Alveolar Ridge Preservation Using Resorbable Bioactive Ceramic Composite: A Histological Study

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Abstract

Purpose: The purpose of this study was to histologically evaluate newly generated vital bone using porous granules of bioactive and resorbable silica-calcium phosphate nanocomposite (SCPC) in extraction sockets.

Material and methods: Six patients with a non-restorable maxillary central incisor requiring extraction followed by implant placement participated in the study. Extraction sockets were grafted with granules of SCPC. After 6 months, a bone core sample was retrieved from the center of the healed socket for histologic analysis, and dental implants were placed. Alveolar bone width was clinically assessed immediately after tooth extraction and 6 months after bone grafting, at the time of implant placement. Alveolar bone height was radiographically assessed immediately after tooth extraction and 6 months after extraction.

Results: Histomorphometric analyses of sockets grafted with SCPC for 6 months revealed 46.8% ± 14% new vital bone and 2.5% ± 1.5% graft material remnants. In these sockets, the mean bone height resorption over the 6-month period of healing was 1.6 mm ± 1.5 mm. The mean bone width resorption of 2 mm ± 0.7 mm was found at the bone crest.

Conclusion: The results of this study suggest that SCPC graft material reduces the amount of change in alveolar ridge dimensions after tooth extraction and facilitates the regeneration of new vital bone.

Key words: Alveolar ridge preservation, bioactive ceramic, bone graft, histology

Introduction

Alveolar ridge resorption is a common sequela of tooth loss. Substantial reduction in the original height and width of alveolar bone may result in prosthetic and surgical limitations (Atwood, 1979; Atwood and Coy, 1971; Bartee, 2001; Lekovic *et al.*, 1998). Clinical studies have documented an average of 4.0 to 4.5 mm of horizontal bone resorption, which contributes to a 60% loss of bone in the first 6 months after extraction (Bartee, 2001; Schropp *et al.*, 2003). In addition, resorption of 1.5 to 2.0 mm of vertical bone contributes to a 40% loss of bone height in the same time period (Lekovic *et al.*, 1998; Lekovic *et al.*, 1997). A recent systematic review reported an average of 3.8 mm reduction in horizontal bone width and 1.24 mm reduction in vertical bone height 6 months after tooth extraction (Hämmerle *et al.*, 2012). After this accelerated bone resorption, a slow progressive resorption occurs as a result of physiologic bone remodeling (Bartee, 2001).

The variations in osseous resorption after tooth extraction are contributed to by several factors. The size of the socket affects the rate of healing, i.e., healing of a molar socket takes longer than a single-rooted tooth socket (Schropp *et al.*, 2003). Facial osseous morphology has an effect on the rate and amount of alveolar ridge resorption (Kan *et al.*, 2007). The rate of ridge resorption is greater in the maxilla than in the mandible (Atwood and Coy 1971). Gingival biotype, surgical trauma, flap elevation, and the presence of infection also have an effect on bone resorption. Healing of the extraction socket has been described as initial clot formation, which is then replaced with granulation tissue, connective tissue and osteoid formation respectively (Amler, 1969, Cardaropoli *et al.*, 2003). In cases of resorbed alveolar ridge, surgical intervention for augmenting the bone is essential before

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an implant can be placed. Therefore, preserving the alveolar ridge after tooth extraction is a highly desirable preventative approach (Darby *et al.*, 2009; Kutkut *et al.*, 2012a; Kutkut *et al.*, 2012b; Levin *et al.*, 2008; Misch and Silc, 2008; Wiesen and Kitzis, 1998).

Several classifications of extraction sockets have been proposed in an attempt to provide clinical guidelines on alveolar socket preservation to prevent or minimize the alveolar bone resorption (Juodzbalys *et al.*, 2008; Elian *et al.*, 2007). Soft tissue quantity and quality of gingival tissue as well as hard tissue morphology are important factors to consider for the preservation and augmentation of extraction sockets. Several studies have proposed the use of various graft materials for the preservation of sockets after tooth extraction (Yilmaz *et al.*, 1998; Camargo *et al.*, 2004; Cardaropoli and Cardarapoli, 2008; Darby *et al.*, 2009).

