Influence of Platelet-rich Plasma on Osseous Healing of Dental Implants: A Histologic and Histomorphometric Study in Minipigs

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Purpose: *In the present study the time course of local bone formation following the application of PRP during implant placement was evaluated histomorphometrically and histologically.* ***Materials and Methods:*** *The mandibular premolars of 12 adult minipigs were removed surgically and 72 sites were prepared for implant placement. Before the implants (MK III, Replace, and MK III TiUnite) were placed, autogenous PRP (8×10^5 to 10×10^5 platelets/μL) was instilled into the host sites on the left side. The animals were sacrificed at 3, 6, and 12 weeks, and undecalcified ground sections were prepared.* ***Results:*** *The histomorphometric evaluation showed significantly more bone-to-implant contact after topical PRP application in the early healing phase (6 weeks), which varied as a function of the distance from the implant surface (controls = 24.2% versus PRP = 44.21%; P = .013). At 12 weeks, the extent of osteoneogenesis was comparable in the 2 groups (controls = 51.3% versus PRP = 44.2%; P = .251). Statistical analysis revealed no significant interaction between implant surface type and PRP.* ***Discussion:*** *Topical PRP application significantly increased the activity of bone regeneration at implant host sites during early healing.* ***Conclusion:*** *In the present study PRP was found to have a time- and site-dependent effect on peri-implant bone healing.* (Int J Oral Maxillofac Implants 2003;18:15–22)

Key words: *animal study, dental implants, platelet-rich plasma*

Numerous studies have shown the success rate of implants in local host bone with poor osteoregenerative potential to be low.[1–5] To promote healing of endosseous implants and bone grafts, several measures designed to improve and accelerate osseous healing by increasing the bone-to-implant contact have been proposed. These include the application of platelet-rich plasma (PRP),[6,7] bone morphogenetic proteins (BMPs),[8–10] and growth factors.[11–14]

Experimental and clinical studies have shown that the local application of platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF), both of which are recombinant growth factors, had an osteoregenerative effect on peri-implant bone and that PRP promoted healing of bone autografts.[6–10] In 1991, Lynch and coworkers documented for the first time that recombinant PDGF and IGF significantly improved peri-implant bone regeneration.[11] Marx and associates reported in 1998 their data on the use of PRP for promoting bone graft healing.[6] These showed greater bone density and quality in grafts with PRP added during pre-implant augmentation. The effects observed were attributed to the pro-angiogenetic effects and the proproliferative and prodifferentiating effects on osteoblasts of transforming growth factor beta (TGF-beta) and PDGF present in PRP in high concentrations.[7]

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The effects of concentrated autogenous growth factors (PRP) on the healing of different dental implants have not been investigated to date. The present experimental study was therefore designed to shed light on the effects of PRP on osseous healing of dental implants both quantitatively and qualitatively. With a split-mouth model, the time course and local effects of PRP on healing, as well as differences, if any, in PRP effects on implants with different surfaces, were evaluated.

MATERIALS AND METHODS

The experimental protocol was submitted to the Ethical Board of Animal Investigations (Madrid, Spain) for the approval of animal experiments and approved by it. During the entire experiment, 12 adult miniature pigs (bred from Minnesota pigs and Vietnamese pot-bellied pigs) with a body weight of 95 (± 5) kg were kept in a confine appropriate for the species and provided with food and water ad libitum.

PRP was prepared as described by Gehring and associates.[15] Twenty-four hours before surgery 450 mL of venous whole blood were withdrawn using a triple blood bag system (Teruflex, Terumo Europe, Leuven, Belgium). The first bag contained citrated phosphate dextrose (CDP), 63 mL, for stabilization. After centrifuging the contents at 2,890 G for 6 minutes (Cryofuge 6000, Heraeus Sepatech, Fell back, Germany) the plasma was manually transferred into the second bag and stored at 22°C with continuous slight shaking until the time of surgery. Immediately before surgery, it was again centrifuged at 153 G for 12 minutes. The redundant platelet-poor plasma was then transferred to the third bag and discarded. This left 30 ± 5 mL of PRP.

