

DIMENSIONAL STABILITY OF THE ALVEOLAR RIDGE AFTER IMPLANTATION OF A BIOABSORBABLE BONE GRAFT SUBSTITUTE: A RADIOGRAPHIC AND HISTOMORPHOMETRIC STUDY IN RATS

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KEY WORDS

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This study evaluated reconstruction of the alveolar ridge after molar extraction in rats with bioabsorbable bone repair scaffolds. The material was prepared from the unsaturated polyester poly(propylene glycol-co-fumaric acid) (PPF), which may be cured in situ to form a porous scaffold. The intention is to use this material either as a stand-alone bone graft substitute or as an extender to autograft harvested from mandibular reconstruction sites. The bioactivity of the graft substitute was investigated in a rat residual ridge resorption model. PPF bone repair material was injected into the defect site, where it cross-linked in situ in the presence of a hydroxyapatite (HA) filler and effervescent agents. The PPF-based material develops porosity during an in situ cure by generating carbon dioxide during the effervescent reaction of citric acid and sodium bicarbonate. The incorporation of HA promotes osteoconduction within the bone repair scaffold. In this study, bioactivity of the porous scaffold was evaluated as a function of HA particle size (micrometer-sized vs nanometer-sized particles). The maxillary or mandibular molars on the right side were extracted from 96 adult Sprague-Dawley rats. A 2-mm round bur was used to create a uniform trench defect measuring 2 mm in diameter, 2 mm in depth, and 4 mm in length at each extraction site. The defect site was (1) treated with PPF bone repair material containing nanometer-sized HA, (2) treated with PPF material containing micrometer-sized HA, (3) treated with demineralized freeze-dried bone allograft, or (4) left untreated. Rats were sacrificed at 2, 4, 7, and 12 weeks postoperative. Resorption of the residual alveolar ridge was assessed by radiographic outcomes. Bone ingrowth through the defect site was measured by histomorphometric outcomes. Mandibular and maxillary ridge

heights increased for all treatments used in this study. There were no clinical indications that addition of either of the PPF bone repair materials retarded hard- or soft-tissue healing of the extraction sites. Although not statistically significant, the mandibular defects treated with PPF containing nanometer-sized HA healed at a faster rate as determined by ridge height and new bone formation measurements when compared with the other treatments. These findings suggest the feasibility of using PPF bone graft substitutes for oral-maxillofacial applications.

INTRODUCTION

Chronic resorption of the alveolar ridge after tooth loss often impairs a patient's ability to successfully tolerate prosthetics. Importantly, the lack of residual bone may also reduce the possibility of dental implant placement. To overcome bone loss, graft materials have been used to augment the dimensions of the ridge while supporting new bone regeneration.¹⁻³ An ideal graft material provides structural integrity at the defect site, maintains dimensions of the reconstructed site, promotes regeneration of native bone, and is easy to apply and use. Bone grafts, either autologous bone collected from the mandible or allograft transplants, are preferred materials for osseous defect repair. However, bone grafts may be limited with respect to supply, may lead to morbidity at the graft collection site,⁴ and do not always result in predictable clinical outcomes.⁵⁻⁷

Synthetic grafting materials have been developed as alternatives to bone grafts and address issues such as supply limitations, handling, and potential risk of infection. The synthetic materials used range from ceramics such as hydroxyapatite (HA) formulations⁸⁻¹⁰ to polymer-based implants such as hard-tissue replacement polymers.^{11,12} Despite advances in the development of these implant materials, the clinical applicability of bone re-

placement materials is limited because of the difficulty in producing sufficient long-term bony ingrowth required to preserve ridge architecture.² Furthermore, the graft material must maintain the dimensions of the reconstructed site throughout the course of bone recovery to promote desired esthetic and functional outcomes. Unfortunately, synthetic implants yield on-growth that is often limited to the periphery of the implant rather than a through-and-through tissue penetration.¹³ The latter process, however, appears eminently important for the successful development and application of viable bone replacement materials.