Synthetic graft materials are available in an unlimited supply and can be used successfully to preserve bone (Al Ruhaimi, 2001). The ideal synthetic graft material must be biocompatible to minimize the immunological response, bioactive to stimulate bone cell function and tissue formation, and resorbable to regenerate bone with a rate of resorption that matches the rate of new bone formation. Bioactive materials such as calcium phosphate ceramics and bioactive glasses have been used in dental surgery (Camargo *et al.*, 2004; Yilmaz *et al.*, 1998). These materials are considered bioactive because they bond to bone and enhance the formation of bone tissue. Their bioactivity property has been attributed to the formation of a hydroxyapatite surface layer similar to the mineral phase of bone. Bioactive glass particles have been shown to enhance preservation of the alveolar ridge, but with some degree of bone loss (Camargo *et al.*, 2000; Yilmaz *et al.*, 1998). Although bioactive glass exhibits excellent surface reactivity, its resorbability is limited by its nonporous structural density. Even though bioactive glass showed the ability to modify the pH in organic medium *in vitro*, its effect on the pH *in vivo* may not be significant because fluid turnover *in vivo* would wash away the sodium ion (El-Ghannam, 2004a; El-Ghannam *et al.*, 2004b; Gupta *et al.*, 2007a).

Silica-calcium phosphate nanocomposite (SCPC) exhibits better bioactivity than traditional bioactive ceramics (El-Ghannam and Ning, 2006). Its crystals have been engineered with ion substitution and the formation of solid solution to achieve enhanced bioactivity and resorbability properties (El-Ghannam, 2004). Data in the literature have demonstrated that the rate of dissolution of SCPC is significantly higher than that of bioactive glass (El-Ghannam, 2004; Gupta *et al.*, 2007a). The porous crystalline structure and the high surface area of SCPC enhance the initial material dissolution and expedite the kinetics of bioactivity reactions in physiological solutions. It enhances the bioactivity reaction, which depends on the dissolution precipitation reaction. The controlled high rate of dissolution of SCPC provides a high pool of calcium ions that stimulate cells to form new bone and enhance resorption of the material, allowing bone regeneration (El-Ghannam and Ning, 2006; Gupta *et al.*, 2007a).

It also helps in the formation of the hydroxyapatite surface layer on the ceramic material. After 2 days in culture, osteoblast-like cells attracted to silica (Si)-rich SCPC50 express significantly higher ratios of osteocalcin and osteopontin mRNA/B-actin mRNA than do those attached to hydroxyapatite (Interpore HA200) granules (El-Ghannam, 2004; Gupta *et al.*, 2007a). This finding indicates that Si-rich SCPC50 provides the maximum stimulating effect on bone cell differentiation.

In the ideal situation, the resorption rate of the graft material matches the rate of new bone formation. The resorption rate of SCPC is dependent on several patient parameters, because the resorption is primarily cell-mediated, as shown in previous study (El-Ghannam and Ning, 2006). Histological results of Si-rich SCPC50 material implanted in experimental osseous defects has been also published and showed direct contact between SCPC particles and newly formed vital bone. Moreover, his tomorphometric analysis showed 19.1% graft material and 32.4% mature bone. The remaining 48.5% (of the region of interest) contained primarily immature woven bone and bone marrow (El-Ghannam *et al.*, 2007). The silica-calcium phosphate nano composite properties of nano-porous structure, superior bioactivity, controlled dissolution kinetics, and strong stimulating effect on osteoblast differentiation, suggest that SCPC has wide application in the field of bone tissue reconstruction (El-Ghannam, 2004; El-Ghannam, 2005; El-Ghannam and Ning, 2006; El-Ghannam *et al.*, 2007; Ning *et al.*, 2005; Gupta *et al.*, 2007a; Gupta *et al.*, 2007b).