Implants of 3 different designs were prepared for placement:

1. Twenty-four threaded commercially pure titanium implants with a machined surface (MK III, Brånemark System, Nobel Biocare, Göteborg, Sweden; 3.75×10 mm, self-tapping, surface roughness, Ra = 0.53 µm according to Wennerberg and coworkers[16])
2. Twenty-four threaded hydroxyapatite (HA) - coated implants (Replace, Nobel Biocare; 3.5×13 mm, non–self-tapping, Ra = 5.1 µm according to Gottlander[17])
3. Twenty-four threaded titanium implants with an anodized surface (MK III TiUnite, Brånemark System, Nobel Biocare; 3.75×8.5 mm, Ra ≥ 1.2 µm + 95% increase in surface area from coronal to apical according to Hall and Lausmaa[18])

Surgical Procedure

The animals were intubated and anesthetized with nitrous oxide, isoflurane, and oxygen; atropine, 0.020 mg/kg body weight; carazolol (Suacron, Boehringer, Mannheim, Germany), 1 mL/50 kg body weight; stresnil (Azaperon, Veterinaria, Zurich, Switzerland), 0.25 to 1 mg/kg body weight; midazolam (Dormicum, Roche, Vienna, Austria), 0.05 mg/kg body weight; and ketamine hydrochloride, 18 mg/kg body weight. A marginal gingival or crestal incision was made from the canine to the first molar on either side of the mandible with mesial vestibular backcuts for relief. The premolars were removed surgically by dividing them with a fissure drill, and the alveolar ridge was flattened with a bur for obtaining comparable host sites. During each step, physiologic saline was applied generously for cooling. While the self-tapping machined and anodized implants were placed without prior tapping, threads were cut with a screw tap before implant placement for the non–self-tapping, HA-coated implants. In each hemimandible the 3 implant designs were placed in a random sequence. In the left hemimandible autogenous PRP, which had been prepared preoperatively, was instilled locally into the ready implant host site with a sterile syringe immediately before implant placement. For this purpose, 6 mL PRP (platelet count, 8×10^5 to 10×10^5/µl) were mixed with 0.5 mL thrombin solution (Tissucol Kit, Baxter, Austria) and 10% calcium solution (0.5 mL, Calcium "Novartis" phials, Novartis, Vienna, Austria). The resulting solution was activated for 2 to 4 seconds and applied with a 10-mL syringe.

Once in place, the implants were covered with cover screws and the wound was tightly sutured in layers for submerged healing.

For antibiotic coverage, the animals received 1.5 g amoxicillin intramuscularly preoperatively. Analgesic and anti-inflammatory medication consisted of butorfanol 0.1 mg/kg administered intravenously.

Sample Preparation

Using a split-plot factorial design, the animals were divided into 3 groups of 4 animals each. The first group was sacrificed at 3 weeks, the second at 6 weeks, and the third at 12 weeks with an overdose of pentothal. This gave 6 measurements for each animal and each outcome variable at each of the sampling times.

After sacrifice, bone blocks with the implants were excised, fixed in 37% formaldehyde solution (Mercu, Darmstadt, Germany), dehydrated in ascending grades of alcohol, infiltrated with Technivit 7200 + BPO (Kulzer & Co, Wehrheim, Germany), and embedded in resin. Using the method

