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Effects of T-PRF and A-PRF on the Osteogenic Biomarkers in Intrabony Defects of Periodontitis Patients

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Research Article

History

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ABSTRACT

Objectives: Different derivatives of platelet-rich fibrin (PRF) have been developed but the efficacy of these derivatives in tissue healing and regeneration is still unclear. The aim of this study was to evaluate the effects of titanium-prepared PRF (T-PRF) and advanced PRF (A-PRF) on osteogenic biomarkers in gingival crevicular fluid (GCF) and clinical parameters.

Materials and Methods*:* Seventeen systemically healthy participants with 30 bilateral intrabony defects were recruited. Following phase I periodontal therapy, intrabony defects were treated either with A-PRF+open flap debridement (OFD) or T-PRF+OFD. Plaque index (PI), gingival index (GI), pocket depth (PD), clinical attachment loss (CAL) was recorded at the baseline and 6th month after treatment. GCF samples were collected at the baseline and 3rd, 6th months after surgery. Nuclear factor receptor activator (RANK), receptor activator nuclear kappa-B ligand (RANKL), osteoprotegerin (OPG) and tumor necrosis factor alpha converting enzyme (TACE) in GCF samples were analyzed by human enzyme-linked immunosorbent assay (ELISA).

Results: In both groups, statistically significant changes were observed in clinical parameters, however, there was no difference between the groups. In terms of osteogenic biomarkers in GCF, there were no statistically significant differences between and within the groups.

Conclusions*:* Different derivatives of PRF can be used to enhance the clinical outcomes of intrabony defects in periodontitis.

Key words*:* Intrabony defects, A-PRF, T-PRF, periodontal surgery, osteogenic biomarkers.

Süreç

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ÖZ

Amaç: Trombositten zengin fibrinin (TZF) farklı türevleri geliştirilmiştir, ancak bu türevlerin doku iyileşmesi ve yenilenmesindeki etkinliği hala belirsizdir. Bu çalışmanın amacı, titanyum ile hazırlanmış TZF (T-TZF) ve geliştirilmiş TZF'nin (G-TZF) dişeti oluğu sıvısındaki (DOS) osteojenik biyobelirteçler ve klinik parametreler üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntemler: 30 çift taraflı kemik içi defekti olan 17 sistemik olarak sağlıklı katılımcı çalışmaya alındı. Faz I periodontal tedavinin ardından, kemik içi defektler ya G-TZF+açık flep debridmanı (AFD) ya da T-TZF+AFD ile tedavi edildi. Plak indeksi (PI), gingival indeks (GI), cep derinliği (CD), klinik ataçman kaybı (KAK) başlangıçta ve tedaviden 6 ay sonra kaydedildi. DOS örnekleri başlangıçta ve ameliyattan sonraki 3., 6. aylarda toplandı. DOS numunelerindeki nükleer faktör reseptör aktivatörü (RANK), reseptör aktivatörü nükleer kappa-B ligandı (RANKL), osteoprotegerin (OPG) ve tümör nekroz faktörü alfa dönüştürücü enzim (TACE), insan enzim bağlantılı immünosorbent testi (ELISA) ile analiz edildi.

Bulgular: Her iki grupta da klinik parametrelerde istatistiksel olarak anlamlı değişiklikler gözlendi ancak gruplar arasında fark yoktu. DOS'taki osteojenik biyobelirteçler açısından, gruplar arasında ve gruplar içinde istatistiksel olarak anlamlı bir fark yoktu.

Sonuçlar: Periodontitiste kemik içi defektlerin klinik sonuçlarını iyileştirmek için TZF'nin farklı türevleri kullanılabilir.

Anahtar Kelimeler: Kemik içi defektler, G-TZF, T-TZF, periodontal cerrahi, osteojenik biyobelirteçler.