The purpose of this study was to histologically evaluate newly generated bone using porous granules of bioactive and resorbable silica-calcium phosphate nanocomposite (SCPC) in extraction sockets.

Materials and methods

Silica-calcium phosphate nanocomposite particles ranging in size from 250 to 425 μm with the chemical composition shown in *Table 1-A* were used to graft the extraction sockets. The percent porosity, the pore size range, and the pore area of the SCPC particles are shown in *Table 1-B*. The study was approved by the Regulation Committee for Good Clinical Practices. Study participants were six patients (aged 20 to 40 years; mean age, 30 years) with a non-restorable maxillary central incisor requiring extraction followed by implant placement. To qualify for the study, patients had to have maxillary central incisor teeth that were deemed unsalvageable because of extensive caries or trauma but not because of periodontal disease. Subjects were excluded if they received radiation therapy, suffered from uncontrolled systemic disorders, had acute

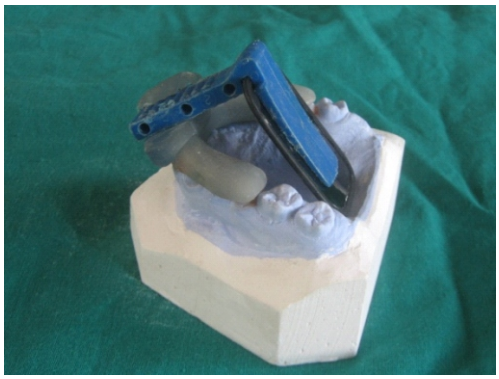

Figure 1. The radiographic stent and the film holder positioned on the patient model.

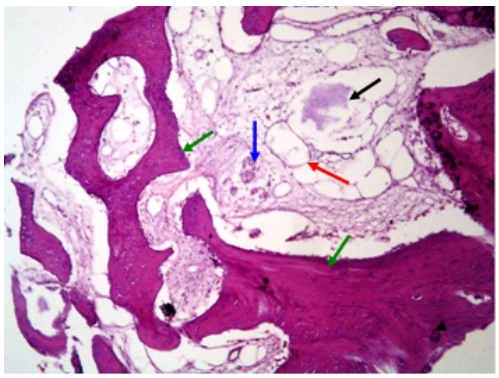

Figure 2. Photomicrograph of bone biopsy sample from socket 6 months after grafting with silica-calcium phosphate nanocomposite (SCPC) shows bony spicules with wide marrow spaces (green arrows), remnants of the SCPC material (black arrow), wide thin-walled capillaries (red arrow) and neurovascular areas (blue arrow). Sample stained with hematoxylin and eosin; magnification at 100×.

odontogenic infections, or were smokers (more than 10 cigarettes a day), pregnant or breastfeeding. A partial denture was used for each patient to replace the missing tooth. The temporary tooth replacement was relieved to prevent any impingement on hard and soft tissue during a healing phase of six months.

All extraction sockets had to be intact with no bone resorption or fenestration after extraction. Extraction sockets were grafted with granules of SCPC. After 6 months of healing, trephine bone core samples were harvested from the most central zone of the healed sockets for histomorphometric analysis, and dental implants were placed in all sites. Core samples were immediately placed in special biopsy tubes containing 10% neutral buffered formalin. The specimens were then sent to a specialized pathology lab. To prepare histologic slides, specimens were cut in the apico-coronal plane to obtain 6 μm thick sections and then stained with hematoxylin and eosin. Histomorphometric analysis was performed on each

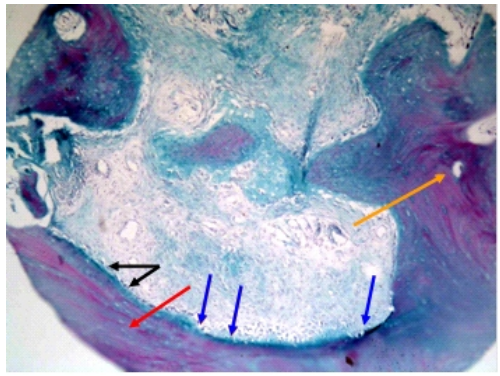

Figure 3. Photomicrograph of bone biopsy sample from socket 6 months after grafting with silica-calcium phosphate nanocomposite (SCPC) shows osteoblasts lining the bony spicules (black arrows), osteon formation (orange arrow), parallel bone lamellae (red arrow), and stages of osteoblast entrapment (blue arrows). Sample stained with trichrome; magnification at 100×.