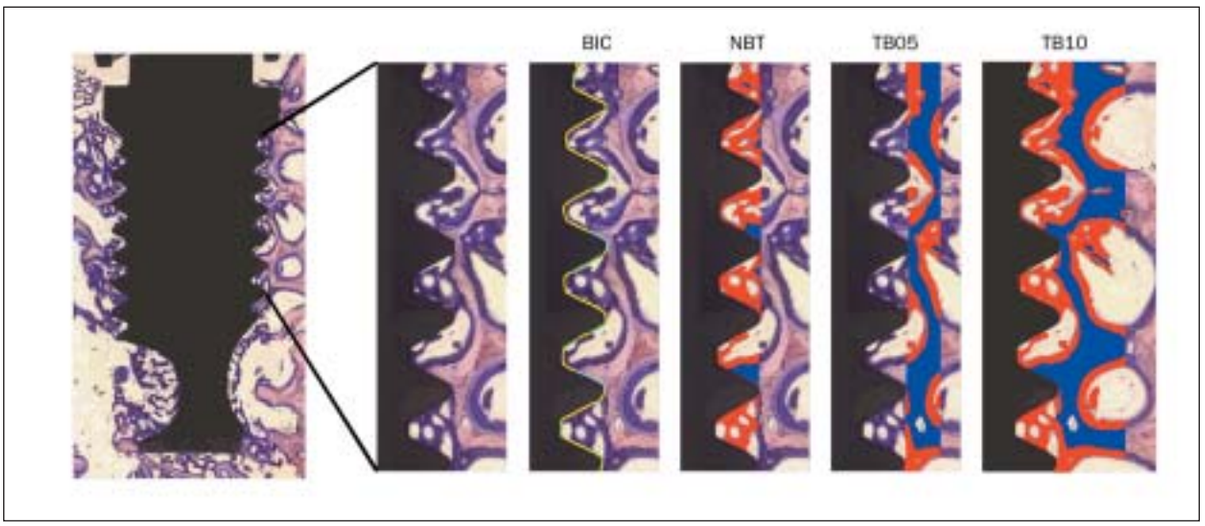

Fig 1 Schematic illustrating the histomorphometric variables evaluated. BIC = length of direct bone-to-implant contacts as a percentage of the implant surface; NBT = percent new bone area within threads; TB05 = percent new bone area within 0.5 mm of the implant surface; TB10 = percent new bone area within 1 mm of the implant surface, including newly formed bone within threads.

described by Donath and Breuner,[19] undecalcified thin cut and ground sections with a thickness of approximately 20 µm were prepared and stained with the Levai Laczko stain (Fig 1). Samples were ground from buccal to lingual along the long axis of the implants so that these were precisely cut into 2 halves. For histology, all sections (2 to 3 of each sample) were used.

Under microscopic view (Nikon Mikrophot-FXA, Leitz, Germany), the stained cut and ground sections were digitized and photographed (Kodak Professional DCS 420, Rochester, NY). The photographs were processed with Adobe Photoshop software (Adobe, San Jose, CA) and color-coded (green = implant surface, blue = host bone, yellow = newly formed bone). For histomorphometric evaluation of 1 representative section per implant, the morphometry package Lucia VGA (Version 4.10, Laboratory Imaging, Prahe, Czech Republic) was used after scale calibration. To ensure comparability of the different implant designs despite dissimilar cross-sectional shapes in their apical regions, the coronal half of the implant contour was chosen including both the buccal and the lingual side.

Variables measured and computed (Fig 1) included:

1. Length of direct bone-to-implant contact (BIC) as a percentage of the implant surface,
2. Percent new bone area within the threads (NBT),
3. Percent new bone area at a distance of 0.5 mm from the implant surface (TB05), and
4. Percent new bone area within 1 mm of the implant surface (TB10).

Statistical Analysis

Analysis of variance (ANOVA) for split-plot factorial designs was used to identify significant covariates. In addition, ANOVAs for randomized block designs were run for a separate evaluation of the data from pigs sacrificed at 3, 6, and 12 weeks postimplantation. *P* values for multiple group comparisons were based on fitted models using the Tukey test. The relationship between missing data of the outcome variables and group membership was evaluated by logistic regression. Means are least square means (LSM) obtained by fitting the complete model and accompanied by the standard errors (SEM). Least square means are the most adequate means for an experiment with a balanced design, but some outcome data are missing (because of early implant loss). Studentized residuals were analyzed to establish the quality of fit of the models. $P < .05$ was considered significant. All statistical analyses were run on the GLM procedure of SAS software (SAS, Cary, NC).[20]

RESULTS

Masticatory parafunctions and habits caused more mucosal dehiscences than usual. Of 61 implants, 33 showed dehiscences around the cover screws. There

were no significant differences in the rate of dehiscences between the 3 implant designs: 42.1% for machined implants, 50.0% for HA-coated implants, and 45.5% for anodized implants. Eleven implants (14.3%) failed during the healing time. The failure rate of implants placed with PRP was not significantly different from that in the controls (controls = 5.6% versus PRP = 9.7%). There was no significant difference in failure rates among the 3 implant designs tested.

