Evaluation of a Porous, Biodegradable Biopolymer Scaffold for Mandibular Reconstruction

Debra J. Trantolo, PhD[1]/Stephen T. Sonis, DMD, DMSc[2]/Benjamin M. J. Thompson, BS[3]/
Donald L. Wise, PhD[4]/Kai-Uwe Lewandrowski, MD[5]/David D. Hile, PhD[6]

Purpose: *Bioresorbable bone graft substitutes could eliminate disadvantages associated with the use of autografts, allografts, and other synthetic materials. The authors investigated the osteoinductive capacity of a bioresorbable bone graft substitute made from the unsaturated polyester poly(propylene glycol-co-fumaric acid) (PPF) for mandibular reconstruction in a rat model. The eventual 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.* ***Materials and Methods:*** *The PPF bone graft was crosslinked in the presence of a hydroxyapatite filler and effervescent foaming agents to develop porosity in situ by generating carbon dioxide during the effervescent reaction of citric acid and sodium bicarbonate. The latter reagents are responsible for foam formation and expansion, resulting in a polymeric scaffold with pore sizes in the range of 100 to 500 μm. Twenty adult Sprague-Dawley rats had 3-mm-diameter cortical defects decorticated on the outer aspect of their left mandibular ramus using a Hall drill. Animals were divided into 2 groups of 10 animals each. Animals in group A were treated with implantation of the PPF-based bone graft substitute. Implants were applied buccally to defects on the left side. In group B animals with similar defects, the drill holes were left to heal unaided. The amount of new bone formation and the presence of an inflammatory infiltrate were evaluated at 7 weeks postoperatively.* ***Results:*** *Histologic analysis of the healing process revealed enhanced in vivo new bone formation with the PPF bone graft substitute. These findings were corroborated by the histomorphometric analysis of new bone formation.* ***Discussion:*** *Results of this study demonstrated biocompatibility of the porous PPF-based scaffold in a mandibular defect.* ***Conclusions:*** *These findings may have applicability to the further development of bone graft substitutes for oral/maxillofacial applications.* (Int J Oral Maxillofac Implants 2003;18:182–188)

Key words: *autologous transplantation, biocompatibility, bioresorbable polymers, bone substitutes, mandible, polypropylenes*

The filling of bony voids remains a challenge in mandibular reconstruction. Graft materials are required that support the structural integrity of the site throughout the course of new bone regeneration.[1–3] Autografts and allografts are used in current bone graft procedures. Autografts are preferable whenever possible, but are not always available in sufficient quantities or may not always produce predictable clinical outcomes. Bone replacement materials for alveolar and mandibular reconstruction are currently in use. Newer techniques include the use of biodegradable membranes for guided periodontal tissue regeneration during bony recovery after grafting procedures.[4] However, despite significant advances in the development of these technologies for tissue regeneration, the development of clinically applicable bone replacement materials remains a challenge. This is related, in part, to the difficulty in producing sufficient bony ingrowth for prolonged periods of time so that the mandibular architecture is preserved.[2] Implantation of such materials in skeletal repair sites commonly produces

[1]President and Chief Executive Officer, Cambridge Scientific, Cambridge, Massachusetts.
[2]Chairman, Department of Oral Medicine and Diagnostic Sciences, Harvard School of Dental Medicine, Boston, Massachusetts.
[3]Medical Student, Albany Medical College, Albany, New York.
[4]Chairman of the Board, Cambridge Scientific, Cambridge, Massachusetts.
[5]Orthopedic Resident, Orthopaedic Research Laboratories, Massachusetts General Hospital, Boston, Massachusetts.
[6]Program Manager, Engineering, Cambridge Scientific, Cambridge, Massachusetts.

Reprint requests: Dr Debra J. Trantolo, Cambridge Scientific, 180 Fawcett St, Cambridge, MA 02138-1112.

on-growth that is often limited to the periphery of the implant rather than a through-and-through tissue penetration.[5] The latter process, however, appears eminently important for the successful development and manufacturing of viable tissue equivalents.

