Various bone graft materials were described and commonly used in practice. The character and application of grafting material varied depending on the source: autogenous grafts from intra- or extra-oral sites of the patient, allograft from human cadavers, xenograft from another species, and synthetic alloplastic products made by manufacturers.[1,2] Generally, these materials demonstrated osteoconductive, osteoinductive, and osteopromotive properties[3,4] but these materials were most commonly applied in loose particles or a soft putty form. The absence of inherent structural integrity made handling the material challenging and impacted the predictability of volume and the degree of bone replacement. Additionally, a protective barrier was typically required to secure the material and prevent fibrous tissue ingrowth.[5,6]

A novel bone grafting material called tetracalcium phosphate and phosphoserine (TTCP-PS) is a synthetic, injectable, cohesive, self-setting, mineral-organic wet-field adhesive. After mixing TTCP-PS with water, the mixture of powders and aqueous medium transitioned from a tacky liquid to a cohesive putty into a multiphased apatitic solid. Once set, TTCP-PS maintained a strong chemical bond to both metal and bone tissue. The strength, as reflected by maximum compressive and shear stress, of cured TTCP-PS was higher than that of the native bone.[4,7] Furthermore, TTCP-PS was eventually resorbed and replaced by native bone in a volume-preserving manner. This study evaluated four formulations of TTCP-PS with varying porosity and compared to two different conventional grafting materials in a preclinical defect model via Microcomputed tomography (microCT) and histologic/histomorphometric methods.[8,9] The null hypothesis was that there would be no statistically significant difference in bone formation, volume maintenance, or stability.

MATERIALS AND METHODS

The study was approved by the Institutional Animal Care and Use Committee from Pine Acres (18–02). Adult male Sprague-Dawley rats, aged 40 days and weighing between 250 g and 300 g each, were randomly assigned to 4- and 12-week groups. There were seven animals in each group. The experimental groups included four TTCP-PS formulations with varying compositions and porosities (Table 1 and Fig 1): TTCP-PS250—consisting

[1]Department of Periodontics, University of Pennsylvania School of Dental Medicine, Philadelphia, Pennsylvania, USA.
[2]RevBio, Lowell, Massachusetts, USA.
[3]Private practice, New York, New York, USA.

Correspondence to: Dr Joseph P. Fiorellini, jpf@dental.upenn.edu

Submitted July 10, 2024; accepted September 4, 2024.

Table 1 Treatment Groups with Formulation and Percent Porosity When Applicable

Treatment group	Formulation	Percent porosity
TTCP-PS250	TTCP-PS base	0% to 5%
TTCP-PS250G	TTCP-PS base + calcium phosphate granules	23%
TTCP-PS250GP	TTCP-PS base + calcium phosphate granules + polylactic-co-glycolic acid fibers	27%
TTCP-PS300	TTCP-PS base with higher phosphoserine concentration	25%
BG (Bioglass)	Silicon dioxide, sodium oxide, calcium oxide, and phosphorous pentoxide	N/A
DCBBM	Deproteinized cancellous bovine bone/bioresorbable collagen membrane	N/A

N/A = not applicable.

of the TTCP-PS base with 0% to 5% porosity; TTCP-PS250G—composed of TTCP-PS base combined with calcium phosphate granules (23% porosity); TTCP-PS250GP—incorporating calcium phosphate granules and polylactic-co-glycolic acid (PLGA) fibers into the TTCP-PS base (27% porosity); and TTCP-PS300—formulated with a higher phosphoserine concentration (25% porosity). The control materials included Bioglass (BG), composed of silicon dioxide, sodium oxide, calcium oxide, and phosphorus pentoxide, and a deproteinized cancellous bovine bone matrix combined with a bioresorbable collagen membrane (DCBBM) (see Table 1).

During the surgical procedures, the animals were anesthetized with an intraperitoneal injection of 75 mg/kg ketamine (Fort Dodge Laboratories), and 5 mg/kg xylazine (Miles Medical Group). The surgical sites on the mandibles were prepared by shaving the skin and disinfecting it with a povidone-iodine scrub and 70% alcohol. Two-centimeter superficial skin incisions were made along the lower border of the jaw to expose the angle of the mandible. Full-thickness flaps were elevated to expose the bony surface. Saline irrigation was used to irrigate the surgical sites, and a standardized through and through five-millimeter diameter circular defect was created using trephine burs. The test materials were immediately placed in the defect, to completely fill the site. The surgical sites were closed in layers with 4-0 vicryl sutures, including muscle replacement. Following the surgical procedures, the animals were closely monitored. Subcutaneous administration of Metacam (2 mg/kg) and ketoprofen (5 mg/kg) provided postoperative pain relief for 3 days.