Implant-related complications were thus randomly distributed and were therefore not considered in the analysis. All implants, other than those that failed, were included in the further procedures and evaluations. ANOVA of the histomorphometric data failed to show any statistically significant interaction between the factor "PRP" and the factor "implant design," so the implant groups were pooled for further analysis.

Histology

Implants Without PRP (Figs 2a to 2c). At 3 weeks postimplantation (Fig 2a), newly formed immature trabeculae were seen to project into the threads of the implants. These reached the machined implant surface in only some spots. In all other areas the cancellous spaces were mostly lined with woven bone. Around the HA-coated implants, bone-to-implant contact had already spread widely and covered larger areas at this point in time. On the surface of the cancellous spaces, newly formed woven bone was present and showed signs of circumscribed osteon-like remodeling. The HA coating was largely preserved and contained sporadic multinucleated foreign body giant cells. Light microscopy of the anodized implants showed abundant peri-implant bone formation with numerous bone-to-implant contacts spread across the implant surface. Within the newly formed bone, osteon-like osteoneogenesis was seen.

At 6 weeks postimplantation (Fig 2b) the woven bone around implants was increasingly replaced by lamellar bone. Bone-to-implant contact was still confined to spots of pseudopodial appositions originating from broad-based trabeculae growing into the machined threads. Around HA-coated implants, newly formed bone spread widely across the implant surface. In areas not covered by bone, an extensive HA particle transport was seen resulting in a reduced thickness of the HA coating. Around anodized implants, still more abundant bone had been deposited on the surface than at 3 weeks and signs of incipient lamellar remodeling were present.

At 12 weeks postimplantation (Fig 2c), bone-to-implant contacts around implants clearly covered larger areas than at the previous sampling times. Within the machined threads, little original host bone was seen. This was surrounded by newly formed bone. On the surface of HA-coated implants, bone-to-implant contact had spread widely at this point in time and filled almost the entire peri-implant gap, with only a few small voids. In areas not covered by bone, the HA surface showed major changes and the thickness of the coating was reduced. Around anodized implants, the peri-implant bone was compact, and widely spread contacts extending across most of the implant surface were present. Bone remodeling had produced a bony lining, mostly at the bottom and the sides of the threads, while the tips were devoid of newly formed bone. Throughout the follow-up time, no disrupted surface particles were present in the peri-implant tissue around anodized implants.

Implants with PRP (Figs 2d to 2f). At 3 weeks postimplantation (Fig 2d), mostly fingerlike bone-to-implant contacts extending along the sides of the threads were seen histologically around the implants. Morphologically, these were similar to those seen around machined implants placed without PRP, but in circumscribed areas more bone had formed with PRP in an osteon-like pattern. Around HA-coated implants, broad-based newly formed bone was seen to have grown toward the implant surface. The peri-implant cancellous spaces showed an extensive lining and signs of osteon-like osteoneogenesis. Bone-to-implant contacts around anodized implants spread across the surfaces of the threads at several sites. As in the other implant groups with PRP, osteon-like new bone structures signaled an increased stimulation of osteoneogenesis.

At 6 weeks postimplantation (Fig 2e), much more new bone was present in the threads of machined implants than in those placed without PRP. While this new bone was broad-based and grew into the implant threads (Fig 3a), only fingerlike extensions made contact with the implant surface. Around HA-coated implants, new bone covered almost the whole implant surface. As on their counterparts without PRP, the HA coating was seen to undergo resorption (Fig 3b). Anodized implants showed new bone deposits spreading widely across their surface. In all 6-week samples, the newly formed bone had a compact lamellar structure.

