Comparison of Bone Grafting Materials in Human Extraction Sockets: Clinical, Histologic, and Histomorphometric Evaluations

Dennis M. Thompson, DDS, MS,* Michael D. Rohrer, DDS, MS,† and Hari S. Prasad, BS, MDT‡

Tooth extraction results in alveolar ridge loss caused by atrophy of the edentulous ridge, which decreases the bone volume available for dental implant placement.1-5 In the first 6-months following tooth extraction, a significant amount of bone resorption (an average of 4.4-mm horizontal and 1.2-mm vertical bone) occurs in the extraction socket and alveolar ridge.3,4 In partially edentulous patients, there was a 91% incidence of anterior ridge deformities. Reduction in alveolar ridge height and width may prohibit optimal implant placement, and often compromises the esthetic and functional results. The resorption process is a particular problem for implant placement, especially in the anterior maxilla, where the dimension and morphology of the alveolar ridge cannot easily accommodate implants.10

A number of bone replacement grafts (BRGs) that derive from human, bovine, or plants have been used to preserve the width of alveolar bone for future implant placement.11-15 One such material, PepGen P-15 228 (DENTSPLY Friadent CeraMed, Lakewood, CO), is a combination of the mineral component of anorganic bovine-derived bone matrix (OsteoGraf®/N-300; DENTSPLY Friadent CeraMed), with P-15, a cell binding peptide derived from type I collagen.16-21 In several studies, PepGen P-15 228 has been shown to promote the treatment of periodontal, alveolar ridge defects, or sinus lifting procedures.22-27 Recently, PepGen P-15 228 has been combined with an inert, bio-compatible hydrogel (PepGen P-15 228 FLOW) that provides biologic spacing for cellular and vascular access to the cell binding peptide.28 PepGen P-15 228 FLOW has shown more abundant vital bone formation in a case study compared to 100% PepGen P-15 228 particulate in extraction sockets.

Puros® (Zimmer Dental, Carlsbad, CA) is a gamma-irradiated human min-

Purpose: Although there are a number of bone replacement graft materials that are currently available for clinical use, there are few studies that directly compare efficacy among graft treatments before implant placement. The purpose of this report was to compare 3 bone replacement graft materials (PepGen P-15 228 FLOW [DENTSPLY Friadent CeraMed, Lakewood, CO], Puros® [Zimmer Dental, Carlsbad, CA], and C-Graft 228 [Clinician’s Preference, Golden, CO]) for bone formation by clinical, histologic, and histomorphometric evaluation.

Materials and Methods: In this prospective, intraoral pilot study, 13 maxillary sockets in 2 patients (both smokers) were grafted immediately after tooth extraction with C-Graft 228, Puros®, or PepGen P-15 228 FLOW (containing additional PepGen P-15 228 particles; FLOW PUTTY). After 4 months, bone cores were retrieved and analyzed histologically.

Results: PepGen P-15 228 FLOW PUTTY produced a significantly (P < 0.01) higher amount of vital bone than C-Graft 228 or Puros®. The amount of vital bone for FLOW PUTTY was 12-fold higher than for C-Graft 228 and 4-fold higher than Puros®. Of 7 FLOW PUTTY treated sites, 7 showed >14% vital bone versus 0 of 3 C-Graft 228 and 0 of 3 Puros® treated sites. FLOW PUTTY treated sites showed new vital bone between particles of residual graft. C-Graft 228 treated sites showed residual particles in a background of connective tissue with very little bone. Puros® treated sites showed nonvital bone particles in a background of connective tissue, with some new vital bone forming around the nonvital bone.

Conclusion: PepGen P-15 228 FLOW PUTTY produced significantly greater vital bone as compared to Puros® and C-Graft 228 after 4 months. A larger clinical study is required to confirm these results. (Implant Dent 2006;15:89–96)

Key Words: bone replacement graft, P-15, bone regeneration

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ISSN 1056-6183/06/01501-089
Implant Dentistry
Volume 15 • Number 1
Copyright © 2006 by Lippincott Williams & Wilkins
DOI: 10.1097/01.id.0000202426.62007.60

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derived graft material. Efficacy has been evaluated in sinus elevation grafting. In 26 patients, C-Graft 228 combined with autogenous bone produced an average of 26% vital bone after a mean healing time of 7 months. In a single case report that compared Algipore with Bio-Oss (Osteohealth, Shirley, NY) in a maxillary sinus augmentation, no remodeling could be observed with Bio-Oss after 4.5 years, although remodeling was observed with Algipore after 6 months.