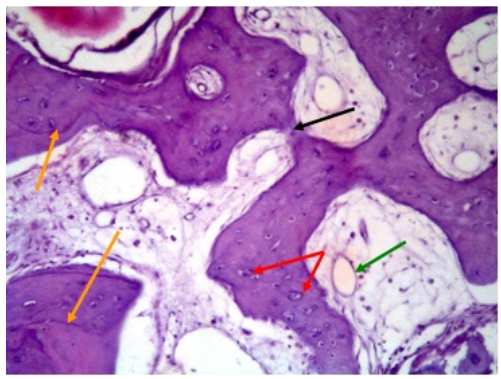

Figure 4. Photomicrograph of bone biopsy sample from socket 6 months after grafting with silica-calcium phosphate nanocomposite (SCPC) shows connection between the bony spicules (black arrow), osteocytes (red arrows), resting and reversal lines (orange arrows), and wide thin-walled capillaries (green arrow). Sample stained with hematoxylin and eosin; magnification at 100×.

section. Percentages of newly formed bone, residual graft material and connective tissue were measured.

Investigation treatment

After administration of a local anesthetic, a full-thickness mucoperiosteal flap was elevated, exposing the alveolar bone from the labial and palatal sides. Teeth were then atraumatically extracted, and the bone crest was referenced with a prefabricated acrylic occlusal template. The midfacial/midpalatal bone width was measured using graduated bone calipers at 2, 4, and 6 mm apical to a fixed prefabricated acrylic occlusal template. Fresh extraction sockets were grafted with SCPC granules to the level of the bone crest. The

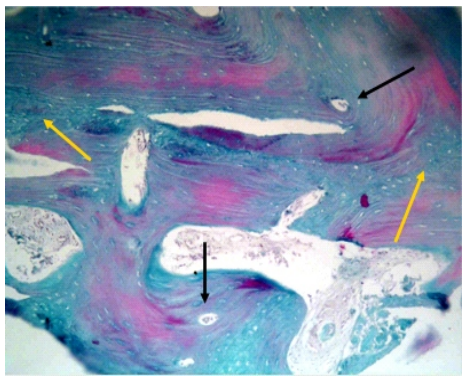

Figure 5. Photomicrograph of bone biopsy sample from socket 6 months after grafting with silica-calcium phosphate nanocomposite (SCPC) shows osteons (black arrows) and coarse fiber woven bone (yellow arrows). Sample stained with trichrome; magnification at 100×.

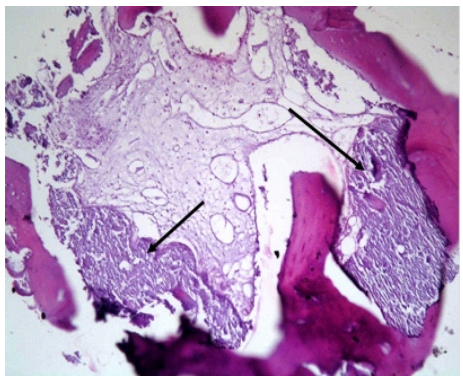

Figure 6. Photomicrograph of bone biopsy sample from socket 6 months after grafting with silica-calcium phosphate nanocomposite (SCPC) shows focal areas of granulation tissue (black arrows). Sample stained with hematoxylin and eosin; magnification at 100×.