Therefore, a bioresorbable scaffold acting as a bone graft substitute appears to be a viable alternative to autografts and allografts. Some currently approved synthetic products have significant drawbacks, including a lack of resorbability, inclusion of animal- or marine-derived components, and poor handling characteristics.[6] The challenge is to create a bone graft substitute material that behaves both biologically and biomechanically more like mandibular bone.

The development of a resorbable bone repair material that does not contain biologic material (either collagen or protein) has been described.[7] This material is made from the unsaturated polyester, poly(propylene glycol-co-fumaric acid) (PPF). The polymer may be mixed with cancellous autograft and crosslinked in the presence of a hydroxyapatite (HA) filler and sodium bicarbonate (SB) and citric acid effervescent reagents. The autograft/substitute formulation may then be grouted directly in a mandibular void. To evaluate the suitability and biocompatibility of this PPF material for mandibular reconstructive applications, the authors investigated the tissue responses to PPF-based mandibular implants by means of an in vivo histologic and histomorphometric analysis.

MATERIALS AND METHODS

PPF was synthesized from an equimolar mixture of fumaric acid and propylene glycol in the presence of p-toluene sulfonic acid.[6,7] The weight-average molecular weight of the polymer was determined to be approximately 5,000 g/mol by gel permeation chromatography. The following materials were purchased from Aldrich Chemical (Milwaukee, WI) and used as received: 1-Vinyl-2-pyrrolidinone (VP), benzoyl peroxide (BP), and N-N-dimethyl-p-toluidine (DMPT).

Formulation of Bone Graft Substitute

An aqueous solution of VP (63% by weight) and DMPT (0.2% by weight) was added to a dry powdered mixture of PPF and HA to form a viscous, putty-like paste. The weight ratios of VP:PPF (0.31) and HA:PPF (0.29) were kept constant. SB, BP initiator (Aldrich Chemical), and citric acid were added, resulting in a crosslinked polymer foam that was applied directly to the defect site. The composition of the PPF porous bone graft substitute formulation is as follows:

- PPF, 53.5% by weight
- HA, 15.5% by weight
- VP, 16.6% by weight
- SB, 1.2% by weight
- Citric acid, 1.0% by weight
- BP, 2.4% by weight
- DMPT, 0.05% by weight

The reaction of citric acid and SB yielded carbon dioxide, which is responsible for foam formation and expansion with respective pore sizes of 100 to 500 μm.[8] The accelerator, DMPT, at a concentration of 0.05% promoted working times of 15 minutes, practical for implantation and in situ curing at body temperature.

Design of Animal Studies

To evaluate the osteoconductive effect as well as the biocompatibility of the PPF-based bone graft substitute, grafts were implanted using a rat mandibular defect model previously described by Pettis and coworkers.[9] Adult male Sprague-Dawley rats weighing approximately 400 g were used as the animal model (Charles River Laboratories, Wilmington, MA). Animals were anesthetized using an intramuscular injection of ketamine HCl (90 mg/kg) and xylazine (10 mg/kg). The rats were also given an intramuscular prophylactic dose of penicillin G (25,000 U/kg); the surgical site was shaved and prepared with a solution of povidone-iodine (Betadine, Purdue Frederick, Norwalk, CT) and alcohol (Dura-Prep; 3M Health Care, St Paul, MN).

Twenty rats (age 3 to 4 months) had 3-mm-diameter cortical defects decorticated on the outer aspect of their left mandibular ramus (Fig 1). Animals were divided into 2 groups of 10 animals each. Group A animals were treated with implantation of the PPF-based bone graft substitute. Implants were applied buccally to the defects on the left side. The formulations were mixed immediately prior to surgery and implanted into the prepared mandibular defect site with use of a spatula. The bone graft substitute formulation was cured in situ. The soft tissues and skin were closed in layers with running absorbable sutures. In group B animals, which had similar defects on the left side, drill holes were left to heal unaided.