A bioabsorbable scaffold acting as a bone graft substitute appears to be an attractive alternative to bone grafts and commercially available synthetic bone replacement materials, which suffer from a lack of resorbability, inclusion of animal- or marine-derived components, and poor handling characteristics.¹⁴ The scaffold is prepared as a composite of the bioabsorbable polymer, poly(propylene glycol-co-fumaric acid) (PPF), and osteoconductive HA. The PPF bone repair scaffold is prepared as a paste, which may be injected or grouted into the defect site. After administration, the PPF material expands in situ to fill the osseous defect site and may be molded by the surgeon.^{15,16} The porous PPF scaffold cures within 2 to 5 minutes, based upon known formulation constraints,

to form a 3-dimensional matrix with mechanical properties comparable with cancellous bone.¹⁷

The objective of the present study was to evaluate the feasibility of applying the PPF bone repair scaffold to reconstruction of the alveolar ridge. To promote bone ingrowth within the porous PPF scaffold, the bioabsorbable implant was augmented with nanometer-sized HA, which has previously been demonstrated to enhance bioactivity of PPF materials.¹⁸ The rates of bone ingrowth and ridge resorption of periodontal defects treated with PPF materials augmented with nanometer-sized HA were compared with defects treated with PPF materials prepared with micrometer-sized HA, demineralized and freeze-dried bone allograft, and untreated defects.

MATERIALS AND METHODS

Materials

PPF was synthesized from an equimolar mixture of fumaric acid and propylene glycol in the presence of *p*-toluene sulfonic acid.¹⁹ The weight-average molecular weight of the polymer was determined to be approximately 5000 g/mol by gel permeation chromatography. The following materials were purchased from Aldrich (Milwaukee, Wis) and used as received: 1-vinyl-2-pyrrolidinone (VP), benzoyl peroxide (BP), citric acid (CA), sodium bicarbonate (SB), and N-N-dimethyl-*p*-toluidine (DMPT).

Bone graft substitute formulations

An aqueous solution of VP (63% w/w) and DMPT (0.2% w/w) was added to a dry powdered mixture of PPF and HA to form a viscous puttylike paste. The weight ratios of VP:PPF (0.31) and HA:PPF (0.29) were kept constant. Sodium bicarbonate, CA, and BP initiator were added, resulting in a cross-linked polymer foam that was applied directly to the defect site. The composition of the PPF porous bone graft substitute formulation is listed in the Table. The reaction of CA and SB yielded carbon dioxide, which is responsible for foam formation and expansion with respective pore sizes of 50 to 1000 μm (Figure 1). The accelerator, DMPT, at a concentration of 0.05%, promoted working times of 5 minutes, practical for implantation and in situ curing at body temperature.

The 2 PPF bone repair material formulations used in this study differed with respect to the particle size of HA used. Micrometer-sized HA (CamCeram Coating Powder) was purchased from Cam Implants (Leiden, The Netherlands) and used as received. Particle sizes of the spherical, micrometer-sized HA material ranged from 10 to 60 μm with an average particle diameter of approximately 30 μm . Nanometer-sized particles of HA were obtained from NanoCat Technologies Corporation (Woburn, Mass). X-ray diffraction analysis indicated that the crystalline size of the spherical, nanometer-sized HA was 28 nm.

Design of animal studies

The ability of the PPF bone repair material formulations to produce dimensionally stable osteoconductive scaffolds was evaluated

Chemical	Amount (% w/w)
Solid components	
Poly(propylene glycol-co-fumaric acid)	71.8
Hydroxyapatite	21.6
Benzoyl peroxide	3.6
Sodium bicarbonate	1.7
Citric acid	1.3
Liquid components	
1-vinyl-2-pyrrolidone	72.6
Water	27.2
N-N-dimethyl-p-toluidine	0.2

and compared. The test materials were applied to a troughlike defect created after extraction of maxillary or mandibular molars in rats, simulating the loss of bone experienced by individuals with long-standing loss of 1 or more molars. The test materials were evaluated based upon their ability to prevent resorption of the residual ridge by using a modification of the model described by Hahn et al.²⁰ Adult male Sprague-Dawley rats weighing approximately 400 g were used as the animal model (Charles River Laboratories, Wilmington, Mass). The study was approved by the institutional animal use committee. Rats were anesthetized with an

intramuscular injection of ketamine HCl (100 mg/kg) and xylazine (5 mg/kg). All maxillary or mandibular molars were extracted on the right side under a dissecting microscope (Dentscope, Johnson & Johnson, Windsor, NJ). Briefly, the periodontal ligament was loosened from the cervical portion of each tooth and the tissue was gently separated. An explorer was then placed interproximally between the molars, which were luxated out. A trough defect was created to simulate bone loss. The trough, measuring 2 mm wide, 2 mm deep, and 4 mm long, was produced with a rotary drill equipped with a 2-mm bur. The site was irrigated