Table 1. A. Chemical composition of silica-calcium phosphate nanocomposite (SCPC) bioactive ceramic in mole percentage. B. Porosity data for SCPC of particle size 250 to 425 µm measured by a mercury intrusion technique.

A. Composition Code	**Na_2O**	**SiO_2**	**CaO**	**P_2O_5**
SCPC	32.9%	32.9%	22.8%	11.4%
B. Properties		**SCPC**		
Porosity (%)		70.32		
Pore size range		20 nm - 340 µm		
Bulk density (g/mL)		0.58		
Total pore area (m^2/g)		18.3		

subperiosteal flap was undermined and coronally advanced to allow for tension-free primary closure. The ridge width was measured immediately after extraction and 6 months after grafting, at the time of implant placement. A standardized intraoral direct digital periapical radiographic measurement of bone height was taken with an occlusal acrylic bite block incorporating a film holder *(Figure 1)*. The radiographic measurements were taken immediately after the operative procedure (as a baseline) and after 6 months of healing, at the time of implant placement.

Results

Six months after tooth extraction, histomorphometric analyses of specimens taken from sockets grafted with SCPC showed evidence of new vital bone formation (mean value of 46.8% ± 1 4%) and graft material remnant (mean value of 2.5% ± 1.5%; *Figure 2*). The remaining 50.7% contained primarily bone marrow. Several bony spicules with wide marrow spaces incorporating remnants of the graft particles were observed (*Figure 3, Table 2*). The osteoblast line was on the periphery of the bony spicules and was separated from them by a layer of osteoid tissue (*Figure 3*). Histologic slides exhibited evidence of formation of mature bone, as indicated by the presence of osteons and osteocytes (*Figures 3, 4*). Resting and reversal lines were consistently evident in the newly formed bony spicules and indicated a normal process of bone remodeling (resting lines demarcate bone deposition, whereas reversal lines indicate bone resorption by osteoclasts; *Figure 4*). The newly formed vital bone was vascularized, as indicated by the presence of wide, thin-walled capillaries. Neurovascular areas in the bone marrow were also evident (*Figures 3, 5, 6*). Focal areas of granulation tissue were also seen (*Figure 6*) and indicated an ongoing healing process. The density of the new vital bone observed was homogenous in the investigated samples. There were no histological differences between the apical and coronal part of the examined samples.

The mean bone height resorption over the 6-month period of healing was 1.6 mm ± 1.5 mm. The mean bone width resorption of 2 mm ± 0.7 mm was found at the bone crest (*Tables 3 and 4*).

Table 2. Histomorphometric analysis of examined sites

Vital Bone (mean % ± SD)	Bone Marrow (mean % ± SD)	Graft Remnants (mean % ± SD)
46.8% ± 14%	50.7% ± 13.5%	2.5% ± 1.5%

Table 3. Changes in bone height over time in the silica-calcium phosphate nanocomposite (SCPC)-grafted sockets.

Period	Baseline Mean ± SD*	6 months Mean ± SD*
	5.5 ± 1.1	7.1 ± 1.9
Mean differences	**Baseline to 6 months** -1.6	
p value	**0.243**	

*SD, standard deviation. Statistical significance set at $p \leq 0.05$.

Discussion

Alveolar ridge resorption after tooth extraction results in loss of bone height and width (Bartee, 2001; Lekovic *et al.*, 1998; Lekovic *et al.*, 1997; Serino *et al.*, 2003). In recent systematic reviews of dimensional changes of extraction sockets in human, it was reported that the horizontal reduction (3.79 ± 0.23 mm) of socket dimension was more than that of vertical reduction (1.24 ± 0.11 mm) at 6 months following extraction. The percentage of vertical and horizontal bone changes of alveolar extraction sockets at 6 months following extraction was 11–22% and 29–63% respectively. A gain of 0.4 – 0.5 mm of soft tissue thickness on the buccal and lingual aspects of alveolar ridge was reported at 6 months following extraction (Tan *et al.*, 2012; Hämmerle *et al.*, 2012).