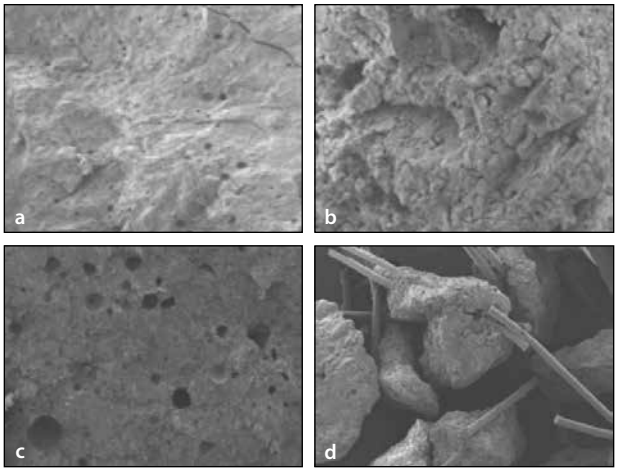

Fig 1 Scanning electron microscopy of the following TTCP-PS formulations: *(a)* TTCP-PS250, *(b)* TTCP-PS250G, *(c)* TTCP-PS300, and *(d)* TTCP-PS250GP.

At the designated time points of 4 and 12 weeks after surgery, the animals were euthanized using CO_2 inhalation. After fixation and prior to sectioning for histologic preparation, the mandibles were examined with microCT. For microCT analysis, the fixed mandibular tissues were scanned using an eXplore Locus SP microCT scanner (GE Healthcare) at a resolution of 48 µm. The microCT data sets were reconstructed using GEHC eXplore Scan Control software, and OsiriX 64 image analysis software was used for evaluation. The original circular defect was located, and a 3D region of interest measuring 5.0 mm in diameter and 0.3 mm in height was established, corresponding to the original defect. A bone/no bone threshold value in CT Hounsfield units was determined to quantify the mineralized bone, including both new bone and bone graft, within the osteotomy defect. Bone fill (0-4), presence of cortical bone (0 or 1), graft containment (0 or 1), and bone formation outside the graft (0 or 1) were assessed independently by two (J.F. and Y.C.) calibrated examiners.

Non-decalcified histologic sections were used for the validation of bone formation and descriptive analysis.[10] Histomorphometric assessments were completed with the decalcified sections.[11,12] Image-J software was used to assess the studied biomaterial, alveolar bone, and bone marrow space within three regions of interest per slide for the 12-week specimens (Fig 2). One region of interest was in the center of the surgical defect, whereas the remaining two areas were at the periphery approximately 1 mm from the edge of the defect. The peripheral regions of interest were averaged for each specimen. The process involved a combination of pixel and color analysis, allowing for differentiation between the studied biomaterial and surrounding tissues. By converting the images into 8-bit grayscale and setting specific color thresholds, the software quantified the

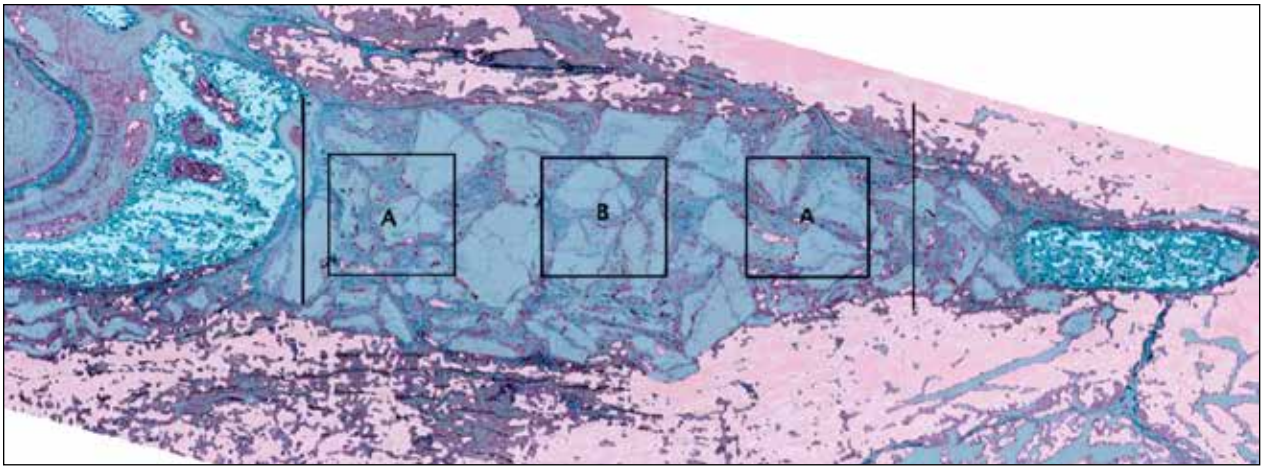

Fig 2 Regions of interest for histomorphometric evaluation. BG histomorphometry at 12 weeks with a color threshold set for the biomaterial: (A) periphery regions of interest and (B) center region of interest.