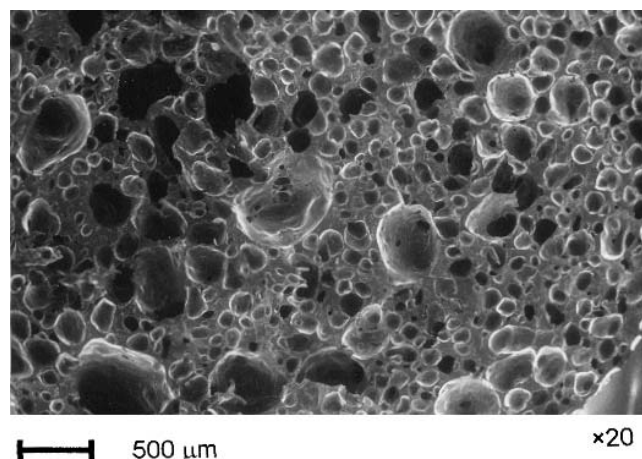


FIGURE 1. Pore sizes of the cured poly(propylene glycol-co-fumaric acid) material ranged between 50 and 1000 micrometers as measured from scanning electron micrographs. The overall void fraction of the cured material was approximately 50%.

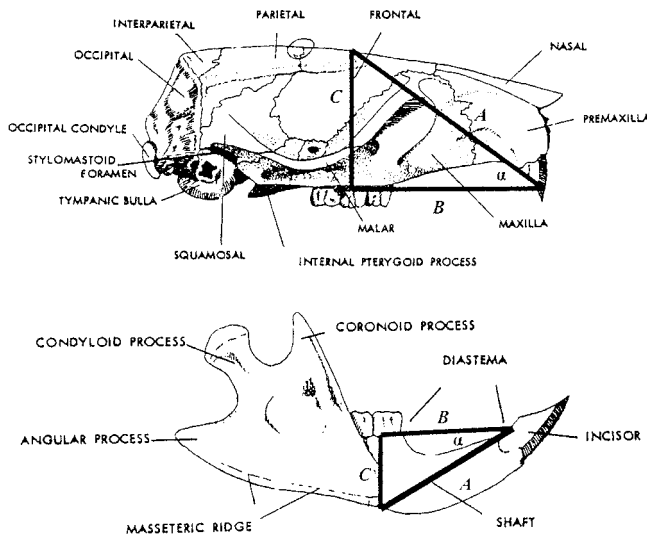


FIGURE 2. Mandibular and maxillary ridge heights (C) were calculated from distance measurements A and B and angle measurement α using the Law of Cosines. Measurements were made on digitized radiographs that were magnified $\times 300$.

with Ringer's lactate solution during defect induction.

After defect induction, the trough was filled with one of the test materials consisting of demineralized freeze-dried human bone allograft (DFDBA) (Grafton Putty, Musculoskeletal Transplant Foundation, Edison, NJ), PPF bone repair material containing μ -micrometer-sized HA, or PPF bone repair material containing nanometer-sized HA, or it was left unfilled to heal unaided. In the case of PPF test material groups, the PPF bone repair material was mixed in a crucible and implanted with a microspatula. The PPF test materials were allowed to cure in situ for 2 to 3 minutes until the material set, and then the surgical site was closed. The DFDBA materials were prepared as a slurry by mixing Grafton Putty with saline. The approximate quantity of implant material used for the PPF material and DFDBA experimental groups was 50 mg. The extraction sites were closed with interrupted sutures to maintain placement of the implant materials. Rats were given a prophylactic

dose of penicillin G (25 000 U/kg) via an intraperitoneal injection immediately after surgery. Buprenorphine (0.05 mg/kg) was administered subcutaneously 1 hour after surgery for pain management. Extractions were performed in 24 rats for each experimental treatment, divided between maxillary and mandibular defects. Six rats from each treatment group (3 maxillary and 3 mandibular) were sacrificed at 2, 4, 7, and 12 weeks postoperative for evaluation.