Alveolar bone resorption may lead to restorative complications and inadequate bone volume for the placement of endosseous dental implants (Moriarty *et al.*, 1999). It may also result in poor esthetics and insufficient occlusal function (Yilmaz *et al.*, 1998). Several studies have proposed the use of various ridge preservation techniques after tooth extraction. These techniques usually include the placement of graft materials, the use of occlusive membranes to cover the extraction sockets, or both (Camargo *et al.*, 2004; Cardaropoli and Cardarapoli, 2008; Darby *et al.*, 2009; Kutkut *et al.*, 2012b; Lekovic *et al.*, 1998; Serino *et al.*, 2003). The potential benefit of socket preservation therapy was documented and resulted in significantly less vertical and horizontal contraction of the alveolar bone crest. The scientific evidence does not provide clear guidelines in regards to the type of biomaterial graft or surgical procedure (Vignoletti *et al.*, 2012). This study evaluated a new graft material for ridge preservation after extraction of a maxillary central incisor, a site at which the labial alveolar bone plate is usually thin and is prone to faster resorption than is palatal alveolar bone.

The results of the present study showed that SCPC was effective in preserving the ridge dimensions after tooth extraction. The bone loss affecting ridge width was minimal and was limited to the crestal portion of the grafted sockets; therefore, it did not affect the orientation of the implant or the selection of implant diameter. In addition, sockets grafted with SCPC material exhibited no significant change in bone height. The decrease in bone width at the alveolar crest (2 mm apical from the occlusal template) of the grafted sockets was statistically significant after 6 months of healing.

Previous studies have reported various degrees of change in the alveolar ridge after extraction with or without socket preservation. Using root form bioglass cones, Yilmaz and coworkers found a significant decrease in bone height in the control group but not in the grafted group (Yilmaz *et al.*, 1998). However, Camargo and coworkers found no significant change in bone height in either ungrafted sockets or in sockets grafted with bioactive glass particles (Camargo *et al.*, 2000). Similarly, Lekovic and coworkers used bioabsorbable (glycolide/lactide acid polyester) membranes and reported no significant difference between the grafted and ungrafted sockets (Lekovic *et al.*, 1998).

The advantages of SCPC graft material over bioactive glass cones or particles are its superior bioactivity and its controlled resorbability (El-Ghannam, 2004). The high bioactivity of SCPC is attributed to its crystalline structure and its hierarchical

Table 4. Changes in bone width (mm) over time in the silica-calcium phosphate nanocomposite (SCPC)-grafted sockets correlated with a fixed reference point on an acrylic occlusal template.

Site	Period	Mean ± SD*	*p* value
2 mm	**Baseline**	6.0 ± 0.7	**0.006***
	6 months	4.0 ± 0.7	
4 mm	**Baseline**	7.3 ± 0.4	**0.778**
	6 months	7.2 ± 0.9	
6 mm	**Baseline**	7.8 ± 1.5	**0.749**
	6 months	7.6 ± 0.5	

*SD, standard deviation. Statistically significant, $p \leq 0.05$.

porosity (Clozza *et al*., 2012). The resorption rate and patterns of SCPC are mainly cell-mediated (El-Ghannam and Ning, 2006; El-Ghannam *et al*., 2007). These unique properties of SCPC facilitate bone cell function and tissue regeneration inside the sockets, as reported in the histologic analysis performed in our study.

Histologic evaluation of the biopsy specimens harvested from the central area of the grafted sockets showed substantial new vital bone tissue formation and incomplete graft material resorption. The newly formed vital bone was vascularized and exhibited all of the histologic characteristics of mature bone, including osteocytes, osteons, blood vessels, and reversal and resting lines. Although concentric bone lamellae were observed near the periphery of the grafted sockets, islands of woven bone and activated osteoblasts were observed in the center of the histologic specimens. This finding indicates that bone formation begins at the edge of the socket and moves inward toward the center of the socket. The mechanism of bone formation was similar to the natural bone remodeling process.