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Introduction

Periodontitis is a progressive chronic inflammation characterized by irreversible loss of connective tissue attachment and alveolar bone. The aim of periodontal therapy is to control active inflammation, halt the progression of the disease and, where appropriate, reconstruction of structures that are lost as a consequence of inflammatory response.[1]

Non-surgical or surgical therapy can be employed to treat periodontitis. Within the context of surgical therapy, open flap debridement (OFD) has been defined as a standard approach in the treatment of residual pockets. A systematic review mentioned that treatment of deep persisting periodontal pockets with OFD resulted remarkable improvement both in PD and CAL compared to non-surgical therapy.[2] As a major challenging condition in clinical approaches, intrabony defects (IBDs) cannot be thoroughly treated by only OFD. In these cases, application of biological agents and bone substitutes produced marked enhancements in PD and CAL compared to OFD alone.[3]

Development of biologically active compounds has been the focus of clinical research for a long while. Surgical adjuvants has been commenced with fibrin glue applications to wound edges[4] which is followed by development of blood derived platelet concentrates such as platelet rich plasma (PRP)[5] and platelet-rich fibrin (PRF).[6] In particular, second generation platelet concentrate, PRF has a strong fibrin matrix enriched with growth factors (GFs) such as Fibroblast Growth Factor (FGF), Vascular Endothelial Growth Factor (VEGF), Platelet-derived Growth Factor (PDGF) and Transforming Growth Factor (TGF).[7] In vivo and in vitro studies have shown the vital role of these GFs on periodontal ligament cells during tissue regeneration.[8,9] These growth factors, when applied exogenously, change the response of periodontal hard and soft tissues during healing phase.[10]

Today, PRF has been used in a broad range of medical applications including plastic,[11] maxillofacial surgeries[12] and sports medicine.[13] Furthermore, it has been employed in dental practice embracing the treatment of gingival recession,[14] intraosseous defects,[15] furcation areas.[16] Various studies have shown the effect of PRF on periodontal healing and regeneration following surgical applications. For instance, Chang *et al*.[17] reported exceptional results in clinical parameters in addition to radiographic filling of the intraosseous defects 6 months following the therapy.

The progress in platelet concentrates was not limited to PRF. Monocytes involve in vascularization, bone growth and synthesis of VEGF. Choukron *et al*.[18] integrated this cells into PRF and obtain advanced platelet-rich fibrin (A-PRF) which accelerate soft tissue healing, possess more BMPs and cytokines than PRF. The other advancement arouse in response to a health hazard concern about unavoidable contact with silica in glass-tubes during the preparation of PRF. Tunali *et al*.[19] introduced titanium-prepared platelet-rich fibrin (T-PRF) which has higher platelet activation and wider fibrin network than PRF.

Osteoclastogenesis is regulated by osteoprotegerin (OPG), nuclear factor kappa B ligand (RANKL), and nuclear factor receptor activator (RANK). These three proteins play key roles in bone metabolism and osteoclast biology. RANKL binds to osteoclast precursors and RANK receptors in dendritic cells, causing bone resorption by affecting the differentiation, proliferation and activation of osteoclasts. OPG competes with RANKL for RANK.[20] In periodontal disease, RANKL and OPG regulate tissue destruction. Higher levels of RANKL and lower levels of OPG have been detected in GCF of periodontitis patients.[21] Chang *et al*.[17] reported elevated protein kinase phosphorylation, osteoprotegerin and alkaline phosphatase activity in periodontal ligament fibroblasts upon treatment with PRF under in vitro conditions.

Tumor necrosis factor alpha converting enzyme (TACE) is a type I transmembrane protein belongs to extracellular zinc-linked protease family and released from T lymphocytes and monocytes. RANKL is a substrate of TACE activity and plays a key role in stimulating bone resorption. The release of TACE increases simultaneously with RANKL release.[22] RANKL levels are higher in GCF samples of individuals with periodontitis, and TACE provides the release of RANKL from the cell membrane more effectively than other enzymes.[23] Therefore, TACE enzyme activity is the target of treatment approaches to prevent bone resorption.

We hypothesized that delayed resorption period and larger fibrin network features of T-PRF provide a long term support during the healing phase and stimulate periodontal enhancement more effectively than A-PRF. Therefore, the aim of this study was to evaluate the effect of T-PRF and A-PRF on clinical parameters and osteogenic biomarkers in bilateral intrabony defects in chronic periodontitis patients.