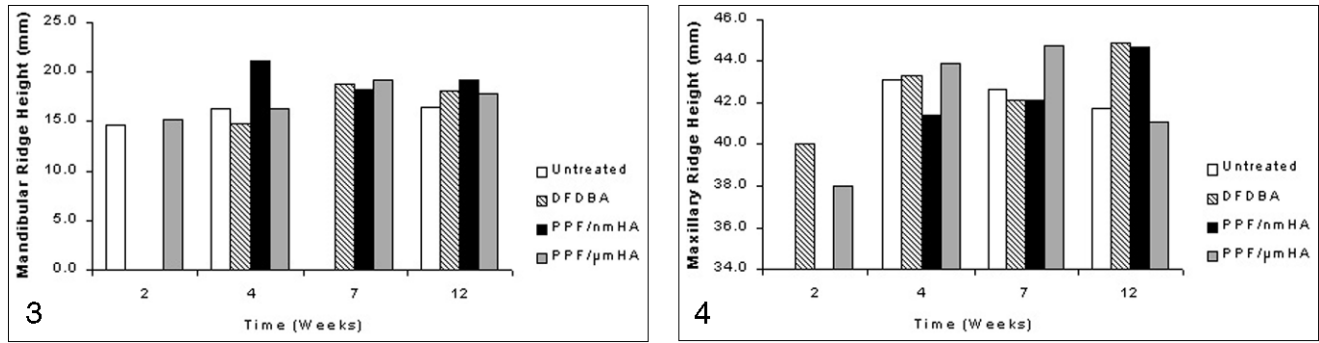
Methods of evaluation

The maxillary and mandibular residual ridge heights were determined from digitized radiographs obtained at 2, 4, 7, and 12 weeks from rats in the 12-week evaluation group. A Hewlett Packard Scanjet 7400 scanner was used to scan the radiographs at 2400 resolution by using PrecisionScan Pro 3.02 Windows software. Images of the complete radiographs were selected, scanned, and converted to Adobe Photoshop ImageReady 7.0.1 soft-

ware. Adjustments were made to enhance the morphology of the radiographs with the "auto levels" and "auto contrast" features. Images were then exported to Adobe Photoshop 7.0 to measure the residual ridge height with the measurement tool. The images were magnified $\times 300$ to visually identify morphologic landmarks of the maxilla or mandible. A triangle was produced on each maxillary or mandibular radiograph as demonstrated in Figure 2. The vertical height of the triangle (C) was calculated by the Law of Cosines ($C = (A^2 + B^2 - 2AB \cos \alpha)^{1/2}$) and reported as the ridge height. Statistical analysis of the radiographic results was not performed because of the limited number of samples ($n = 3$) in this study.

Mandibular and maxillary bone samples containing the defect site were taken at sacrifice. The samples were fixed in 10% neutral buffered formalin, decalcified in 4 N formic acid, and embedded in paraffin. Pairs of stepped serial cross sections 4- to 6- μ m thick at 50- μ m intervals were cut from both halves (profiles), comprising the full extent of the defect. The sections were stained with hematoxylin-eosin. Slides were examined for resorptive activity at the perimeter of the defect, new bone formation within the implantation site, and inflammatory responses to the bone graft extender material. Conventional histologic criteria were used to distinguish residual mandibular or maxillary bone from newly formed nonlamellar bone.

New bone formation in response to treatment with the different test materials and resorption at the defect site was quantified by histomorphometric outcomes. Images of the serial cross section were digitized and



FIGURES 3–4. FIGURE 3. The mandibular ridge height associated with periodontal defects treated with nanometer-hydroxyapatite (HA)-augmented poly(propylene glycol-co-fumaric acid) (PPF) was higher than other treatments at 4 weeks. The ridge heights for all filled defects were approximately equivalent at 7 and 12 weeks. FIGURE 4. The maxillary ridge heights were approximately equivalent at 4 and 7 weeks postoperative. The ridge height associated with the micrometer-HA-augmented PPF fill material decreased between weeks 7 and 12. The ridge heights for defects treated with the demineralized freeze-dried human bone allograft and nanometer-HA-augmented PPF materials increased between weeks 7 and 12.

analyzed for areas occupied by new bone in the defect site, areas of resorption, and number of osteoclasts identified within the defect site. New bone formation was reported as the percentage of new bone present in the defect site per the total area of tissue within the site. The percentage of new bone was defined as the *new bone area index* (new bone area per total tissue area). The quantity of bone resorption was quantified as the area of resorbed bone per the defect perimeter. This value was reported as the *resorption perimeter index* (resorbed bone per defect perimeter). The number of osteoclasts identified within the defect area was quantified and reported as the *osteoclast index* (number of osteoclasts per defect area). Statistical analysis of the histomorphometric results was not performed because of the limited number of mandibular samples (n = 3) in this study.