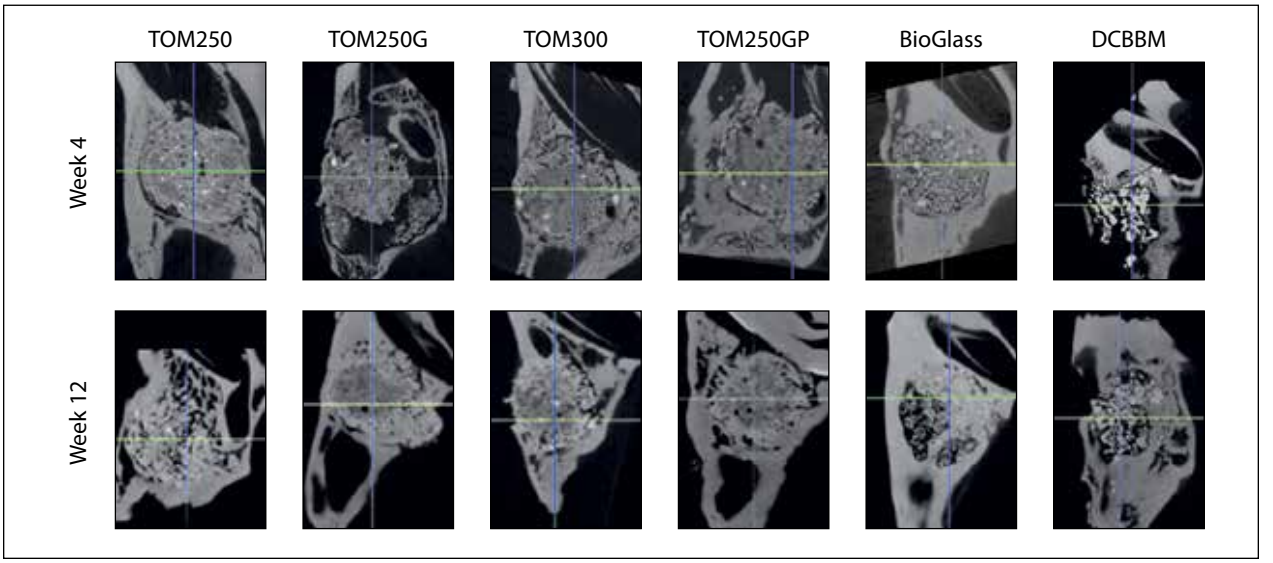

Fig 3 MicroCT of treatment site at 4 and 12 weeks.

presence and integration of the studied biomaterial within the defect sites.

Statistical analyses were performed using mean and standard deviation. Student's *t*-tests and ANOVA were employed to determine the significance, with $P < .05$ indicating statistical significance.

RESULTS

The surgical and postoperative phases had been uneventful for all groups. The descriptive histologic evaluation indicated the dissolution of the graft material. Remanent particles were integrated into the surrounding newly regenerated bone, in which had osteoblasts and osteocytes. There were few, if any, osteoclasts present in the sections.

The assessment of radiographic parameters indicated a significant increase in bone formation between 4 and 12 weeks in all the TTCP-PS graft-treated defects as compared to those treated with BG or DCBBM (Fig 3 and Tables 2 to 4). At the 4-week time point, mean bone formation was as follows: 2.3 mm with TTCP-PS250, 2.0 mm with TTCP-PS250G, 2.7 mm with TTCP-PS250GP, and 2.3 mm with TTCP-PS-300G, compared to 1.5 mm with BG and 0.5 mm with DCBBM. At the 12-week time point, mean bone formation was 2.8 mm with TTCP-PS250, 3.0 mm with TTCP-PS250G, 2.6 mm with TTCP-PS250GP, and 2.8 mm with TTCP-PS300 compared to 2.0 mm with BG and 1.4 mm with DCBBM. The differences between the TTCP-PS grafts and controls (BG and DCBBM) were statistically significant ($P < .05$). In general, graft materials had been well contained within the defect, with the exception of DCBBM at the 4-week

Table 2 Bone Formation Within the Surgical Defect of All Four TTCP Formulations

Time	TTCP-PS250	TTCP-PS250G	TTCP-PS250GP	TTCP-PS300	BG	DCBBM
4 weeks	2.3 ± 0.57 mm	2.0 ± 0.71 mm	2.3 ± 0.51 mm	2.7 ± 0.51 mm	1.5 ± 0.54 mm	0.5 ± 0.5 mm
12 weeks	2.8 ± 0.51 mm	3.0 ± 0.0 mm	2.6 ± 0.55 mm	2.8 ± 0.41 mm	2.0 ± 1.0 mm	1.4 ± 0.54 mm