Although direct comparison among graft materials is limited, 1 in vitro study compared cell attachment, proliferation, and bone differentiation among several BRGs. The investigators found higher proliferation and bone formation rates for PepGen P-15 228 as compared to Algipore (C-Graft 228), Bio-Oss and OsteoGraf/N. The purpose of this prospective, intraoral human pilot study was to compare 3 BRGs (PepGen P-15 228 FLOW, Puros, and C-Graft 228) in 13 maxillary extraction sockets for bone formation by clinical, histologic, histomorphometric evaluation.

**Materials and Methods**

In this prospective, intraoral comparison pilot study, 13 maxillary teeth in 2 patients (45-year-old male and 30-year-old female) who were heavy smokers, were extracted. In 1 patient, the select teeth were hopeless because of deep carious lesions and advanced periodontal bone loss. In the other patient, the select teeth were nonrestorable because of a combination of severe decay and generalized advanced periodontal disease.

Both patients met the established physical and psychologic criteria for treatment that included a willingness and ability to comply with all study related procedures, including: maintenance of good oral hygiene and compliance with reevaluation appointments; an ability to read, understand, and a willingness to sign the informed consent statements; teeth for extraction were not restorable because of advanced decay and/or periodontal disease; 4-5 wall defects; systemically healthy patients who did not have any medical conditions and were not taking any medications that were associated with compromised bone healing (e.g., diabetes, autoimmune dysfunction, cortisone therapy, or chemotherapy); and the subjects desired implant treatment. Both patients were smokers (2 packs per day). They both had no known allergy to tetracycline and had not received any antibiotic over the previous 6 months. Patients were provided an explanation of the study and, after expressing a desire to participate, signed a written consent form before the study initiation.

**Surgical Protocol**

After administration of local anesthesia, crestal, intrasulcular, and, where necessary, vertical incisions were made to expose the involved roots and alveolar crest. Full-thickness buccal and lingual flaps were raised using blunt dissection to view adequately the teeth to be extracted. After extraction of the tooth, the sockets were debrided, measured, and decorticated with a half-round bur under irrigation. All sockets had adequate bleeding following decortication. After extraction, each socket was marked with a surgical guide for accurately identifying the socket at the second-stage core removal surgery. Each of the sockets treated had a combined 4-5-wall configuration.

Of the 13 sockets treated, 7 received the FLOW PUTTY, 3 C-Graft 228, and 3 Puros (Table 1). PepGen P-15 228 granules (about 0.4 g/1 cc FLOW) were added to PepGen P-15 228 FLOW to make a thick, putty consistency. The purpose of adding additional PepGen P-15 228 particles to FLOW was to provide more body to the FLOW. Puros is human cancellous bone in a 0.25-1-mm particle size range and was used according to the instructions provided. C-Graft 228 (Clinician’s Preference, Golden, CO) is derived from calcified marine algae in the 0.3-0.5 mm particle size range. C-Graft 228 is known as Algipore outside the United States. The C-Graft 228 was crushed and hydrated in blood following the instructions for use.

A nonresorbable barrier (Cytoplast® Regentex GBR-200; Osteogenic Biomedical, Inc., Lubbock, TX), 11–13

<table>
<thead>
<tr>
<th>Patient Sites Nos.</th>
<th>Male</th>
<th>Female</th>
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<tr>
<td>FLOW PUTTY</td>
<td>3–6</td>
<td>11–13</td>
</tr>
<tr>
<td>Puros</td>
<td>8</td>
<td>9, 10</td>
</tr>
<tr>
<td>C-Graft™</td>
<td>9</td>
<td>7, 8</td>
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Vicryl (Johnson & Johnson; Norderstedt, Germany). Patients were placed on 100 mg of doxycycline beginning at least 1 hour before surgery and continuing for 13 days after surgery. Appropriate postoperative analgesics were administered. Patients’ sutures were removed at 1-2 weeks, and the BRG barrier removed at 1 month. As is typical for the smoking population, the postoperative course was slightly delayed with moderate flap edema, but no overt infection was observed.