Material and Methods

Patient Population

In this randomized, split-mouth design, double-blinded, controlled clinical trial, seventeen systemically healthy, non-smoker individual (7 females and 10 males; age range 30-60 years; mean ± SD: 42.7 ± 8.91 years) who had two interproximal intrabony defects were included. The study was completed in the Department of Periodontology, Faculty of Dentistry at Kirikkale University from 2016 to 2018. The study design was approved by the ethics committee of Kirikkale University (Number: 13/03-Date: May 25, 2015) and guided in accordance with the Declaration of Helsinki and written informed consent from all participants was obtained.

Following non-surgical periodontal treatment, two- or three-wall intrabony defects ≥ 3 mm deep along with an interproximal probing depth ≥ 5 mm were included into the study. The exclusion criteria were determined as presence of systemic conditions and any medication, pregnancy and lactation and plaque index > 1.

Presurgical therapy

Phase I periodontal therapy was completed at first visit. 6 weeks after this initial periodontal treatment [scaling and root planning with curets (Hu-Friedy, Chicago, Illinois, USA) and polishing], a re-evaluation visit was performed to confirm the eligibility of sites to periodontal surgery. In the re-evaluation, individuals who were decided to have an OFD procedure were given an appointment 1 week later. Immediately before the periodontal surgery, clinical parameters (including PI, GI, PD and CAL) were recorded and GCF samples were collected (Figure 1).

Collection and preparation of GCF Samples

After isolation of sample sites, GCF samples were collected with the standardized strips (Periopaper; Ora Flow Inc., Amityville, New York, USA) at baseline and the 3rd and the 6th months after surgery (Figure 1) and GCF volume was measured on a precalibrated device (Periotron 8000; Oraflow Inc., Plainview, New York, USA). All samples were stored at -80 C until analysis. Total amounts of RANKL, RANK, OPG and TACE were measured by ELISA using commercial kits according to the manufacturer's instructions.

PRF preparation

Two tubes of 10 ml venous blood samples were collected from each participant to make T-PRF and A-PRF. To obtain T-PRF, blood sample was transferred to the titanium tube. After centrifugation (2700 rpm, 12 minutes for T-PRF; 1300 rpm, 8 minutes for A-PRF) at room temperature, PRF clots were removed from the tubes with sterile tweezers and were placed on sterile woven gauze and kept humidified until application to the intrabony defect.

Surgical procedures

All surgical procedures were performed by the same operator (S.S.S.). Before surgery, 0.12% chlorhexidine solution and an iodine solution were used for intraoral and extraoral antisepsis. Following local anesthesia, buccal and lingual/palatinal sulcular incisions were made and a full-thickness flap was reflected. The defects were debrided and root planed with area-specific curettes. The selected sites were randomly (by coin-toss method) assigned to the T-PRF and A-PRF group. Each surgery site were treated with only assigned PRF. 4-0 non-absorbable silk suture (Ruschmed, 4-0 Silk Black, Istanbul, Turkey) was used for the closure of the flaps.

Postoperative care

After surgery, an analgesic (Sanovel, Istanbul, Turkey) (100 mg flurbiprofen, two times per day, for 5 days) and chlorhexidine digluconate rinses (Drogsan, Istanbul, Turkey) (0.12%, twice daily for 10 days) were prescribed. The sutures were removed 10th day postoperatively. Gentle brushing with a soft toothbrush for 2 weeks and appropriate interdental brush devices after 4 week were recommended. If necessary, professional plaque control and reinforcement of oral hygiene were reinformed.

Statistical analysis

To achieve 90% power and detect differences among groups, 24 defects were essential for each group. The Shapiro-Wilk test was used for the normality of the data distribution. Non-normally distributed data were expressed as median (interquartile range).

The differences between groups and to determine the groups leading to differences were examined by Friedman nonparametric repeated measurements analysis of variance test and Bonferroni correction, respectively. The SPSS program (SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses and $p<0.05$ was accepted for statistical significance level.

Results

Demographics

Ten male and seven female, totally 17 individual with chronic periodontitis met the inclusion criteria of the study. 30 bilateral intraosseous defects were treated according to study protocol and out of this number, on 22 defects all clinical measurements completed at all study period. Participants age and gender distribution were shown in Table 1. Postoperative wound healing was uneventfully in all participants. No side effects were observed in patients related to the use of anti-inflammatory medication prescribed following surgical procedure. Only antimicrobial mouthwash discoloration was recorded on teeth and the tongue of the patients.