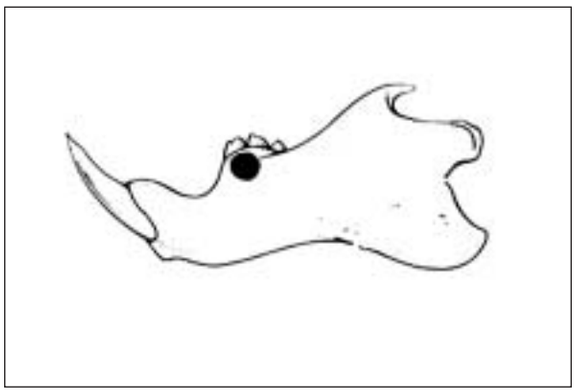

Fig 1 Cortical defects were drilled to one half the depth in rat mandibular rami. Implants were applied buccally to the defects on the left side. The black dot indicates the position of the graft.

Methods of Evaluation

Following sacrifice at 7 weeks postoperatively, all animals underwent block excision biopsies of the mandibular rami and surrounding soft tissues. The biopsies were fixed in 10% neutral buffered formalin and decalcified in 4 N formic acid. Pairs of stepped serial cross sections 4 to 6 μm thick at 50-μm intervals were cut from the 2 halves (profiles), comprising the full extent of the defect. The sections were stained with hematoxylin-eosin (H&E) or with van Gieson.

Slides were examined for resorptive activity and new bone formation at the implantation site, as well as for inflammatory responses to the bone graft material. A semi-quantitative method was adopted to score the number of both inflammatory and multinucleated giant cells in the bony defects and adjacent tissues on H&E sections obtained from 6 animals: 0 = no cells, 1 = few cells, 2 = mild infiltrate, 3 = moderate infiltrate, and 4 = severe infiltrate. The scores were assigned by 2 examiners, who were blinded to the sections.[4] Conventional histologic criteria were used to distinguish residual mandibular bone from newly formed non-lamellar bone.

In addition, histomorphometric evaluation of new bone formation in response to implantation of the graft material was done by acquiring images of serial cross sections of the specimen using the Spot Insight charge-coupled distributor video camera system (Diagnostics Instruments, Sterling Heights, MI), which was mounted on a Nikon Eclipse E600 microscope (Tokyo, Japan). Images were digitized and analyzed using Image Pro Plus software (Media Cybernetics, Silver Spring, MD). The areas occupied by new bone in the defect were quantified by the same observers using H&E-stained slides (from 10 animals at 7 weeks) and were viewed in conjunction with the computerized image analysis system. The new bone formation, expressed as a percentage compared to the untreated defects, was calculated for each defect using 3 templates, or region-of-interest masks. These were placed in 3 areas across the defect and a mean was obtained for each animal from a minimum of 6 and a maximum of 12 stepped serial sections. This allowed an approximate absolute volume to be obtained for the newly formed bone, which was given as an average (mean ± SD) of these volume measures for each bone specimen. This parameter was given as a percentage rate and was presented as the average of all sections of 8 grafted animals per graft type. It was called the New Bone Volume Index (NBVI).

Statistical Analysis

Differences in the amount of new bone formed in response to implantation of the PPF grafts were analyzed for statistical significance by employing analysis of variance for normally distributed samples. A P level of less than .05 was considered statistically significant.

RESULTS

At the 20 surgical sites, there were no postoperative complications or clinical signs of implant reaction. No fractures or deep infections were observed over the entire postoperative period. Specimens were inspected macroscopically after having been dissected, sectioned, and embedded for histologic and histomorphometric analysis. All grafted specimens were inspected manually and found consistently to be filled with newly formed bone. No empty defect sites were found. All grouted bone specimens were retrieved intact. Implantation of the PPF-based bone graft substitute material into a mandibular defect resulted in benign tissue responses, as evidenced by the absence of excessive macroscopic fibrous tissue formation. At 7 weeks postoperatively, all surgical sites appeared to have healed well. There was no apparent adverse reaction of the surrounding soft tissues to the in situ cured material.