Table 3 Graft Containment of All Four TTCP Formulations

Time	TTCP-PS250	TTCP-PS250G	TTCP-PS250GP	TTCP-PS300	BG	DCBBM
4 weeks	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	0.0 ± 0.00 mm
12 weeks	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	0.0 ± 0.00 mm

Table 4 Cortical Bone Formation of All Four TTCP Formulations

Time	TTCP-PS250	TTCP-PS250G	TTCP-PS250GP	TTCP-PS300	BG	DCBBM
4 weeks	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	0.0 ± 0.00 mm	0.0 ± 0.00 mm
12 weeks	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	1.0 ± 0.00 mm	0.0 ± 0.00 mm	0.0 ± 0.00 mm

timepoint. There were no statistical differences between treatment groups at either 4 or 12 weeks.

The evaluations for the presence, or not, of cortical bone revealed that TTCP-PS250, TTCP-PS250G, TTCP-PS250GP, and TTCP-PS300 all scored an average of 1.0, indicating that there was presence of cortical bone (on average) at both 4 and 12 weeks. In contrast, the mean for the BG and DCBBM were zero, indicating that there was a lack of cortical bone; however, BG at week 12 had a mean score of 0.5. A statistically significant difference was found between TTCP-PS grafts and controls at both 4 and 12 weeks for the presence of cortical bone at both timepoints.

The histologic examination of the deposition sites at 12 weeks revealed a biocomposite consisting of the remaining biomaterial and abundant newly generated bone tissue, both mineralized and bone marrow, inside of the original deposit volume as well as newly deposited bone overlying the deposit subperiosteally (Fig 4). Note that a majority of the bone was lamellar. The remaining biomaterial appeared quite heterogeneous, which was expected given its multiphasic composition. At this postoperative stage, some segments of the biomaterial were substantially fragmented, with new bone encasing individual fragments, while other segments were less fragmented but were generally penetrated by bone tissues. The bone marrow stroma appeared normal, with sheets of osteoblasts lining the interface with mineralized bone.

The histomorphometric evaluation confirmed bone formation within the surgical defect (Tables 5 and 6) for all treatment groups, with the regions of interest evaluated at 12 weeks. At 12 weeks, the mean ± SDs for the percent of histologic new bone formation were

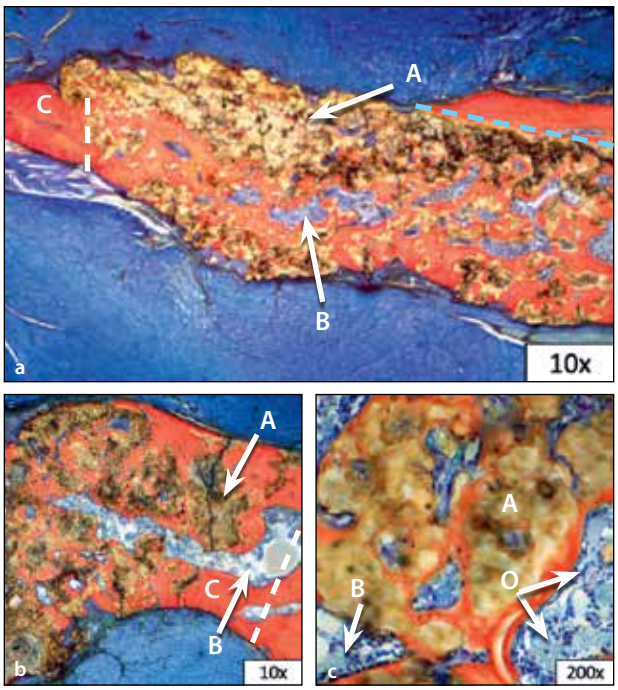

Fig 4 *(a to c)* Photomicrographs of nondecalcified resin-mounted sections stained with Stevenel's blue and Van Gieson's picrofuchsin for histologic analysis by means of brightfield microscopic examination. (A) The heterogeneous *sepia, tan, and brown colors* represent biomaterial; (B) the *blue colors* inside the bone envelope represent bone marrow; (C) the *orange-pink color* represents bone; and the section marked with an *O and white arrows* represents osteoblasts. The *white dashed line* shows the boundary between the original host bone and the biocomposite consisting of the remaining biomaterial and the newly generated bone. The *blue dashed line* shows the boundary between the biocomposite and the newly generated bone overlying it.

