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Research Article

Efficacy of PRF Alone or Mixed With 1% Metformin Gel in Augmenting Narrow Ridge With Split-Crest Technique and Implant Installation

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Abstract

This study aimed to evaluate the efficacy of PRF either alone, or mixed with 1% metformin gel, in horizontal ridge augmentation with split-crest technique, for implant placement.

Patients & Methods

24 implants were inserted in narrow ridges of twelve patients who were randomly assigned into one of two groups. In group 1, patients were treated by split crest technique with implant placement and

PRF only. In group 2, patients received SCT with implant placement and 1% metformin gel mixed with PRF. Implant stability was recorded for every single implant immediately after insertion during surgery, and at 6 months. Modified Gingival Index, modified Plaque Index, and probing depth were recorded and repeated at one, 3, and 6 months. Immediately after surgery, at the time of loading, and 6 months after loading ridge width, crestal bone loss as well as bone density were evaluated.

Results

The mean alveolar crest width, bone density and implant stability measurements were significantly higher in metformin mixed with PRF group than PRF alone. Crestal bone loss (CBL) measurements were lower in metformin mixed with PRF group than PRF alone.

Conclusion

The results of the present study may provide a clinical evidence for the possible osteogenic potential of MF, indicated that, adding it to PRF which is known with short time stability may increase its therapeutic performance.

Abbreviations

SCT: split crest technique
MF: metformin
PRF: Platelet rich fibrine
MGI: Modified gingival index
MPI: Modified plaque index
PD: Probing depth
RBD: Relative bone density
CBL: Crestal bone loss
ACW: Alveolar crest width

Introduction

Insufficient alveolar ridge is common for edentulous patients, especially when alveolar fracturing occurs during dental extraction. When the bone loss results from a maxillofacial trauma, or from extensive periodontal/endodontic diseases, the effects are even more severe. These factors might result in insufficient vertical and horizontal support for installing dental implants and may impair, or even limit, the options for prosthetic rehabilitation. In such cases, bone volume improving techniques may be considered as effective alternative treatment [1]. split Crest technique (SCT) [2] is a surgical procedure that divides the cortical bone crests, moving them to create an opening in the center, which is then mainly occupied by simultaneously inserted implants. The main benefit of the SCT is the simple, quick, and predictable way in which the alveolar atrophic crest can be expanded [3].

The areas around implants (peri-implant gabs) can be filled with bone grafts or substitutes [4], as well as autologous biological therapies such as PRF [5]. This permits the use of bone grafts without the need for a second surgical site, thereby minimizing the risk of oedema, nerve injury, and pain [3].

In clinical practice, PRF has already been largely applied as an inexpensive carrier and way to obtain many growth factors in physiological proportions. This natural material seems to accelerate the physiological wound healing with or without bone grafts to accelerate new bone formation and hence, enhancing bone regeneration [6]. PRF has been successfully used as a sole filling material during a simultaneous SCT technique and implantation. It resulted in stabilizing high volumes of naturally regenerated bone in the spaces unoccupied by the implants [7-10].

Metformin (MF), an antidiabetic agent, that lately has been suggested to possesses osteogenic potential and induce the growth of osteoblast precursor cells. It has been successfully used as a local drug delivery agent in chronic periodontitis patients. Moreover, several human studies have reported the use of MF alone or combined with PRF in the treatment of bony defects [11-14].

Short time stability of PRF may not give it superiority over commonly used bone grafts in promoting bone formation [15]. Adding a medical formula with possible osteogenic potential such as MF to PRF may potentiate its therapeutic performance and may present a graft material, with an additional benefit of being cost-effective. Testing this hypothesis constituted the primary aim of work in the present study.

Subjects and Methods

In this study a total of 27 implants were inserted in 16 patients, 7 males, and 9 females, ranging in age from 23 to 45 years with the average of 38.7 years. The patients were divided into two groups and each group was dedicated to PRF grafting (group 1), and MF mixed with PRF (group 2). Group 1 included 3 males and 5 females, 5 implants in the mandible, and 8 implants in the maxilla. Group 2 included 4 males and 4 females, 6 implants in the mandible, and 8 implants in the maxilla. All patients were recruited from the Outpatient Clinic of the Department of Oral Medicine, Periodontology, Oral Diagnosis, and Oral Radiology, Faculty of Dental Medicine, Boys, Cairo, Al-Azhar University. Clinical examination including taking medical and dental histories, evaluation of general and oral health status, and assessment of future implant site was performed for each patient. Radiographic evaluation was done using cone-beam computed tomography CBCT using (Planmeca ProfaceTM 3 DX-ray unit) scan for assessment of bone height, width, mesiodistal space, and inter-arch relationship (implant treatment plan). With Romix dental software (version 5.3.4.39 field of view 8*10, voxel size 150 micron), it was possible to correctly assess the buccolingual width of each implant site.