One of the most important observations was the presence of large numbers of wide blood vessels. This finding indicates that the interconnected pores of SCPC particles provide pathways that allow cell invasion and endothelialization. In addition, few remnants of the graft material were incorporated inside the regenerated bone with direct bone apposition on their surfaces. This observation suggests that the rate of bone regeneration matches the rate of SCPC resorption. The new bone formation was observed both on the outer surface and in the pores inside the SCPC particles, thus expediting the bone regeneration process. In a recent histologic human study using bioactive glass particles to preserve the extraction sockets, Clozza *et al*. reported that vital bone formation and residual graft material were 54 ± 31% and 8.1 ± 7.8%, respectively. Clozza's findings are in accordance with the present study findings (Clozza *et al*., 2012). Several bone grafts were tested for extraction site preservation. When bovine bone mineral graft was used, new vital bone formation was ranged from 22.8% (coronal) to 36.3% (apical) after 9 months of healing (Perelman-Karmon *et al*., 2012). Approximately 5 months after ridge preservation using human demineralized bone matrix putty with different-sized bone particles, new vital bone regeneration ranged from 49% to 53% (Hoang and Mealey, 2012). At 4 months post-extraction, an allograft and a bovine-derived xenograft used in ridge preservation reported 61% versus 26% of vital bone, respectively (Vance *et al*., 2004). A clinical and histomorphometric study of calcium sulfate compared with freeze-dried bone allograft for alveolar ridge preservation showed 32% new bone formation for the calcium sulfate and 16.7% new bone formation for freeze-dried bone allograft after 3 months of healing (Toloue *et al*., 2012). In a histologic comparison of healing after tooth extraction with ridge preservation using mineralized versus demineralized freeze-dried bone allograft (DFDBA), it was reported that DFDBA showed a significantly greater percentage of vital bone: 38.42% versus FDBA at 24.63% after 5 months of healing (Wood and Mealey, 2012). The healing of extraction sockets implanted with bioactive glass or DFDBA 6 to 8 months post-implantation showed mean vital bone present was 59.5% for bioactive glass, 34.7% for DFDBA, and 32.4% for unfilled sites (Froum *et al*., 2002). In a split-mouth design study comparing magnesium-enriched hydroxyapatite (MHA) and porcine bone (PB) in human extraction socket healing, mean vital bone measurements for the MHA, PB, and unfilled sites were 36.5%, 38.0%, and 30.3%, respectively (Crespi *et al*., 2011). Extraction sockets grafted with calcium sulfate hemihydrate and platelet-rich plasma for 3 months before implant placement showed 66.5% new vital bone regenerated compared to 38.3% new vital bone in sockets in sockets packed with a collagen resorbable plug (Kutkut *et al*., 2012a).

Previous studies have shown that SCPC granules up-regulate osteogenic gene expression of osteocalcin, osteopontin, osteonectin, collagen I, and mineral formation (Gupta *et al*., 2007a; Gupta *et al*., 2007b; Ning

et al., 2005). Therefore, ridge preservation in SCPC-grafted sockets is attributed to the stimulatory effect of SCPC on bone cell function. The SCPC particles serve as a scaffold for cell migration, proliferation, and tissue deposition. The histologic findings correlate well with the radiographic picture of the grafted sockets and clinical ridge preservation. Within the limitations of this SCPC study, histologic findings showed the same biologic behavior in bone formation and resorption processes when compared with the performances of the marketed bone graft materials according to scientific available data reported previously. Sometimes, alloplasts are a predictable clinical alternative bone substitute when patients decline to receive allografts or xenografts in their treatment. Synthetic alloplast bone substitutes such as SCPC reduce the morbidity and possibility of cross infection when compared to allografts or xenografts.

Conclusion

Silica-calcium phosphate nanocomposite graft material reduces the amount of change in alveolar ridge dimension after tooth extraction. New vital bone and minimal residue of the material are histologically evident after 6 months. Our findings suggest that SCPC can be used successfully as a bone graft substitute for preservation of extraction sockets.

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