At 12 weeks postimplantation (Fig 2f), bone regeneration around implants was no longer distinguishable histologically from the controls. As in the controls without PRP, bone contacts with the machined implant surface were broad-based with voids at the thread tips, but much less extensive than on rough implant surfaces (Fig 3a). Bone regeneration around HA-coated implants was also

Figs 2a to 2f *Details from histologic sections of the control and PRP group showing bone-to-implant contacts. Newly formed bone within threads and near implants is highlighted in a darker shade.*

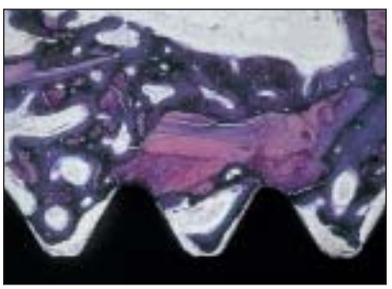

Fig 2a Control section at 3 weeks postimplantation.

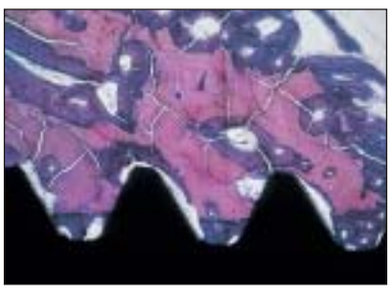

Fig 2b Control section at 6 weeks postimplantation.

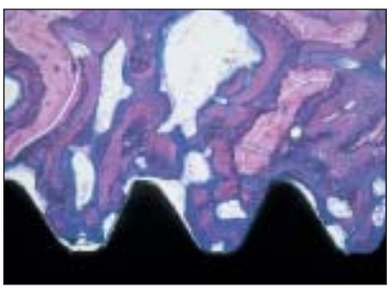

Fig 2c Control section at 12 weeks postimplantation.

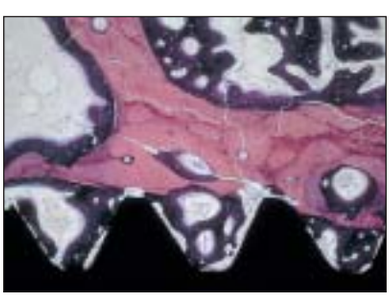

Fig 2d PRP section at 3 weeks postimplantation.

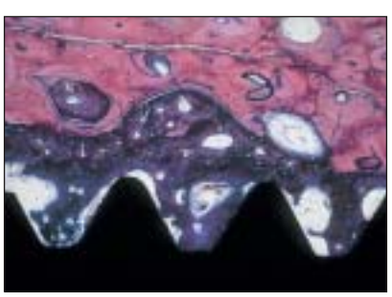

Fig 2e PRP section at 6 weeks postimplantation.

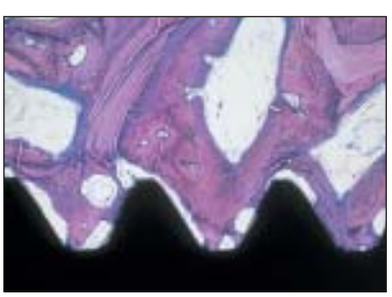

Fig 2f PRP section at 12 weeks postimplantation.

Figs 3a to 3c *Histologic ground sections of the 3 implant types after a healing time of 12 weeks.*

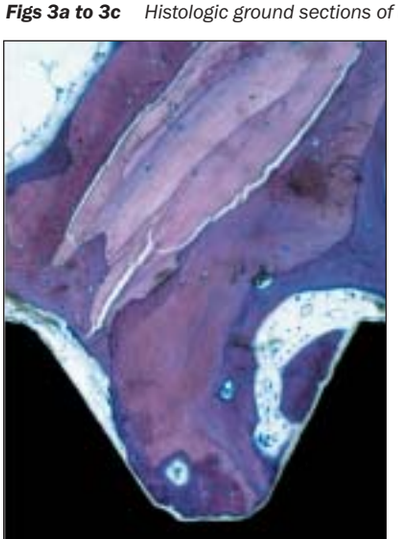

Fig 3a Machined implants. Bone-to-implant contact is more broad-based than at 3 and 6 weeks, but less than on rough-surfaced implants.