Radiographic Studies

Radiographic analysis of grafted mandibles at the endpoint of the study showed sufficient evidence of bone healing at the implantation sites at 7 weeks postoperatively. There were no radiolucent areas around the implanted graft. On radiographs, the surrounding soft tissues were normal in appearance, without any evidence of swelling or fluid collection

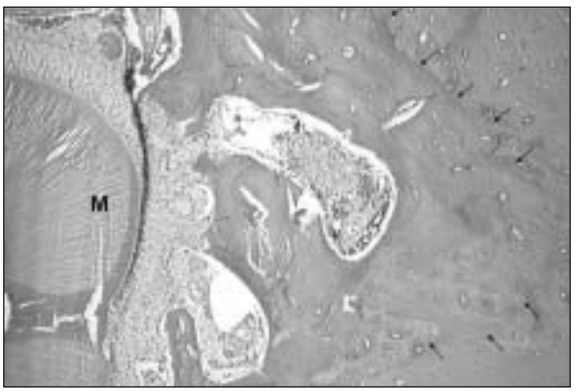

Fig 2 Cross section of a rat mandible in the control group (H&E; magnification ×10) in which a surgical defect was created in the left mandibular ramus near the first molar (M). The site was left to heal unaided. The samples were retrieved at 7 weeks postoperatively. The defect is filled with newly formed bone, which is undergoing remodeling. The area of remodeling is relatively small *(arrows)* and is confined to the original defect site. A very thin layer of granulation tissue within the defect separates the newly formed bone from the molar.

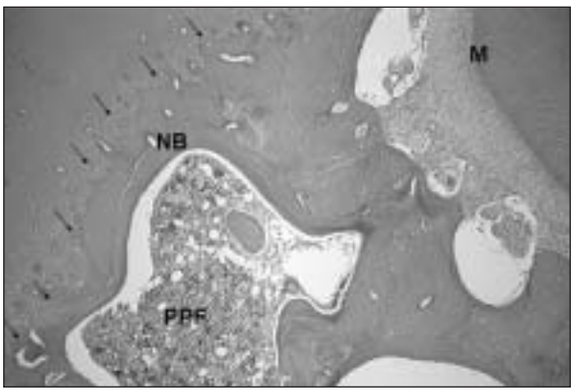

Fig 3 Cross section of a rat mandible in which the PPF bone graft substitute was implanted in the left mandibular ramus near the first molar (M) (H&E; magnification ×10). The samples were retrieved at 7 weeks postoperatively. The defect is filled with the PPF scaffold and newly formed bone (NB). The area undergoing remodeling *(arrows)* is larger than in the control group. A very thin layer of granulation tissue within the defect separates the newly formed bone from the molar.

at the implantation sites. Regardless of the group assignment, there was some occasional periosteal bone formation adjacent to the defect sites.

Histologic Analysis

At 7 weeks, complete bony reparation of the defects produced in the mandibular rami had not occurred, with either the PPF implant or in the control (empty) defects.

Histologic analysis of the group A specimens (PPF bone graft substitute) showed that the in situ cured bone graft substitute materials remained intact throughout the entire postoperative follow-up period. In contrast to control defects, where newly formed bone was confined to the bony margins of the original defect, PPF-implanted defects showed more extensive bone formation centrally (Figs 2 and 3). There was an accompanying soft tissue response, with formation of a thin layer of granulation tissue between the grafting material and the host bone. The implant was surrounded by newly formed bone expanding the shape of the mandibular bone. The thickness of the newly formed bone at the PPF implant site averaged 250 μm (Fig 4). Implants appeared porous, and invasion of the implant by the surrounding granulation tissue was essentially limited to pores with communication to the implant surface. Soft tissues remained outside the defect area in all animals that received a PPF implant. In some instances, new bone tissue formation could be identified on the outer surfaces of the PPF implant between the repositioned muscle flap and the implant (Fig 5).