Clinical Outcomes

Periodontal clinical parameters including PI, GI, PD and CAL were recorded at baseline and 6th month following periodontal surgery. PI was not statistically different between and within the groups at baseline and 6th month (Table 2). In both A-PRF and T-PRF groups, GI was markedly reduced at 6th month compared to baseline. However, there was no significant difference between two groups in terms of GI. In line with GI records, we observed significant improvement in PD and CAL. In both treatment groups, PD and CAL were significantly decreased at 6th month compared to baseline measurement. There was no significant change between the PRF groups.

Osteogenic Biomarkers in GCF

Figure 2 (A-E) showed the change of osteogenic biomarkers in GCF samples collected at baseline, 3rd and 6th months following open flap surgery. At baseline, in both A-PRF and T-PRF groups, RANK, OPG and TACE levels were not statistically different. Similarly, following OFD with PRF application at 3rd and 6th months, RANK, OPG and TACE expressions were not statistically different between two treatment groups. When we compared the osteogenic markers within the group during the time frame of the study we did not observe any remarkable change.

In both treatment groups, at baseline total RANKL levels were not statistically different but at the 6th month following surgery in T-PRF group total RANKL level decreased while it increased in A-PRF group. At the 6th month following surgery, total RANKL expression was markedly different between two treatment groups. But we didn't observe any remarkable alteration in terms of RANKL expression at baseline, 3rd and 6th months following surgery within both T-PRF and A-PRF group.

RANKL and OPG has a role in bone turn over and were reported in periodontal destruction. Increased RANKL levels decreased OPG were detected in GCF samples of chronic periodontitis patients. In this study, we evaluated the RANKL/OPG ratio and we observed statistically different RANKL/OPG ratio between A-PRF and T-PRF group at all time points. This ratio was significantly less in T-PRF group than A-PRF group at baseline, 3rd and 6th months following surgical therapy.

Table 1: Descriptive statistics of study population

Age (years); Mean±SD	42.7±8.91
Gender, N (%)	7 female (41.2); 10 male (59)

SD, Standart deviation

Table 2: Comparison of clinical parameters of treatment groups at baseline and 6th month following periodontal surgery

	GROUPS		
	A-PRF	**T-PRF**	**p**
PI			
Mean (SD)			
Baseline	0.413 ± 0.54	0.478 ± 0.51	0.328
6th month	0.478 ± 0.57	0.456 ± 0.52	0.803
p	0.705	0.883	
GI			
Median (IQR)			
Baseline	1 (0)	1 (0)	1.000
6th month	0.5 (1)	0 (1)	0.266
p	0.005*	0.001*	
PD			
Mean (SD)			
Baseline	6.13 ± 1.28	5.54 ± 1.11	0.091
6th month	4.06 ± 1.31	3.86 ± 0.66	0.506
p	0.000*	0.000*	
CAL			
Mean (SD)			
Baseline	6.47 ± 1.70	5.86 ± 1.15	0.132
6th month	4.82 ± 2.00	4.47 ± 1.01	0.281
p	0.000*	0.000*	

*PI: Plaque index, GI: Gingival index, PD: Probing depth, CAL: Clinical attachment loss, IQR, interquartile range; SD, standard deviation. * Significant difference within groups*

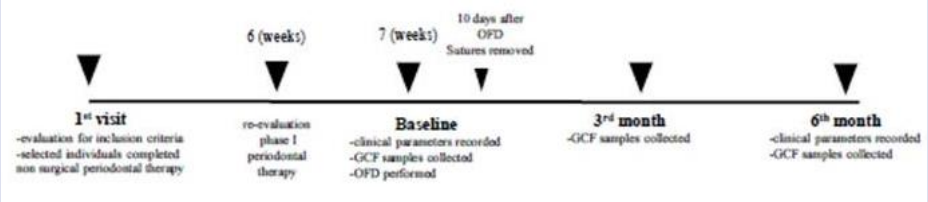

Figure 1: Study flowchart showing the each visit.