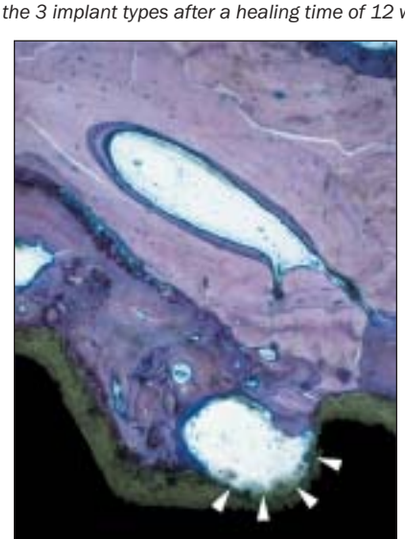

Fig 3b HA-coated implants. Broad-based bone contact is evident. The HA coating not covered by bone shows signs of resorption *(arrowheads).*

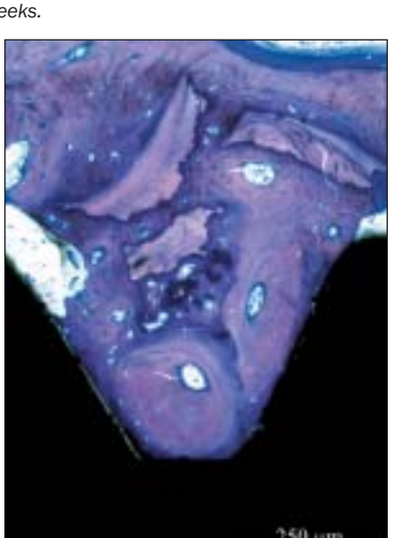

Fig 3c Anodized implants. Broad-based bone apposition can be seen.

indistinguishable histologically from that in the controls without PRP: Numerous osteons were identifiable near immature bone areas side by side with broad-based, spread out bone-to-implant contacts. Around anodized implants (Fig 3c), contact was comparable to that seen in the 6-week samples with PRP and in the 12-week samples without PRP and spread widely across the surface. In many cases, the newly formed bone extended to the sides, the bottom, and the tips of the threads.

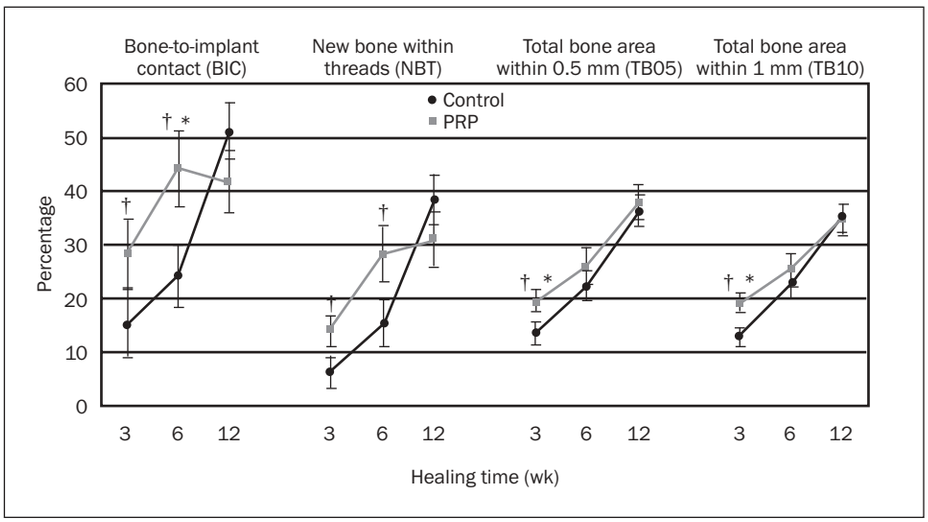

Fig 4 Bone regeneration with and without PRP over time (3, 6, and 12 weeks postimplantation) and at variable distances from the implant surface.*$P < .05$; †$P < .05$ 3- and 6-week aggregates.