In the control group, in which the rats were left to heal unaided, the host bone generally appeared to have undergone some remodeling, with the thickness of the area of newly formed bone averaging 50 μm. The mandibular cortex had healed completely.

The inflammatory reaction both within the defect and in the adjacent tissues differed significantly between the 2 groups (Table 1). Although PPF-based bone graft substitute material promoted an inflammatory response associated with lymphocyte and macrophage infiltration, there was more new bone formation in each PPF-implanted specimen than in the control defects. This was supported by the histomorphometric analysis. By quantitative volume measures as expressed by the NBVI, the experimental defects treated with PPF implants showed increased new bone formation (mean 45.6 ± 5.1, n = 10) compared with control defects (without implant; mean 24.2 ± 3.4, n = 10; $P < .02$). Comparison using the Kruskal-Wallis test revealed that this difference was statistically significant.

DISCUSSION

The major clinical application for this resorbable bone graft substitute would include its use as an adjunct to filling of defects that arise from surgical removal and treatment of cysts, tumors, and osteolytic defects, or surgical debridement of infections. Autologous bone grafts may not maintain their desired shape over a long period of time, and

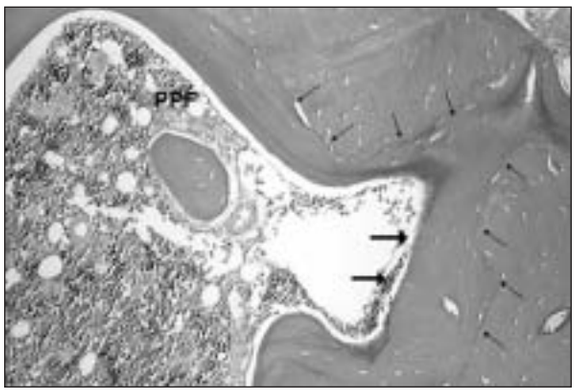

Fig 4 Cross section of a rat mandible in which PPF bone graft substitute was implanted in the left mandibular ramus near the first molar (H&E; magnification ×20). The samples were retrieved at 7 weeks postoperatively. The defect is filled with the PPF scaffold and newly formed bone. There is appositional bone growth at the defect site, with osteoblasts lined up against the host bone *(large arrows)*. There is intimate contact between the newly formed bone and the surrounding mandible bone *(small arrows)*.

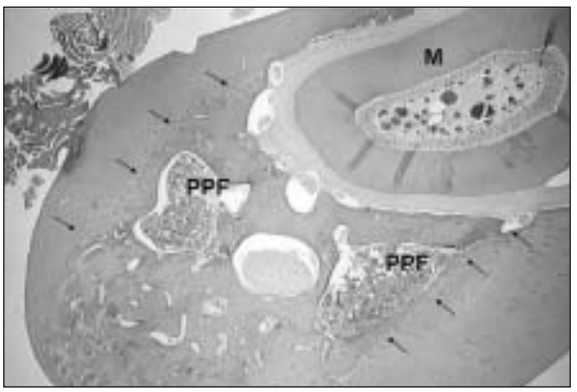

Fig 5 Cross section of a rat mandible in which a PPF bone graft substitute (PPF) was placed as an onlay implant (H&E; magnification ×2.5). The sample was retrieved at 7 weeks postoperatively. The area of the implant *(arrows)* near the first molar (M) is undergoing extensive remodeling, with appositional new bone growth expanding the mandibular bone near the root of the first molar substantially. The bone graft substitute material was found dispersed throughout the newly formed bone filling the defect at the implantation site. Mild inflammatory changes were noted. New bone formation within and around the implant took place without interposition of fibrous tissue.