Table 5 Percentage of Histologic Bone Formation Within the Surgical Defect at 12 Weeks for All Four TTCP Formulations

Region of interest	TTCP-PS250, %	TTCP-PS250G, %	TTCP-PS250GP, %	TTCP-PS300, %	BG, %	DCCM, %
Center, mean (SD)	18.2 ± 6.1	29.7 ± 6.9	5.6 ± 3.7	19.9 ± 4.1	25.8 ± 20.1	43.4 ± 24.2
Periphery, mean (SD)	48.3 ± 28.9	52.2 ± 25.3	35.8 ± 28.0	35.6 ± 20.3	46.8 ± 23.4	31.2 ± 25.1
Total, mean (SD)	37.5 ± 6.5	33.2 ± 18.5	17.6 ± 8.3	28.7 ± 8.6	36.8 ± 21.7	40.7 ± 9.8

Table 6 Percentage of Remnant Graft Material Within the Surgical Defect at 12 Weeks for All Four TTCP Formulations

Region of interest	TTCP-PS250, %	TTCP-PS250G, %	TTCP-PS250GP, %	TTCP-PS300, %	BG, %	DCCM, %
Center, mean (SD)	59.7 ± 18.2	42.1 ± 25.4	93.9 ± 29.4	73.4 ± 30.1	42.1 ± 28.3	57.8 ± 16.2
Periphery, mean (SD)	43.3 ± 18.5	44.3 ± 12.0	84.6 ± 32.2	67.3 ± 20.4	44.4 ± 13.9	55.2 ± 19.0
Total, mean (SD)	34.4 ± 20.1	28.8 ± 13.6	60.2 ± 34.3	47.1 ± 21.7	32.3 ± 14.9	37.5 ± 20.2

as follows: TTCP-PS250 (37.5% ± 6.5%), TTCP-PS250G (33.2% ± 18.5%), TTCP-PS250GP (17.6% ± 8.3%), TTCP-PS300 (28.7% ± 8.6%), BG (36.8% ± 21.7%), and DCBBM (40.7% ± 9.8 %).The 12-week analysis of the percentage of remnant graft material found were as follows: TTCP-PS250 (34.4% ± 20.1%), TTCP-PS250G (28.8% ± 13.6%), TTCP-PS250GP (60.2% ± 34.3%), TTCP-PS300 (47.1% ± 21.7%), BG (32.3% ± 14.9%), and DCBBM (37.5% ± 20.2%). There was a statistically greater bone formation and resorption of graft material with TTCP-PS250, TTCP-PS250G, BG, and DCBBM than TTCP-PS250GP and TTCP-PS300 ($P < .05$).

DISCUSSION

The results of this study found differences between groups, therefore rejecting the null hypothesis. The combination of TTCP-PS, a synthetic, injectable, cohesive, self-setting, mineral-organic wet-field adhesive, improved outcomes in bone grafting procedures of a critical-sized defect in rat mandibles. Uniquely, TTCP-PS demonstrated a superior performance for maintaining the original placement volume and position, as well as the development of a radiographic cortical bone layer.[7,13] The healing process was further enhanced by the TTCP-PS adhesive's ability to maintain stability and integrity over time, a characteristic that was crucial for the success of alveolar ridge augmentation.[7,10,14] In addition, specific formulations of TTCP-PS were as effective as the conventional grafting material in bone formation, thus indicating that TTCP-PS is a material with overall excellent handling and bone substitution characteristics.[4,15,16]

A fundamental concern with bone regeneration procedures is space maintenance and volume preservation. The field has evolved from the harvesting of a block graft and fixation to the defect bed to the use of particulate materials with containment adjuncts. In an early study evaluating the use of ePTFE membranes in the same model used in the present study, Alberius et al[5] reported that osteopromotive effects of materials substantially increased bone formation and reduced volume loss. The data from the present study also indicated that the osteopromotive properties of TTCP via the recruitment of osteogenic cells, can result in volume maintenance.[5,17] More recently, Ngo et al[17] evaluated hydroxyapatite and poly-L-lactide-co glycolide (PGLA) material in the rat mandibular angle defect model. Their results demonstrated accelerated bone formation with the constructions and that this more rapid bone growth occurred at early stages. These results with constructs containing PLGA were more promising than those in the present study, in which there was a higher percentage of remanent material.[5,17]

Recent advancements in calcium phosphate grafting materials significantly impacted the field of dental implants, offering innovative solutions for bone defects and tissue reconstructions.[18,19] One such development was the use of biphasic calcium phosphate in combination with Leukocyte- and Platelet-Rich Fibrin, which demonstrated promising results in horizontal alveolar ridge augmentation in the mandibular posterior region, resulting in dental implant placement and prosthetic rehabilitation.[20,21] Additionally, randomized clinical trials demonstrated the stability of guided bone regeneration using biphasic calcium phosphate with varying hydroxyapatite/β-tricalcium phosphate

ratios. These studies indicated that specific ratios could maintain facial bone thickness more effectively, which is a crucial factor for dental implant site esthetics.[3,9,22]