Four months after extraction socket surgery, a core of bone 3.5 × 12 mm was obtained from each patient. The cores were coded and sent to the Hard Tissue Research Laboratory at the University of Minnesota, School of Dentistry. Two investigators, who had no involvement with the treatment, performed the processing for histologic and histomorphometric evaluation.

**Histology and Histomorphometry**

The specimens were retrieved and placed in 10% neutral buffered formalin. Upon receipt in the Hard Tissue Research Laboratory, the cores were immediately dehydrated with a graded series of alcohols for 9 days. Following dehydration, the specimens were infiltrated with a light-curing embedding resin (Technovit 7200 VLC; Kulzer, Wehrheim, Germany). After 20 days of infiltration with constant shaking at normal atmospheric pressure, the specimens were embedded and polymerized by 450-nm light, with the temperature of the specimens never exceeding 40°C. The specimens were then prepared by cutting/grinding, a modified method of Donath. The specimens were cut to a thickness of 150 μm on an EXAKT cutting/grinding system (EXAKT Technologies, Oklahoma City, OK). Following this process, the slides were polished to a thickness of 45 μm using the EXAKT
microgrinding system followed by alumina polishing paste. The slides were stained with Stevenel blue and van Gieson picro fuchsin. Photomicrographs were obtained using a Zeiss Axiolab photomicroscope (Carl Zeiss, Jena, Germany) and a Nikon Coolpix 4500 digital camera (Nikon Corp., Tokyo, Japan).

Histomorphometric measurements were completed using a Macintosh G4 computer (Apple Computer, Inc., Cupertino, CA), the public domain NIH Image program, which was developed at the US National Institutes of Health, in combination with Adobe® Photoshop® (Adobe Systems, Inc., San Jose, CA).

Statistical Evaluation
Statistical analysis was expressed using mean values and standard deviations of the measurements. The Student 2-tailed t test was performed that assumed unequal variance. A P value <0.05 was statistically significant.

RESULTS

Clinical Evaluation
Upon retrieval of the core, clinical measurements were made at each site. The mean clinical hardness of the bone formed from both the FLOW PUTTY and the Puros® treated sites were comparable and ranged between types II and III bone qualities. In contrast, 3/3 C-Graft 228 treated sites resembled less dense type IV bone.

Histologic Evaluation
FLOW PUTTY histology showed new vital bone and separated particles of residual graft material. Fig. 1A shows a low-power photomicrograph of a specimen with the average percentage (24%) of vital bone. Figs. 1B and 1C illustrate an area of new vital bone bridging between residual PepGen P-15 228 particles. C-Graft 228 histology showed residual particles in a background of connective tissue with very little bone formation. Fig. 2A is a photomicrograph of a specimen showing particles of C-Graft 228 within connective tissue and very little bone formation. Fig. 2B is a high-power view of a single particle of C-Graft 228, with green-staining osteoid forming around its perimeter. Osteoblasts are noted lining the osteoid. Red-staining new bone is seen within the osteoid.

Puros® histology showed nonvital bone particles in a background of connective tissue, with some new vital bone forming around the edges of some of the particles of the nonvital bone. Fig. 3A shows a representative photomicrograph of a specimen with the average percentage (8%) of vital bone. Figs. 3B and 3C illustrate Puros® particles, with new bone formation intimately in contact with the nonvital bone. Fig. 3D shows Puros® particles that have not been implanted. Note the similarities to the low-power photomicrograph in Fig. 3A.

Histomorphometric Evaluation
PepGen P-15 228 FLOW PUTTY produced a statistically significant (P < 0.01) higher amount of vital bone than C-Graft 228 or Puros® (Table 2). The amount of vital bone for FLOW PUTTY was 12-fold higher than for C-Graft 228 and more than 4-fold higher than Puros®. Puros® produced statistically significant greater vital bone than C-Graft 228. Of 7 FLOW PUTTY treated sites, 7 showed >14% vital bone versus 0 of 3 Puros® or C-Graft 228 treated sites. Host bone (nongrafted) was taken from the facial plate from site No. 15 as a positive control. That core showed 43% vital bone, which was substantially greater than the vital bone observed in any of the other grafted sites. The amount of residual graft particles was significantly (P < 0.05) higher for C-Graft 228 treated sites than for sites treated with Puros® or FLOW PUTTY. There were no significant differences in residual graft particles between Puros® and FLOW PUTTY.