Histomorphometry

ANOVA for split-plot factorial designs to identify covariates did not show any significant interaction between the factors "implant surface" and "PRP." As a result, the implants were pooled for evaluating the factor "PRP" histomorphometrically.

Bone-to-Implant Contact (BIC). At 3 weeks, the percent length of direct BIC (Fig 4) was 15.41% (LSM ± 6.32 SEM) in the controls (ie, implants without PRP) by statistical evidence. Percentages at 6 and 12 weeks were 24.20% (LSM ± 7.00 SEM) and 51.34% (LSM ± 5.92 SEM), respectively. Data for the PRP group were 28.31% (LSM ± 6.32 SEM) at 3 weeks, 44.21% (LSM ± 5.96 SEM) at 6 weeks, and 41.76% (LSM ± 5.24 SEM) at 12 weeks postimplantation. The differences for the 3-week data were not statistically significant ($P = .068$), but reached significance for the aggregated 3- and 6-week data ($P = .043$) and for the 6-week data alone ($P = .013$). At 12 weeks the factor "PRP" did not have a statistically significant effect ($P = .251$).

New Bone Within Threads (NBT). In the controls, the NBT (Fig 4) was 6.35% (LSM ± 2.95 SEM) at 3 weeks, 15.49% (LSM ± 4.41 SEM) at 6 weeks, and 38.43% (LSM ± 4.59 SEM) at 12 weeks. Percentages in the PRP group were 14.03% (LSM ± 2.95 SEM) at 3 weeks, 28.30% (LSM ± 5.18 SEM) at 6 weeks, and 31.07% (LSM ± 5.19 SEM) at 12 weeks. The small number of samples ruled out significant differences for the 3-week and the 6-week data ($P = .084$ and $P = .073$, respectively), but the differences for the aggregated 3- and 6-week data were highly significant ($P = .009$). At 12 weeks PRP did not have a statistically significant effect ($P = .312$).

Total Bone Area Within 0.5 mm (TB05). In the controls, the TB05 (Fig 4) was 13.50% (LSM ± 2.14 SEM) at 3 weeks, 22.43% (LSM ± 2.97 SEM) at 6 weeks, and 36.28% (LSM ± 2.14 SEM) at 12 weeks. In the PRP group, percentages were 19.58% (LSM ± 2.14 SEM) at 3 weeks, 25.96% (LSM ± 3.49 SEM) at 6 weeks, and 37.91% (LSM ± 3.38 SEM) at 12 weeks. Differences at 3 weeks were weakly significant ($P = .062$). At 6 weeks and at 12 weeks, PRP did not have a significant effect ($P = .439$ and $P = .726$, respectively).

Total Bone Area Within 1 mm (TB10). In the controls, the TB10 (Fig 4) was 12.84% (LSM ± 1.74 SEM) at 3 weeks, 23.08% (LSM ± 2.72 SEM) at 6 weeks, and 35.05% (LSM ± 2.68 SEM) at 12 weeks. In the PRP group, percentages were 19.26% (LSM ± 1.74 SEM) at 3 weeks, 25.35% (LSM ± 3.20 SEM) at 6 weeks, and 34.70% (LSM ± 3.03 SEM) at 12 weeks. Differences at 3 weeks were significant ($P = .019$). At 6 weeks and at 12 weeks, PRP did not have a significant effect ($P = .584$ and $P = .934$, respectively).

DISCUSSION

In an experimental study, Lynch and coworkers first examined recombinant PDGF-beta and recombinant IGF-I for their potential of promoting the healing of specially designed dental implants.[11] They found the growth factors to have a statistically significant early effect on bone regeneration. However, BIC was not significantly increased. In 1995, Sumner and associates reported their data on bone regeneration around orthopedic implants obtained

in a dog model.[12] At 4 weeks, animals treated with recombinant TGF-beta1 showed 3 times more new bone than the paired controls. In clinical studies Marx and coworkers[6] and Anitua[7] showed that autogenous PRP, which contains numerous autogenous growth factors (PDGF and TGF) in high concentrations, had a positive effect on healing of bone autografts. To date PRP has only been studied for purposes of bone augmentation. However, its potential to optimize healing of dental implants has not yet been investigated. The present study was therefore designed to shed light on the effects of PRP on the healing of dental implants of different surface types in a minipig model.