Furthermore, the application of calcium phosphate-based coatings on Ti dental implants—produced using methods like radiofrequency magnetron sputtering—was investigated to evaluate the enhancement of osseointegration and antibacterial properties.[23–26] These coatings, incorporating elements such as zinc chloride and silver nitrate, demonstrated the potential for preventing peri-implant infections.[27–30] Another notable technique was the pulsed electrochemical deposition of calcium phosphate coatings, which offered improved compositional control and coating uniformity. Such application methods are a promising approach for producing high-quality coatings tailored for dental implants.[31–34]

Mimicking a component of the sandcastle worm adhesive protein, a bone adhesive based on TTCP-PS was developed. This adhesive cured in minutes in an aqueous environment and provided high bone-to-bone or bone-to-metal adhesive strength.[7,8] TTCP-PS was 10 times more adhesive than bioresorbable calcium phosphate cement and 7.5 times more adhesive than nonresorbable poly(Methyl methacrylate) bone cement.[7,35] The material also demonstrated osseointegration and replacement with bone over a 52-week period in a rabbit critical-sized distal femur defect.[4,36–38] One of the most significant benefits was that it did not require any additional adjunctive materials for application, structural integrity, or volume maintenance, simplifying the procedure and reducing the risk of complications.[4,39–41] Furthermore, TTCP-PS was easy to apply and could be used in a wet field, making the material highly suitable for dental procedures.[4,42] The adhesive also exhibited rapid mechanical stability.[7] The physical characteristics of freshly mixed TTCP-PS were similar to that of a dental cement. The initial mixture formed a highly adhesive sticky substance which gradually hardened within a few minutes.[7] The material showed excellent adhesive affinity in vitro for bone and metals (including Ti) with resistance to tensile and shear stresses of > 3 MPa.[7] TTCP-PS also formed strong cohesive bonds within the material itself with similar resistance to cohesive shear, as well as both compressive strength and an elastic modulus which compared very favorably to native cancellous bone, exhibiting over five times ultimate compressive strength at its peak.[7]

TTCP-PS grafting materials had broad potential applications, particularly in the fields of orthopedics where calcium phosphate-based bone cements had been widely adopted.[4] Recent advancements in bioresorbable bone adhesives have opened new possibilities for applications in trauma and orthopedic surgery.[4] The use of degradable reinforcement strategies such as PLGA fibers and chitosan lactate significantly improved the mechanical properties of bone adhesives like TTCP-PS. These reinforcements not only enhanced compressive and shear strength but also improved fatigue performance, making them suitable for a wide range of clinical applications such as arthroplasty and vertebroplasty. The ability of these reinforced adhesives to form strong bonds in wet environments further underscored their clinical potential.[4,5]

In dental applications, recent studies identified that monomeric phosphoserine (pSer) could serve as a setting reagent for calcium phosphate cements.[4] This was particularly relevant for dental applications where adhesive functionality and biomechanical potential were crucial.[4] An application of the adhesive properties of TTCP-PS has been made for immediate implant stabilization.[4] Current practices in dentistry aimed for minimally invasive and an accelerated overall treatment. However, the immediate placement of implants in fresh extraction sockets often posed challenges due to insufficient native bone and implant instablity.[2] One formulation of TTCP-PS (Tetranite for Implant Stabilization, TN-ISM) has been used to improve immediate primary stability, thus potentially reducing treatment times, costs, and postoperative complications.[2] The concept of "primary" and "secondary" stability for implant placement further supported the use of TTCP-PS in dental applications.[2,3] While advancements in implant surface technology had improved secondary bone contact and faster healing times, they did not solve the problem of immediate implant stability in sites lacking adequate bony support.[3] A recent study[2] in a canine model demonstrated that a formulation of TTCP-PS (Tetranite Stabilization Material [TN-SM]) provided immediate implant stabilization, outperforming traditional bone graft methods. The stability of the implant during healing was a critical aspect of osseointegration. As the quality of the host bone became less dense, implant stability torques decreased.[3] A 12-month evaluation of TN-SM in an animal model demonstrated that the adhesive provided significant and clinically relevant immediate implant stability, which persisted through 12 months.[2] The adhesive established an intimate contact with the implant and bony walls and was replaced with new bone without compromising stability.[2] The authors of that study concluded that TN-SM had the potential to stabilize implants placed in sites with inadequate bony support and allowed for osseointegration without loss of stability through 12 months of follow-up.[2,3]

The preclinical studies offered a promising solution for enhancing the success rate of dental implant procedures during the initial healing period of otherwise unstable implants. Moreover, the use of adhesive biomaterials could potentially reduce the need for additional surgical procedures, such as

augmentation surgery prior to implant placement, therefore reducing the overall treatment cost and likely improving patient satisfaction.[4] Lastly, in veterinary dentistry, particularly for small breed dogs, mandibular fractures were a common challenge. A recent study[7] tested a TTCP-PS-based grafting material ex vivo for its effects on augmenting the strength of different noninvasive fracture fixation techniques. That study reported that the use of this mineral-organic adhesive and composite might provide a stronger fixation construct over interdental wire and composite for mandibular fracture repair in dogs.[7]