DISCUSSION
In this prospective intraoral pilot study, PepGen P-15 228 FLOW
PUTTY produced significantly greater vital bone as compared to Puros® and C-Graft 228 after 4 months in maxillary, human extraction sockets. The FLOW PUTTY produced 1200% and 400% higher amounts of vital bone than did C-Graft 228 or Puros®, respectively. Previous studies with C-Graft 228 showed a much higher quantity of vital bone after maxillary sinus augmentation after a longer period (7 months) and when mixed with autogenous bone than was observed for C-Graft 228 in this study. One possible reason is that we evaluated C-Graft 228 in human sockets in the absence of autogenous bone. In addition, to our knowledge, this is the first histomorphometric evaluation of Puros®. Interestingly, Puros® histology has been previously described in a single case study, but quantification of vital bone was not performed.

Distinguishing the new bone formation from the residual Puros® particles to make reasonably accurate histomorphometric measurements is extremely difficult. Histomorphometric measurement of BRGs is usually performed using computer image analysis. Because unique histologic staining characteristics of graft material and bone separate the materials optically, digitized images allow a computer image analysis program to distinguish graft from bone and subsequently measure the area of the different materials. Virtually all BRGs differ significantly from new bone formation histologically, either because they are totally different materials such as bioactive glass, hydroxyapatite, or they consist of demineralized bone. Puros® is a gamma-irradiated human mineralized allograft that cannot be easily distinguished from mineralized native bone.

Although qualitative examination can generally distinguish vital from nonvital bone by looking for osteocytes in lacunae, one cannot simply use the fact of “empty lacunae” as evidence that an area of bone is nonvital to perform an accurate histomorphometric measurement. A very significant number of lacunae appear empty in vital bone because of fixation and dehydration shrinkage of the osteocytes. Staining residue often leaves material in empty lacunae of nonvital bone that can be confused with osteocytes. Layers of new bone often are not thick enough to have osteocytes visibly trapped in lacunae. This parameter is not sufficient to identify, separate, and measure accurately thin layers of new bone forming on the Puros® particles in an entire core specimen.

Because the bone harvested for Puros® is mature bone, the polarization patterns of mature (lamellar) versus immature (woven) bone can assist in the differentiation. In many areas of new bone formation, osteoblastic rimming is evident as well as formation of osteoid. These factors also help in the differentiation of new bone from Puros®. Using nondecalcified sections with appropriate stains, one can easily differentiate osteoid from calcified bone. Droplets of calcification within the osteoid are readily apparent. Staining intensity and quality emphasize differences in bone maturity. The quality of polarization of nondecalcified sections is better than decalcified sections.

The investigators conducting the histomorphometric measurements used a combination of digital photomicrographs, both standard and polarized, and concurrent microscopic examination to identify and differentiate the nonvital bone of the Puros® graft from the new bone formation. Because of all the factors mentioned, which made it complicated to differentiate clearly between new bone formation and Puros®, it is difficult for the computer to make this distinction. An investigator performing computer image analysis must trace the junction of new bone and Puros® by hand. Once the areas are
clearly delineated, standard computer image analysis is used to analyze the remainder of the specimen. In future studies, vital staining during the course of the experiment using tetracycline, or multiple stains in animal studies, could possibly be used to show clearly the demarcation of the new bone additions to the Puros® particles.

In our pilot report, histologically, the graft site contained bone. However, histomorphometry revealed that approximately two thirds of this bone was non-vital (e.g., was composed of residual graft material). Of the entire graft area, only 6%, on average, was composed of vital bone. The amount of vital bone in Puros® grafted sites was significantly higher than C-Graft 228 treated sites.

To our knowledge, this is also the first report of FLOW PUTTY in an extraction site case series. In a previous extraction socket case study, PepGen P-15 228 FLOW produced 18% vital bone after 13 weeks. The mean 24% vital bone after 4 months (16 weeks) observed in our study compares favorably.