Table 1 Subjective Scoring of Inflammatory and Multinucleated Giant Cells at 4 Weeks (n = 10)

Cells/material	Score
Inflammatory cells	
PPF implant	2.12 ± 0.48
Empty control	1.60 ± 0.34
Giant cells	
PPF implant	0.94 ± 0.27
Empty control	0.12 ± 0.04

outcomes may vary considerably from patient to patient.[10] A biodegradable bone graft substitute that could aid in restoration of the normal mandibular and alveolar anatomy by improving upon the performance of conventional autografts through maintenance of particular forms and shapes is in demand for clinical applications. The technical objective of the present study was to demonstrate the feasibility of promoting bony ingrowth into a PPF-based bioresorbable bone graft substitute when placed in a mandibular implantation site.

The PPF-based bone graft substitute of this study has several unique material features. First, because the bone graft substitute results from the reaction of a preformed polymer (PPF) with a liquid crosslinker (VP), the composite has the capacity to be applied as a viscous slurry that cures in situ to a hard, bonelike mass.[11] Second, the inclusion of effervescent agents in the formulation facilitates material expansion when applied to a defect and the formation of pores upon cure; this ensures that the resulting porous, bonelike graft substitute is in intimate contact with neighboring tissues throughout all areas of the defect.[8] Third, HA fillers promote osteoconduction in the final scaffold.[12,13] A graft substitute that has these features could eliminate disadvantages associated with the use of autografts, allografts, and other synthetic materials currently used in clinical bone graft procedures.

In previous in vitro and in vivo studies, development of porous bone repair scaffolds has relied primarily on the hypothesis that a more rapid ingrowth of bone cells will occur in these types of materials.[5,14,15] It is generally assumed that a material with such properties would initially provide structural support to the defect site. Thereafter, as the implant degrades, the net result of newly formed bone plus residual implant—the "repair-composite"—must continue to provide support to the defect reconstruction, while yielding to the establishment of native bone. Biodegradable bone graft substitute materials could better resemble native bone by addressing biologic, mechanical, and functional outcomes of shape and form maintenance. In addition, they could offer a reasonable solution to the clinical dilemma of deficient autologous bone stocks.

The use of porous biodegradable scaffolds as bone graft substitutes and extenders has been demonstrated. Porosity has been generated with various techniques, such as leaching soluble components out of biopolymer composites. Yaszemski and coworkers[14] demonstrated a novel method for manufacturing 3-dimensional, biodegradable poly(DL-lactic-co-glycolic acid) (PLGA) foam scaffolds. The technique involved the formation of a composite material consisting of gelatin microspheres surrounded by a PLGA matrix. In another study, Thomson and associates[5] reported manufacturing of reinforced biodegradable composite foams. Three-dimensional foam scaffolds were made from composite materials consisting of a porogen material (either gelatin microspheres or salt particles) and HA short fibers embedded in a PLGA matrix.[5,15] After the porogen was leached out, an open-cell composite foam remained, which had a pore size and morphology defined by the porogen. By changing the weight fraction of the leachable component, it was possible to produce composite foams with controlled porosities ranging from 0.47 ± 0.02% to 0.85 ± 0.01%.[14]

Other studies by the same group used a mixture of PPF cross-linked by N-vinyl-pyrrolidone in the presence of composite material consisting of a porogen material (either gelatin microspheres or salt particles such as sodium chloride) and beta-tricalcium phosphate.[16,17] In comparison, Domb and coworkers utilized calcium carbonate and tricalcium phosphate as a particulate filler[18] and Gerhart and colleagues employed a composite matrix consisting of gelatin, water, and sodium salicylate.[19] In the latter study, the particulate phase was made up of powdered and particulate (355 to 600 μm in diameter) tricalcium phosphate. Other techniques to generate porous scaffolds not involving leachable components have been developed by Mikos and associates,[20] who reported construction of 3-dimensional biodegradable polymer foams with precise anatomic shapes. The technique involved the lamination of highly porous membranes made of poly(L-lactic acid) and copolymers of PLGA resulting in porosities of up to 90%.[20]