CONCLUSIONS

This study demonstrated the potential for TTCP-PS to be used as a viable candidate for bone grafting procedures. With the limitations of this small animal study, the observed bone fill—coupled with the adhesive, cohesive, and osteopromotive properties—improved bone healing. The clinical implications of these adhesive formulations include potentially reducing the need for complex procedures using adjunctive materials such as membranes and fixation devices, reducing the need for additional surgical procedures, and reducing costs. Lastly, the unique ability to tailor the porosity of TTCP-PS formulations, thereby modulating the rate of resorption and bone ingrowth, further enhances its appeal for future indications.

ACKNOWLEDGMENTS

Funding for this interdisciplinary translational project was provided by the Translational Resource Center (TRC) under NIDCR project no. 5U24DE029462-05. TRC awarded the funding to RevBio under contract no. SUBK00014114.

REFERENCES

1. Bagno A, Di Bello C. Surface treatments and roughness properties of Ti-based biomaterials. J Mater Sci Mater Med 2004;15:935–949.
2. Do MP, Neut C, Delcourt E, Certo TS, Siepmann J, Siepmann F. In situ forming implants for periodontitis treatment with improved adhesive properties. Eur J Pharm Biopharm 2014;88:342–350.
3. Jung RE, Herzog M, Wolleb K, Ramel CF, Thoma DS, Hämmerle CHF. A randomized controlled clinical trial comparing small buccal dehiscence defects around dental implants treated with guided bone regeneration or left for spontaneous healing. Clin Oral Implants Res 2017;28:348–354.
4. Chouirfa H, Bouloussa H, Migonney V, Falentin-Daudre C. Review of titanium surface modification techniques and coatings for antibacterial applications. Acta Biomater 2019;83:37–54.
5. Alberius P, Dahlin C, Linde A. Role of osteopromotion in experimental bone grafting to the skull: A study in adult rats using a membrane technique. J Oral Maxillofac Surg 1992;50:829–834.
6. Norton MR, Kay G, Brown M, Cochran DL. Bone glue - The final frontier for fracture repair and implantable device stabilization. Int J Adhes Adhes 2020;102:102647.
7. de Oliveira P, Bonfante EA, Bergamo ETP, et al. Obesity/metabolic syndrome and diabetes mellitus on peri-implantitis. Trends Endocrinol Metab 2020;31:596–610.
8. Cochran DL, Jones A, Sugita R, et al. Immediate dental implant stabilization in a canine model using a novel mineral-organic adhesive: 4-month results. Int J Oral Maxillofac Implants 2020;35:39–51.
9. He Q, Mu Z, Shrestha A, et al. Development of a rat model for type 2 diabetes mellitus peri-implantitis: A preliminary study. Oral Dis 2022;28:1936–1946.
10. Wen Z, Shi X, Li X, et al. Mesoporous TiO(2) coatings regulate ZnO nanoparticle loading and Zn(2+) release on titanium dental implants for sustained osteogenic and antibacterial activity. ACS Appl Mater Interfaces 2023;15:15235–15249.
11. Scarano A, Valbonetti L, Degidi M, et al. Implant-abutment contact surfaces and microgap measurements of different implant connections under 3-dimensional x-ray microtomography. Implant Dent 2016;25:656–662.
12. Fiorellini JP, Sourvanos D, Crohin CC, et al. Diabetic serum inhibits osteoblast adhesion to titanium surface through advanced glycation end products: An in vitro study. Int J Oral Maxillofac Implants 2020;35:551–559.
13. Hong Q, Pierre-Bez AC, Kury M, et al. Shear bond strength and color stability of novel antibacterial nanofilled dental adhesive resins. Nanomaterials (Basel) 2022;13:1.
14. Froum SJ, Tarnow DP, Wallace SS, et al. The use of a mineralized allograft for sinus augmentation: An interim histological case report from a prospective clinical study. Compend Contin Educ Dent 2005;26:259–260, 262–264, 266–268; quiz 270–1.
15. Mathur A, Kharbanda OP, Koul V, Dinda AK, Anwar MF, Singh S. Fabrication and evaluation of antimicrobial biomimetic nanofiber coating for improved dental implant bioseal: An in vitro study. J Periodontol 2022;93:1578–1588.
16. Ferraris S, Spriano S. Antibacterial titanium surfaces for medical implants. Mater Sci Eng C Mater Biol Appl 2016;61:965–978.
17. Ngo HX, Dong QN, Bai Y, et al. Bone regeneration capacity of newly developed uncalcined/unsintered hydroxyapatite and poly-l-lactide-co-glycolide sheet in maxillofacial surgery: An in vivo study. Nanomaterials (Basel) 2020;11:22.
18. Peppas NA, Langer R. New challenges in biomaterials. Science 1994;263:1715–1720.
19. de Avila ED, van Oirschot BA, van den Beucken JJJJP. Biomaterial-based possibilities for managing peri-implantitis. J Periodontal Res 2020;55:165–173.
20. Subramani K, Jung RE, Molenberg A, Hammerle CHF. Biofilm on dental implants: A review of the literature. Int J Oral Maxillofac Implants 2009;24:616–626.
21. Astolfi V, Rios-Carrasco B, Gil-Mur FJ, et al. Incidence of peri-implantitis and relationship with different conditions: A retrospective study. Int J Environ Res Public Health 2022;19:4147.
22. Angelo T, Marcel W, Andreas K, Izabela S. Biomechanical stability of dental implants in augmented maxillary sites: Results of a randomized clinical study with four different biomaterials and PRF and a biological view on guided bone regeneration. Biomed Res Int 2015;2015:850340.
23. Alqahtani F, Alqhtani N, Alktani F, et al. Clinicoradiographic markers of peri-implantitis in cigarette-smokers and never-smokers with type 2 diabetes mellitus at 7-years follow-up. J Periodontol 2020;91:1132–1138.
24. Liu Z, Liu X, Ramakrishna S. Surface engineering of biomaterials in orthopedic and dental implants: Strategies to improve osteointegration, bacteriostatic and bactericidal activities. Biotechnol J 2021;16:e2000116.
25. Kirillova A, Kelly C, von Windheim N, Gall K. Bioinspired mineral-organic bioresorbable bone adhesive. Adv Healthc Mater 2018;7:e1800467.
26. Krishnan V, Lakshmi T. Bioglass: A novel biocompatible innovation. J Adv Pharm Technol Res 2013;4:78–83.
27. Song F, Koo H, Ren D. Effects of material properties on bacterial adhesion and biofilm formation. J Dent Res 2015;94:1027–1034.