Using the Misch bone quality scale,³⁶ both FLOW PUTTY and Puros® were comparable clinically. However, FLOW PUTTY had 400% greater vital bone. Clinical evaluation of the bone quality appears to be a much less precise measure as compared to histomorphometry. Because the final goal of any grafting procedure is to achieve formation of 100% living bone tissue surrounding the implants,³⁷ a BRG resulting in more vital bone should enhance osseointegration. In a recent article,³⁸ implants were placed into a Puros® grafted site 4 months after grafting. Although histology and histomorphometry were not performed in that study, only 1/35 implants failed after ridge reconstruction. In this pilot study, FLOW PUTTY showed much greater vital bone than Puros® after 4 months of healing. This result suggests that bone formation is more predictable at this early time. Additional research in this area is clearly needed to evaluate better the remodeling process.

In the FLOW PUTTY treated sites, there was a substantial amount of vital bone in the apical and middle portions of the core, and a lesser amount of bone in the crestal portion after 4 months. Progressive ossification or advancing bone formation from the apex toward the gingival crest has been previously reported,³⁹ which explains why clinicians can observe BRG particles embedded in the gingival flap connective tissues at reentry for implant placement.

Because both patients included in this pilot study were smokers, the amount of bone formed after only 4 months is substantial. Additional cores are required to determine whether even higher bony defect fill is observed in nonsmokers and whether a similar trend is observed in a higher number of patients. The study design used a majority (10/13) of single-rooted sockets, and 3 sites were multirooted. One previous study showed no difference in vital bone percentages between single rooted and multirooted extraction sockets.⁴⁰ In addition, the study design did not use a negative (no fill) control group because the bone loss after tooth extraction of non-grafted sites is well studied.¹ ¹ ¹ and ethically, within a private practice, we were unable to perform a control.

It is difficult to compare these study results with reported graft treatment results from other reports because of differences in study design that include timing of trephine cores, patient health (e.g., smoking or not, age, sex, others), location of defect (e.g., mandible, maxilla), and differences in inclusion/exclusion criteria (number of walls remaining, single tooth extraction vs. fully edentulous, etc.). For example, less vital bone has been observed in repaired maxillary sockets compared to mandibular sockets.⁴¹ Thus, one cannot accurately compare vital bone formation when it occurs in different regions of the oral cavity (mandibular versus maxillary sockets). However, because this intraoral study took place only in maxillary sockets, we are able to discern differences clearly.

There are several potential reasons for the large differences in vital bone observed among graft treatments. An in vitro study showed superior cell attachment, proliferation, and osteodifferentiation for PepGen P-15 228 compared to C-Graft 228 (e.g., Algipore®).³³ Thus, these attributes of the peptide-modified surface may contribute to the superior bone formation compared to other materials. Another potential contributor is the hydrogel component of FLOW PUTTY, which provides spacing to facilitate cell and vessel ingrowth throughout the graft site.²⁸ Such facilitation may lead to accelerated bone formation and may not impede the osteoconductive process from the apex. Because all grafts were used according to the instructions provided by the manufacturer, graft mishandling was not a valid explanation of the differences. In addition, because all 3 grafts were compared within each patient in maxillary sites only, patient variability was not a contributing factor to the differences observed.

CONCLUSION

This prospective, intraoral pilot study of 13 grafted extraction sockets showed that PepGen P-15 228 FLOW with additional PepGen P-15 228 particles (FLOW PUTTY) produced the highest amount of vital bone as compared to the other BRGs tested (Puros® and C-Graft 228 /Algipore®). The clinically evaluated bone quality after healing presented high density for the PepGen P-15 228 FLOW grafted in sites compared with the C-Graft 228 or Puros® grafted sites.

Disclosure

The authors claim to have no financial interest in any company or any of the products mentioned in this article.

ACKNOWLEDGMENT

DENTSPLY Friadent CeraMed provided some of the tested materials.

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Abstract Translations [German, Spanish, Portugese, Japanese]

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SCHLÜSSELWÖRTER: Transplantat zum Knochengewebsersatz, P-15, Knochengewebswiederherstellung

Comparación de los materiales de injerto de hueso en las cavidades de extracción humanas: Evaluaciones clínicas, histológicas e histomorfométricas: Estudio piloto.