RESULTS

Eight rats died because of procedural complications. Three anesthesia deaths occurred in the 12-week study group during the radiography procedure. The 5

remaining deaths occurred within 48 hours after surgery. Thus, the mortality rate in this study was approximately 8%. Mortality rates between 30% and 40% have been reported for this model, particularly when both maxillary and mandibular molars were extracted.²⁰ In this study, deceased rats were categorized among all 4 treatment materials: 5 deaths occurred in the demineralized bone group and 1 death occurred in each of the other 3 groups. A Kaplan-Meier log rank survival analysis indicated no significant differences were in the survival rates among the different treatments (P = .084).

Surgical sites were evaluated in the 88 surviving rats. No postoperative complications or clinical signs of implant reaction were evident. No deep infections were observed throughout the postoperative period. Specimens were inspected macroscopically after dissection of the bone-implant construct. No visual signs of an inflammatory response in any of the samples or macroscopic fibrous tissue formation were observed. All grafted specimens were manually inspected and consistently found to be filled with newly formed bone. No

empty defect sites were found. All grouted bone specimens were retrieved intact, and there was no evidence of implant migration or movement from the defect site. Furthermore, there was no apparent adverse reaction of the surrounding soft tissues to the in situ cured material.

Radiographic studies

Temporal mandibular and maxillary ridge heights were measured on radiographs taken at 2, 4, 7, and 12 weeks postoperative. An overall increase was observed in the mandibular ridge height between 2 and 7 weeks for untreated defects and defects treated with DFDBA or micrometer-HA-augmented PPF material (Figure 3). The ridge height associated with defects treated with nanometer-HA-augmented PPF material peaked at 4 weeks and remained approximately the same between 4 and 12 weeks. Although the ridge heights among the different treatment materials were approximately equivalent at 7 and 12 weeks, the nanometer-HA PPF material reached this final height at a faster rate.

The maxillary ridge heights peaked at a faster rate (approximately 4 weeks) than did the

mandibular defects (7 weeks). The maxillary ridge heights for all treatments were comparable at 4 and 7 weeks postoperative (Figure 4). However, the ridge heights of the defects treated with DFDBA and nanometer-HA-augmented PPF increased between weeks 7 and 12. The ridge heights of untreated defects and defects filled with micrometer-HA-augmented PPF material decreased over this same period.

Histologic analysis

Healing of the mandibular extraction defects occurred for all treatment materials as evidenced by new bone formation (Figure 5). Bone ingrowth within the PPF materials initially occurred within the pores of the material, and bone progressively replaced the scaffold during the concurrent bone remodeling and polymer absorption processes. Remnants of the nanometer-HA-augmented PPF (Figure 5a) and micrometer-HA-augmented PPF (Figure 5b) matrices were observed to be surrounded by new bone at 12 weeks. Defects treated with DFDBA were filled with new bone at 12 weeks (Figure 5c). Bone recovery in untreated defects was still occurring at 12 weeks postoperative (Figure 5d). The cancellous nature of the maxilla made histology sectioning difficult when using the paraffin embedding technique. Therefore, only the mandible specimens could reliably be analyzed by histology.

Histomorphometric analysis

Quantification of new bone formation in mandibular defects corresponded with the radiographic outcomes in that bone ingrowth generally increased during the first 7 weeks post-

operative. At 2 weeks, the new bone area index within the PPF-treated defects was less than defects treated with DFDBA or untreated controls (Figure 6). However, new bone formation in PPF-treated defects were at least equivalent to DFDBA controls at 4 weeks postoperative. The relatively higher percentage of new bone formation measured at 4 weeks in the nanometer-HA-augmented PPF material in comparison with the other groups may suggest a faster bone ingrowth rate. The quantity of new bone at the defect site at 7 and 12 weeks were comparable among the different treatment methods. All defect sites, regardless of treatment, were filled with new bone by 7 weeks postoperative.

Analysis of the defects sites indicated a slight increase in bone resorption associated with untreated defects. The quantity of osteoclasts within the defect site peaked at 4 weeks postoperative for all treatments (Figure 7). The osteoclast index reached a maximum of 2.0 for untreated defects at 4 weeks. In addition, the average resorption perimeter index was highest in the untreated defects at each period of evaluation (Figure 8). The resorption perimeter index, like the osteoclast index, peaked for each treatment at 4 weeks except for DFDBA, in which the values of the resorption perimeter index were comparable at 2 and 4 weeks.