28. Busscher HJ, Rinastiti M, Siswomihardjo W, van der Mei HC. Biofilm formation on dental restorative and implant materials. J Dent Res 2010;89:657–665.
29. Greenstein G, Cavallaro J. Failed dental implants: diagnosis, removal and survival of reimplantations. J Am Dent Assoc 2014;145:835–842.
30. Zhang C, Hui D, Du C, et al. Preparation and application of chitosan biomaterials in dentistry. Int J Biol Macromol 2021;167:1198–1210.
31. Chokaree P, Poovarodom P, Chaijareenont P, Yavirach A, Rungsiyakull P. Biomaterials and clinical applications of customized healing abutment-A narrative review. J Funct Biomater 2022;13:291.
32. Raphel J, Karlsson J, Galli S, et al. Engineered protein coatings to improve the osseointegration of dental and orthopaedic implants. Biomaterials 2016;83:269–282.
33. Xia P, Luo Y. Vascularization in tissue engineering: The architecture cues of pores in scaffolds. J Biomed Mater Res B Appl Biomater 2022;110:1206–1214.
34. Kotsakis GA, Olmedo DG. Peri-implantitis is not periodontitis: Scientific discoveries shed light on microbiome-biomaterial interactions that may determine disease phenotype. Periodontol 2000 2021;86:231–240.
35. Hasani-Sadrabadi MM, Pouraghaei S, Zahedi E, et al. Antibacterial and osteoinductive implant surface using layer-by-layer assembly. J Dent Res 2021;100:1161–1168.
36. Jemt T, Hager P. Early complete failures of fixed implant-supported prostheses in the edentulous maxilla: A 3-year analysis of 17 consecutive cluster failure patients. Clin Implant Dent Relat Res 2006;8:77–86.
37. Korde JM, Kandasubramanian B. Biocompatible alkyl cyanoacrylates and their derivatives as bio-adhesives. Biomater Sci 2018;6:1691–1711.
38. Levin L. Dealing with dental implant failures. J Appl Oral Sci 2008;16:171–175.
39. Yu T, Acharya A, Mattheos N, et al. Molecular mechanisms linking peri-implantitis and type 2 diabetes mellitus revealed by transcriptomic analysis. PeerJ 2019;7:e7124.
40. Bressan E, Sbricoli L, Guazzo R, et al. Nanostructured surfaces of dental implants. Int J Mol Sci 2013;14:1918–1931.
41. Zaky SH, AlQahtani Q, Chen J, et al. Effect of the periapical "inflammatory plug" on dental pulp regeneration: A histologic in vivo study. J Endod 2020;46:51–56.
42. Hong D, Zaky SH, Chong R, et al. Controlling magnesium corrosion and degradation-regulating mineralization using matrix GLA protein. Acta Biomater 2019;98:142–151.