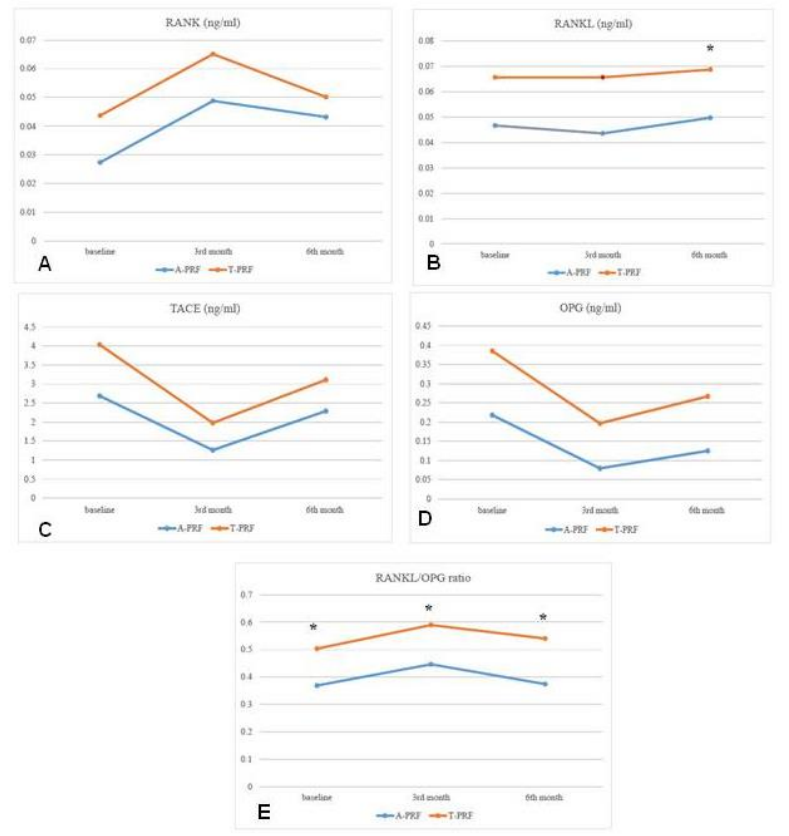

Figure 2: Comparison of osteogenic biomarkers in GCF of treatment groups at baseline, 3rd and 6th months following periodontal surgery.
*GCF concentrations of A)RANK, B)RANKL, C)TACE, D)OPG, and E)RANKL/OPG ratio in the time course of study in T-PRF and A-PRF groups. *indicates significant differences between the groups; p<0.05.*

Discussion

The aim of the periodontal therapy is to control the inflammation which leads to destruction of periodontal tissues and to regenerate lost periodontal structures. Successful periodontal regeneration is based on the formation of new cementum, new periodontal ligament and alveolar bone with the regeneration of the junctional epithelium.[24]

PRF is the second generation platelet concentrate widely used to accelerate soft and hard tissue healing.[25] Previous findings showed that PRF improves early wound closure, maturation of bone grafts, peri-implant and periodontal soft tissue aesthetic outcomes. Its ease of preparation, application and affordable rates can be counted as an advantages of this autogenous material.[14]

The fibrin network in the PRF structure provides the migration of endothelial cells during angiogenesis and the wound healing process is accelerated by the release of growth factors such as PDGF, TGF-β, IGF-1. Besides its positive effects on soft tissue healing, PRF has a function as a supportive matrix for bone morphogenetic proteins. These properties supports PRF use in periodontal and maxillofacial surgery.[12] Application of PRF in addition to flap debridement in the periodontal intra-osseous defects without graft material was evaluated in a systematic review and they concluded that the level of clinical attachment increased and the depth of the intra-osseous defect decreased.[26] This finding suggests that intraosseous defects can be treated by PRF without an exogenous graft material.

Besides aforementioned benefits, PRF has a disadvantage due to silica particles in glass tubes. This health hazard concern is eliminated by Tunali *et al*.[19] by developing T-PRF in which the activation of the clot is performed in titanium tubes. Moreover, authors reported higher and a wider fibrin network in T-PRF. In their rabbit model, T-PRF stimulated the formation of new bone and connective tissue in 30 days following application. Histomorphometric analysis in that study showed thicker fibrin network in T-PRF. Therefore, in relation to thick fibrin structure, growth factors may be released longer duration in T-PRF compared to PRF. Chatterjee *et al*.[26] compared the use of PRF and T-PRF without graft material in intra-osseous defects during open flap debridement and obtained significant results in clinical and radiographic parameters in both groups compared to open flap surgery alone. Any significant difference was observed between PRF and T-PRF in terms of clinical parameters and bone filling percentages. These findings obtained at the 9th month after surgical therapy and showed that bone filling can be achieved by using different platelet concentrates in intra-osseous defects

without any graft material.[27] In addition to T-PRF, A-PRF developed by Choukran *et al*.[18] and has a loose structure between fibrous spaces and contains more granulocytes compared to standard platelet-rich fibrin.