DISCUSSION

The major clinical application for the bioabsorbable bone graft substitute described in the present study would include its use to fill extraction defects and thereby maintain ridge height and integrity. The functional outcome of the PPF implant would be to

maintain long-term dimensional stability of the ridge to enhance esthetic and clinical outcomes. Presumably, the need for preprosthetic or preimplant surgery would thereby be reduced. Potential benefits of a PPF-based material include ease of handling and administration, in situ expansion of the material to fill the defect site and form intimate contact with the surrounding tissues, formation of an osteoconductive scaffold capable of supporting new bone formation, and mechanical integrity desired for use as an adjunct for implant placement. This combination of properties may provide a clinical alternative to the use of bone grafts or synthetic graft substitutes, which provide some but not all of these properties.

Biodegradable bone graft substitutes could better resemble native bone by addressing both biological and mechanical, as well as functional, outcomes of shape and form maintenance. In addition, they could offer a reasonable solution to the clinical dilemma of deficient autologous bone stocks. A previous study with the PPF-based bone repair material demonstrated the osteoconductive potential of a porous PPF scaffold in a mandibular onlay model.²¹ The current study is an extension of the previous research in that the current defect model specifically evaluates the temporal dimensional stability of the alveolar ridge in response to treatment of periodontal defects with the PPF-based bone repair material.

Stability of the ridge dimensions through 12 weeks, as measured by the ridge height, was demonstrated in defects treated with the PPF bone repair material. Temporal ridge height was comparable among the PPF materials and DFDBA controls. All