ABSTRACTO: Objetivo: A pesar de que hay una cantidad de materiales para el injerto de hueso (BRG por sus siglas en ingles) que están actualmente disponibles para uso clínico, hay pocos estudios que comparen directamente la eficacia entre los tratamientos de injertos antes de la colocación del implante. El propósito de este informe fue comparar tres BRG (PepGen P-15™ Flow, Puros™ y C-Graft™) para la formación del hueso a través de la evaluación clínica, histológica e histomorfométrica. Métodos y materiales: Desde esta perspectiva, un estudio piloto intraoral, se injeraron trece cavidades maxilares en dos pacientes (ambos fumadores) inmediatamente luego de la extracción de un diente con C-Graft, Puros o PepGen P-15 Flow (con un contenido adicional de partículas de PepGen P-15; Flow Putty). Luego de cuatro meses, se sacaron los núcleos del hueso y se analizaron histológicamente. Resultados: PepGen P-15 Flow Putty produjo una significativa (p < 0,01) mayor cantidad de hueso vital que C-Graft o Puros. La cantidad de hueso vital de Flow Putty fue 12 veces mayor que C-graft y 4 veces mayor que Puros. Siete de siete cavidades tratadas con Flow Putty demostraron más de un 14% de hueso vital comparado con 0 de 3 cavidades tratadas con C-Graft y 0 de 3 con Puros. Las cavidades tratadas con Flow Putty mostraron nuevo hueso vital entre las partículas del injerto residual. Las cavidades tratadas con C-Graft demostraron partículas residuales con fondo de tejido conectivo con muy poco hueso. Las cavidades tratadas con Puros mostraron partículas de hueso no vital con un fondo de tejido conectivo con algo de nuevo hueso vital formado alrededor del hueso no vital. Conclusión: PepGen P-15 Flow Putty produjo una cantidad significativamente mayor de hueso vital comparado con Puros y C-Graft
After four months. More extensive clinical studies are needed to confirm these results.

PALABRAS CLAVES: emplazamiento con injerto de hueso, P-15, regeneración del hueso.

Comparação de Materiais de Enxerto Ósseo em Alvéolos de Extração em Humanos: Avaliações Clínicas, Histológicas e Histomorfométricas: Estudo-Piloto.

RESUMO: Objetivo: Embora haja um número de materiais de enxerto ósseo de substituição (BRG’s) que estão atualmente disponíveis para uso clínico, há poucos estudos que comparem diretamente a eficácia entre tratamento por enxerto antes da colocação do implante. O propósito deste relatório é comparar três BRGs (PepGen P-15™ Flow, Puros™, C-Graft™) para formação óssea por avaliação clínica, histológica e histomorfométrica. Métodos & Materiais: Neste estudo em perspectiva e intra-oral, treze alvéolos maxilares em dois pacientes (ambos fumantes) foram enxertados imediatamente após a extração do dente C-Graft, Puros ou PepGen P-15 Flow (contendo partículas adicionais de PepGen P-15; Flow Putty). Após quatro meses, núcleos ósseos foram recuperados e analisados histologicamente. Resultados: PepGen P-15 Flow Putty produziram quantidade significativamente (p < 0.01) maior do osso vital do que C-Graft ou Puros. A quantidade do osso vital para Flow Putty era 12 vezes maior do que para C-graft e 4 vezes maior do que para Puros. Locais tratados com 7/7 Flow Putty mostraram >14% de osso vital versus 0/3 de locais tratados com C-Graft e 0/3 Puros. Locais tratados com Flow Putty mostraram nosso osso vital entre partículas de enxerto residual. Locais tratados com C-Graft mostraram partículas residuais num fundo de tecido conjuntivo com muito pouco osso. Locais tratados com Puros mostraram partículas de osso não-vital num fundo de tecido conjuntivo com algum osso vital novo formando-se em torno do osso não-vital. Conclusão: PepGen P-15 Flow Putty produziu osso vital significativamente maior em comparação com Puros e C-graft após quatro meses. Exige-se um estudo clínico mais amplo para confirmar estes resultados.

PALAVRAS-CHAVE: enxerto de substituição do osso, P-15, regeneração óssea.