ANOVA of the histomorphometric data failed to show a statistically significant interaction between the factor "PRP" and the factor "implant surface." As a result, the implant groups were pooled for further analysis. Also, the implant failures observed were randomly distributed and not implant-specific by statistical evidence, so that an effect on the measurements was highly unlikely. The higher rate of implant losses compared to other reports was attributed to a higher incidence of wound dehiscences during healing related to masticatory parafunctions.[21–24] Histomorphometric analysis of the factor "PRP" on bone regeneration showed a significant increase in BIC (Fig 4) early during submerged healing (at 3 and 6 weeks). In the controls, by contrast, BIC did not substantially increase before the second half of the healing time. At 12 weeks, BIC with and without PRP was comparable with slightly higher percentages in the controls. The total new bone area was the same in both groups 12 weeks postimplantation (Fig 4). The effect of PRP decreased with increasing distance from the site of application. This was reflected by the total bone area within the threads, at a distance of 0.5 mm from the implant surface, and at a distance of 1 mm from the implant surface (Fig 1). In summary, PRP was found to have a significant effect in the early healing phase at 3 and 6 weeks postimplantation.

The biologic actions of autogenous and recombinant growth factors such as TGF and PDGF and the underlying mechanisms were investigated in numerous studies.[13,25,26] These factors belong to a class of biologic mediators with an important stimulatory and regulatory function in cellular processes such as mitogenesis, differentiation, and chemotaxis, as well as angioneogenesis during bone and soft tissue healing. Marx and associates[6] attributed the osteoregenerative effect of PRP to an increased release of PDGF and TGF and the resultant enhanced stimulation of angiogenesis, mitogenesis of marrow stem cells and (pre)osteoblasts, and their activation and differentiation into mature osteoblasts. This complex stimulatory action and the effect of highly concentrated autogenous growth factors on early bone repair may well explain the increase in the amount of BIC and the amount of newly formed peri-implant bone seen during the early healing time. Stefani and coworkers also reported recombinant growth factors (PDGF and IGF-I) to promote peri-implant bone regeneration in the early phase.[14]

In a comparison of a mixture of bovine HA (Bio-Oss, Geistlich Pharmaceutical, Wolhusen, Switzerland) and PRP with bovine HA alone in a sinus lift model with simultaneous implantation, Fürst and coworkers, by contrast, failed to detect a stimulatory effect on the number of BIC.[27] They presumed the cause to be the poor osteoregenerative potential of the local bone stock of the sinus floor. Yildirim and colleagues followed up 38 human biopsy samples taken after sinus floor elevation with autogenous venous blood plus bovine HA (Bio-Oss) and implant placement and reported similar data.[28] All of these data suggest that the osteoregenerative potential of local bone, ie, its capacity to regrow, is a major factor in determining the effectiveness of growth factors, both autogenous and recombinant. To develop their stimulatory action, they apparently need a local bone stock with an adequate cellular reactivity in terms of the pre-osteoblast count and the angiogenetic potential.

This study showed that topical PRP enhances bone regeneration at implant host sites in the posterior mandible during early healing. However, this requires an adequate osteoregenerative potential, which can be stimulated by autogenous growth factors. The highly predictable acceleration and enhancement of bone regeneration by PRP first reported by Marx and associates and Anitua for autogenous bone grafting was confirmed in this study for the healing of dental implants.[6,7] Local PRP administered during dental implant placement thus is a relatively simple method to enhance early BIC. However, because of the limited ability to extrapolate the data to human conditions, further investigations are needed in controlled clinical trials before this approach can be used routinely. Moreover, future studies will have to show whether the use of PRP during implant placement improves the prognosis of implants placed in bone of poor quality and whether it contributes to shortening the healing time of dental implants.

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