Evaluation of molecules involved in osteoclastogenesis to prevent bone damage is important in developing therapeutic approaches. Osteoclastogenesis is regulated by members of the tumor necrosis factor superfamily such as OPG, RANKL and RANK. RANKL binds to osteoclast precursors and RANK receptors on dendritic cells, causing bone damage by affecting the differentiation, proliferation and activation of osteoclasts. OPG competes with RANKL to bind to the same receptor.[20] Increased RANKL/OPG levels in GCF samples of periodontitis patients have been observed.[21] TACE is a protein released from T lymphocytes and monocytes which plays a role in stimulating bone resorption. It effectively ensures the release of RANKL from the cell membrane.[23]

To our knowledge, this is the first study to compare the expression of osteogenic biomarkers and to evaluate periodontal clinical parameters in intrabony defects treated either with T-PRF+OFD or A-PRF+OFD. Similar to other studies reported[3,10], statistically significant results were obtained at the 6th month following periodontal surgery in clinical parameters including GI, PD and CAL in both PRF groups. When T-PRF and A-PRF groups were compared, no difference was observed between the groups in terms of these clinical parameters.

In addition to clinical parameters we focused on osteogenic biomarkers and the total amount of these molecules in GCF was determined by ELISA at baseline, 3rd and 6th months following OFD and PRF application. There was no significant difference in RANK, OPG and TACE levels within and between the groups. We observed remarkable difference in RANKL levels between the T-PRF and A-PRF groups at 6th month. However, there was no difference within the group compared to the baseline. This change observed at the 6th month between the two groups may be due to the difference in baseline levels.

The increase in RANKL/OPG ratio in GCF is an indicator of the destruction in periodontal tissues. This ratio was evaluated in this study and we found no difference within the group. A significant difference was observed between the groups at the baseline, 3rd and 6th months following surgical therapy. At the 3rd and 6th months, RANKL / OPG ratio was higher in the T-PRF group than the A-PRF group. This state may be due to the difference between the groups at the baseline values. Arabaci *et al*.[27] evaluated the ratio of RANKL / OPG in GCF samples at 2, 4, and 6 weeks following the application of PRF and T-PRF in intrabony defects, and they reported significant decrease of RANKL/OPG ratio in T-PRF group at the 4th and 6th weeks after the surgery. Therefore, the lack of significant changes in the levels of osteogenic markers evaluated in this study may be due to the time points selected. Third and 6th months measurements might not include the early changes observed in osteogenic biomarkers. Considering the resorption times of PRF derivatives in the defect area, significant changes in these markers might be observed in an early period. Increased RANKL/OPG ratio is a valuable indicator of active periodontal disease. However, it is controversial that periodontal therapy reduce this ratio and provide an acceptable value for the treatment of periodontitis. For instance, in a study, gingival tissue samples were collected 4-6 weeks after initial periodontal therapy and RANKL, OPG gene expressions were determined by PCR. Authors reported no significant change in RANKL/OPG ratio.[28] Furthermore, Buduneli *et al*.[29] evaluated the effect of periodontal therapy on RANKL/OPG ratio in GCF. They observed significant increase in this ratio 4 weeks after the treatment. Another group reported no significant difference in RANKL/OPG ratio at the 4th month after initial periodontal therapy.[30] These findings suggest that RANKL/OPG ratio is a good marker for periodontal disease activity but it might not reflect the periodontal treatment outcomes.

Conclusions

This study showed that different derivatives of PRF might be a preferable option in the treatment of intraosseous defects in individuals with chronic periodontitis, without utilizing allografts. In addition to improved clinical outcomes observed in this work, further studies needs to elucidate the effect of different types of PRF on bone regeneration and bone filling.

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Conflicts of Interest Statement

The authors declare no conflict(s) of interest.

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