In comparison, a different technology to generate porosity of the PPF-based bone graft substitute material was applied in this preliminary investigation. The addition of citric acid and SB to the formulation leads to formation of carbon dioxide during the reaction; the net result of polymer cure is the immediate development of porosity upon material placement. It has been determined that the carbon dioxide produced generates pressures within the PPF-based bone graft material of up to 50 psi, resulting in foam formation and expansion with respective pore sizes of the graft substitute in the range of 100 to 500 μm.[8] This material property, combined with practical handling characteristics and with working times on the order of 5 minutes, might make a PPF-based bone graft "foaming scaffold" an ideal bone graft substitute material. The material was easily implantable into the mandibular sites used in this rat model.

The PPF graft was tested in an animal model developed by Pettis and coworkers[9] and further utilized by Salata and associates.[4] It was straightforward and easily exploitable experimentally as a useful screening model. It allowed facile evaluation of the grafting process and easy visualization of tissue bonding. The biocompatibility study of this investigation focused on the qualitative and semi-quantitative assessment of osteoinduction with the PPF-based bone graft substitute in a rat mandibular onlay model and reports on histologic and histomorphometric findings. The PPF formulation was compared to a surgical defect that was left to heal unaided. In this model, it allowed comparative histologic and histomorphometric assessments of the degradation and bone cell ingrowth.

Results of this study showed maintenance of the structural integrity of the bone graft substitute material. Implantation of the PPF-based bone graft substitute material into a mandibular defect resulted in overall benign tissue responses, as evidenced by the absence of excessive macroscopic fibrous tissue formation. At 7 weeks postoperatively, all surgical sites appeared to have healed well, and there was no apparent adverse reaction of the surrounding soft tissues to the in situ cured material. Although there was an accompanying soft tissue response (formation of a very thin layer of granulation tissue between the grafting material and the host bone), the implant was surrounded by newly formed bone expanding the shape of the mandibular bone whose thickness averaged 250 μm. In comparison, the thickness of the layer of reactive new bone averaged only 50 μm in the control group. These findings were corroborated by the histomorphometric analysis of new bone formation, with the quantitative volume measures showing a higher NBVI in the PPF-implanted group. This was a statistically significant difference.

SUMMARY

These results clearly suggest that a porous polymer-based scaffold could function as a bone graft material in a mandibular defect. These findings have

immediate applicability to the further development of bone graft substitutes for oral/maxillofacial applications, with emphasis on the influence of shape and form on functional outcomes.

ACKNOWLEDGMENTS

The authors wish to thank Dr Joseph Alroy, DVM, Associate Professor in Pathology, Tufts University Schools of Medicine and Veterinary Medicine, for his assistance in the histologic analysis of this study. This work was supported in part by NIH/NIDR Grant No. 1 R43 DE 14272 (to Debra J. Trantolo).