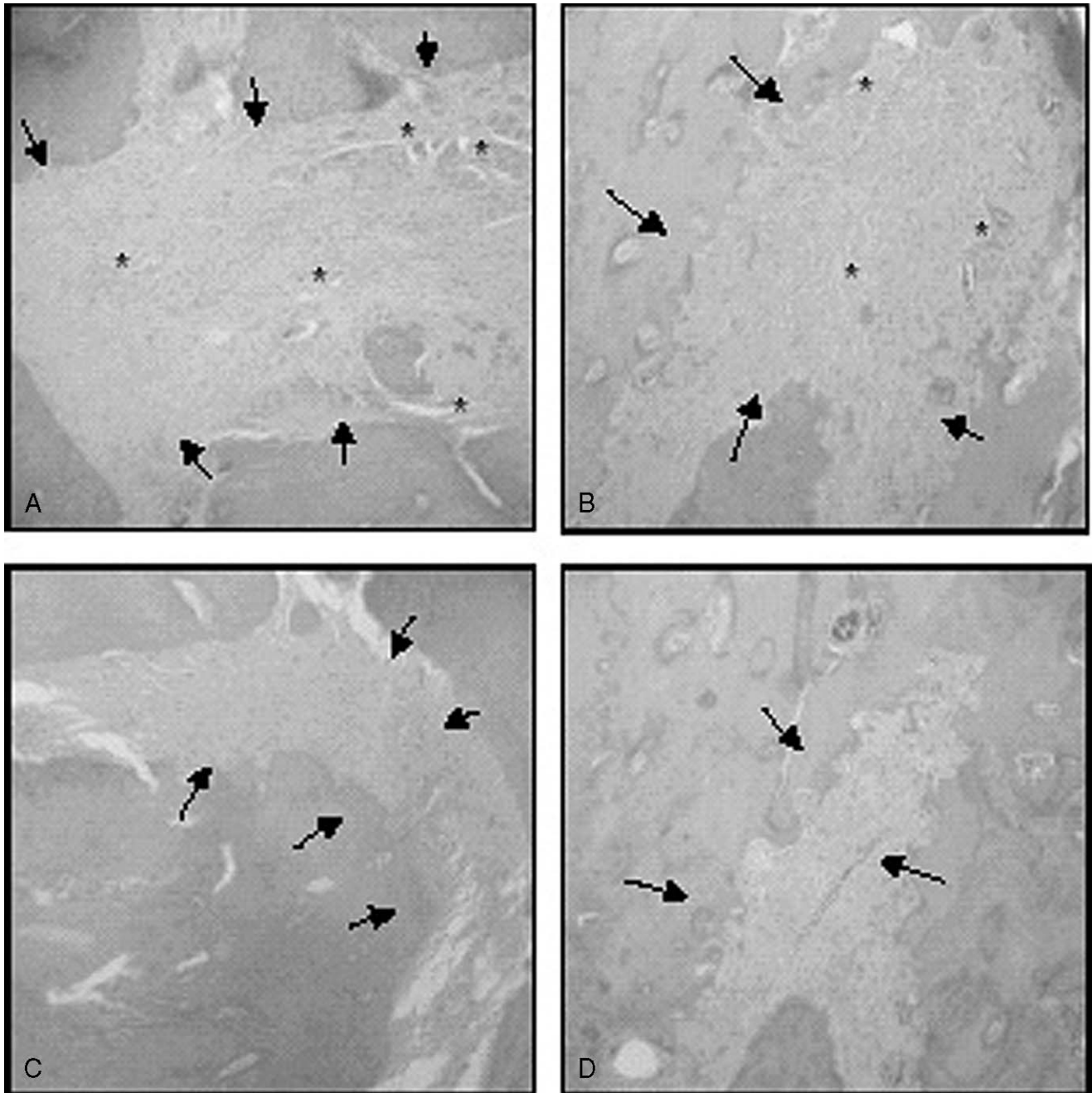


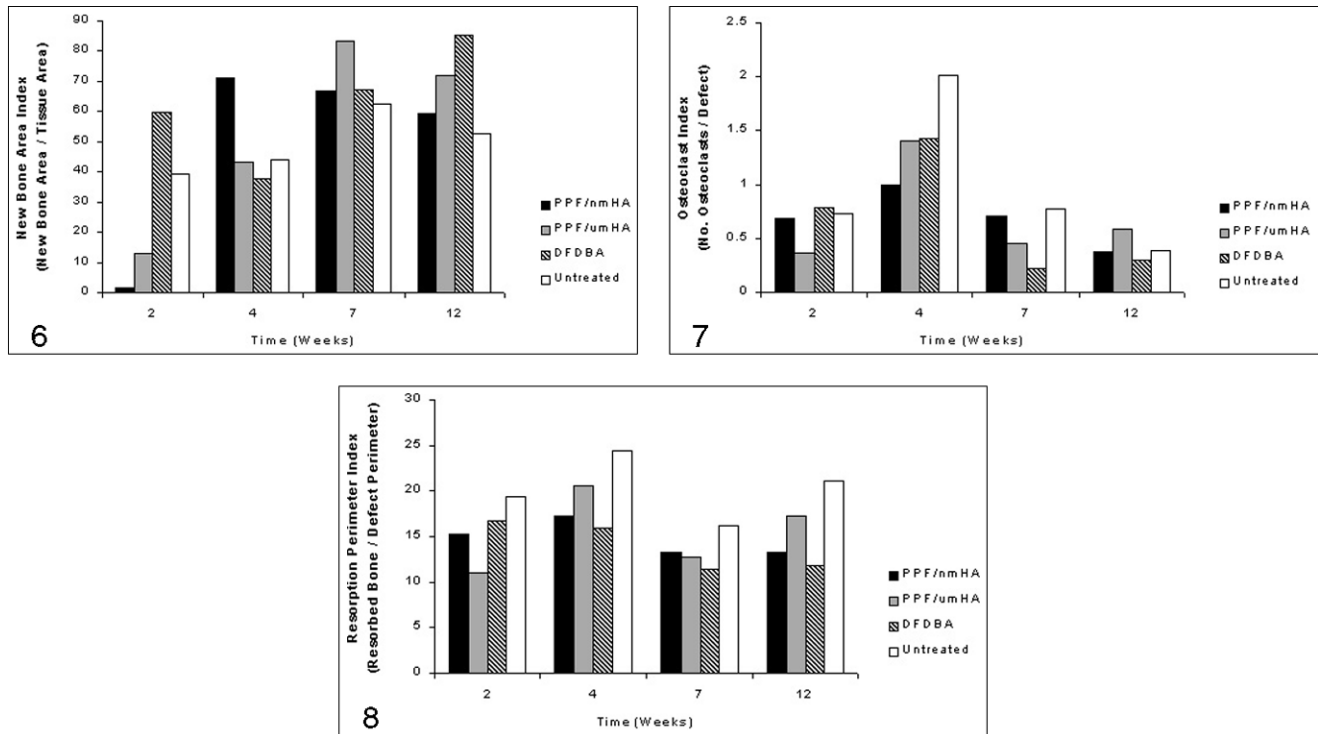
FIGURE 5. Extraction defects had healed by 12 weeks postoperative. Remnants of the poly(propylene glycol-co-fumaric acid) (PPF) scaffold (examples are marked with an asterisk) were observed to be surrounded by newly formed bone (marked with black arrows) in (A) nanometer-hydroxyapatite (HA)-augmented PPF and (B) micrometer-HA-augmented PPF materials. Defects filled with (C) demineralized freeze-dried human bone allograft were filled with new bone, whereas bone recovery was still occurring in (D) untreated defects.