REFERENCES

1. Yilmaz S, Efeoglu E, Kilic AR. Alveolar ridge reconstruction and/or preservation using root form bioglass cones. J Clin Periodontol 1998;25(10):832–839.
2. Hayes BK, Flynn C, Hardwick R. Devices for dentoalveolar regeneration: An up-to-date literature review. J Periodontol 1995;66(6):495–505.
3. Paillon R, Lehnert S, Wahl G. Reconstruction of dentoalveolar defects with porous hydroxyapatite ceramic material. Dtsch Zahnärztl Z 1988;43(1):68–70.
4. Salata LA, Craig GT, Brook IM. Bone healing following the use of hydroxyapatite or Ionomeric bone substitutes alone or combined with a guided bone regeneration technique: An animal study. Int J Oral Maxillofac Implants 1988;13:44–51.
5. Thomson RC, Yaszemski MJ, Powers JM, Mikos AG. Hydroxyapatite fiber reinforced poly(alpha-hydroxy ester) foams for bone regeneration. Biomaterials 1998;19(21): 1935–1943.
6. Cook DS, Salkeld SL, Rueger DC. Comparison of osteoinductive and osteoconductive biomaterials in healing large segmental bone effects. American Academy of Orthopaedic Surgeons. 1995 Annual Meeting, Paper No. 005, Orlando, Florida.
7. Gresser JD, Hsu SH, Nagaoka H, et al. Analysis of a vinyl pyrrolidone/poly(propylene fumarate) resorbable bone cement. J Biomed Mater Res 1995;29:1241–1247.
8. Lewandrowski KU, Cattaneo MV, Gresser JD, Wise DL, Trantolo DJ. Effect of a poly(propylene fumarate) foaming cement on healing of critical size bone defects. Tissue Eng 1999;5(4):305–316.
9. Pettis GY, Kaban LB, Glowacki J. Tissue response to composite ceramic hydroxyapatite/demineralized bone implants. J Oral Maxillofac Surg 1990;48(10):1068–1074.
10. Szabo G, Suba Z, Hrabak K, Barabas J, Nemeth Z. Autogenous bone versus beta-tricalcium phosphate graft alone for bilateral sinus elevations (two- and three-dimensional computed tomographic, histologic, and histomorphometric evaluations): Preliminary results. Int J Oral Maxillofac Implants 2001;16(5):681–692.
11. Lewandrowski KU, Gresser JD, Wise DL, White RL, Trantolo DJ. Osteoconductivity of an injectable and bioresorbable poly(propylene glycol-co-fumaric acid) bone cement. Biomaterials 2000;21(3):293–298.
12. Lewandrowski KU, Gresser JD, Wise, DL, Trantolo DJ. Bioresorbable bone graft substitutes of different osteoconductivities: A histologic evaluation of osteointegration of poly(propylene glycol-co-fumaric acid)–based cement implants in rats. Biomaterials 2000;21(8):757–764.
13. Lewandrowski KU, Gresser JD, Wise DL, White RL, Trantolo DJ. Osteoconductivity of an injectable and bioresorbable poly(propylene glycol-co-fumaric acid) bone cement. Biomaterials 2000;21:293–298.
14. Yaszemski MJ, Payne RG, Hayes WC, Langer R, Mikos AG. In vitro degradation of a poly(propylene fumarate)-based composite material. Biomaterials 1996;17(22):2127–2130.
15. Wake MC, Patrick CW Jr, Mikos AG. Pore morphology effects on the fibrovascular tissue growth in porous polymer substrates. Cell Transplant 1994;3(4):339–343.
16. Ishaug SL, Crane GM, Miller MJ, Yasko AW, Yaszemski MJ, Mikos AG. Bone formation by three-dimensional stromal osteoblast culture in biodegradable polymer scaffolds. J Biomed Mater Res 1997;36(1):17–28.
17. Ishaug-Riley SL, Crane-Kruger GM, Yaszemski MJ, Mikos AG. Three-dimensional culture of rat calvarial osteoblasts in porous biodegradable polymers. Biomaterials 1998;19(15): 1405–1412.
18. Domb AJ, Manor N, Elmalak O. Biodegradable bone cement compositions based on acrylate and epoxide terminated poly(propylene fumarate) oligomers and calcium salt compositions. Biomaterials 1996;17(4):411–417.
19. Gerhart TN, Miller RL, Kleshinski SJ, Hayes WC. In vitro characterization and biomechanical optimization of a biodegradable particulate composite bone cement. J Biomed Mater Res 1988;22(11):1071–1082.
20. Mikos AG, Sarakinos G, Leite SM, Vacanti JP, Langer R. Laminated three-dimensional biodegradable foams for use in tissue engineering. Biomaterials 1993;14(5):323–330.