the defects created in this study healed regardless of treatment type. The increase in ridge height associated with untreated defects was attributed to normal growth of the rats, which experienced a weight gain of approximately

60% during the study. Implantation of the PPF materials did not retard the natural growth of the ridge. The ability of the PPF material to support bone growth at rates comparable with untreated defects and defects

treated with DFDBA suggests that PPF-based bioabsorbable bone repair materials may be useful for pediatric cases.

In addition to maintenance of the ridge height, the bioactivity of the PPF material as a function



FIGURES 6–8. FIGURE 6. Quantification of new bone formation suggested that nanometer-hydroxyapatite-augmented poly(propylene glycol-co-fumaric acid) materials supported new bone formation at a faster rate through 4 weeks than did the other treatments. The quantity of newly formed bone was approximately equivalent for all treatments at 7 and 12 weeks postoperative. FIGURE 7. The number of osteoclasts identified in the defect site peaked at 4 weeks postoperative and was highest in the untreated defects. FIGURE 8. Bone resorption at the defect perimeter peaked at 4 weeks postoperative for all treatments except demineralized freeze-dried human bone allograft, where resorption was approximately equivalent at 2 and 4 weeks. Resorption was highest in the untreated defects at all evaluation periods.

of HA particle size was investigated. Previous work demonstrated that augmentation of the PPF material with nanometer-sized HA particles enhanced the bioactivity of the scaffold as demonstrated by more reactive new bone formation vs similar PPF materials augmented with micrometer-sized HA.¹⁸ In this study, bioactivity with respect to bone formation in an extraction defect was assessed. The radiographic and histomorphometric results suggest that the rate of new bone formation within nanometer-HA-augmented PPF implants may have been enhanced as evidenced by an increased new bone area and ridge height at 4 weeks postoperative. In maxillary implants, nanometer-HA-

augmented PPF supported new bone formation at the same rate as DFDBA through 12 weeks. Ridge heights associated with nanometer-HA-augmented PPF implants were greater than both untreated defects and micrometer-HA-augmented PPF treated defects at 12 weeks.

The literature reference used for the extraction defect model averaged the ridge heights from the maxilla and mandible because the radiographs were “virtually superimposable.”²⁰ Because of the triangulation method used to calculate the total ridge heights in this study, values for the maxilla and mandible were not directly comparable. In addition, bone recovery within PPF implants may not be equivalent between

ridges because the mandible contains more cortical bone than the maxilla, in which cancellous bone is prevalent. Furthermore, the cancellous nature of the maxilla made histology sectioning difficult when using the paraffin embedding technique. Therefore, only the mandible specimens could reliably be analyzed for histomorphometric outcomes. Finally, the study length may not have been optimal for evaluating long-term effects of ridge resorption. Untreated defects exhibited a slight decrease in mandible and maxilla ridge heights compared with the other treatments; however, the effect may be more pronounced if animals were to be evaluated through longer periods (eg, 24 weeks).

CONCLUSION

These results suggest that a porous polymer-based scaffold could function as a bone graft substitute in an alveolar defect. Dimensional stability of periodontal defects was demonstrated when treated with PPF-based bone repair materials augmented with nanometer- or micrometer-sized HA. The rate of new bone formation in mandibular defects as determined by radiographic and histomorphometric outcomes was enhanced in defects treated with the nanometer-HA-augmented PPF material. The ridge heights of maxillary defects treated with nanometer-HA-augmented PPF implants were equivalent to DFDBA treated controls through 12 weeks. These findings have immediate applicability to the further development of PPF-based bone graft substitutes for oral-maxillofacial applications with emphasis on the influence of bioactivity and implant size on functional outcomes.

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