Before the surgery, each patient was given careful instructions on proper oral hygiene measures. Full mouth supra- and sub-gingival scaling and root planing procedures, if needed, were performed in quadrants under local anesthesia using a combination of hand Gracey curettes (Hu Friedy, Chicago, IL) and ultrasonic scaler with the P10 tip (Cavitron Corp., Long Island City, NY).

Patients were assigned into two groups (matched for age and gender) each group was dedicated after

receiving an SCT by ultrasonic bone surgery with implant placement and use PRF only (Group 1), and metformin mixed with PRF (Group 2) as gap-filling materials.

Preparation of PRF Membrane

A blood sample of 10 ccs was obtained from the patient for every single implant. The blood sample is then put to a 10ml plain vacutainer without an anticoagulant and centrifuged at 3000 rpm for 10 min [16] using Heraeus Megafuge 16R centrifuge. The result was platelet-poor plasma in the top of the tube, red corpuscles in the bottom, and a fibrin clot (PRF) in-between. PRF clots were separated from the bottom layer and placed in the PRF box until the time of use.

Preparation of 1% Metformin Gel

MF gel was prepared as described by Mohapatra *et al.* [17] Initially, dry gellan gum powder and distilled water were mixed with a magnetic stirrer at 95°C for 20 min. Then the temperature was maintained at ≥80°C, and mannitol was added. MF was incorporated in addition to the citric acid, sucralose, and preservatives (propylparaben and methylparaben). The mixture was continuously stirred throughout the procedure. To this mixture, the required amount of liquefied sodium citrate was incorporated. This blend produced a gel at once, it was then cooled at around 20°C-25°C, and the concentration of the final MF gel was adjusted to ~1%.

Pre-Surgical Medication

The patients were initiated on a daily dose of antibiotic amoxicillin plus clavulanic acid twice daily about 20-25mg/kg/day (Augmentin 1g tab., MUP, Smithklin Ebeecham), one day before surgery as prophylactic. One tablet from Ibuprofen 400mg (ibuprofen 400mg tab. SEDICO) and Paracetamol 500mg (Panadol Alexandria, GLAXO Smithklin) were given to the patients an hour before surgery.

Surgical Procedures

Surgical procedures were proceeded under local anesthesia using articaine hydrochloride 4% and epinephrine (artinibsa, inbsa, Spain). After crestal incision, a full thickness mucoperiosteal flap to expose the donor area was raised. A horizontal osteotomy terminated 2-3mm shorter in-depth than the full length of the planned implant to ensure primary stability with a clearance of 1mm from the roots of adjacent teeth was performed on the recipient alveolar using the CS1 and CS2 tips from the Crest-Splitting Kit of Peizotome Solo Led (Satelec, Acteon, France).

After completion of osteotomy, the facial and lingual walls were separated apart by using the conical CS4, thereafter, CS5 and CS6 were then used gradually to increase the resulting osteotomy-gap.

Following sufficient lateralization of the buccal plate, the implant sites were prepared with progressive twist drills or threaded expanders up to the preimplant size. Then the implant (J dental care two-stage implant system) was placed submerged at least 1mm apical to the alveolar ridge crest. The gaps between or around

dental implants were filled with Xenograft in group1, PRF in group 2and metformin mixed with PRF in group 3. The closure was tension-free performed with 3-0 black silk sutures by continuous interlocking and interrupted sutures.

Post-Surgical Management

The sutures were removed at 10 to 14 days, and the patients were maintained on the dose of antibiotics (amoxicillin plus clavulanic acid twice daily, about 20-25mg/kg/day) for the next 5-7 days after surgery. The analgesics were continued for the next 3-5 days. The Patients were placed on a systemically administered anti edematous agent (Alphintern, Amoun pharmaceutical Co SAE) thrice daily half an hour before meals or two hours after. The patients were instructed to use chlorhexidine mouthwash twice daily was up to 2 weeks.

Clinical Evaluation

At 6 months implant exposure was done under local anesthesia utilizing crestal incision followed by unscrewing the covering screws and screwing the appropriate smart peg to each implant. Implant stability was recorded (for the second time) for every single implant by placing the Osstell ISQ's probe 2mm away from the smart peg. Three measurements were recorded at different angles.

Healing abutments were then screwed to implants 10-14 days. Thereafter, the final restoration was fabricated and cemented to abutments with temporary cement. One month later (1M), the modified gingival index [18] (MGI), modified plaque index [18] (MPI), and probing depth (PD) were recorded and repeated at 3, and 6 months.

Radiographic Evaluation

CBCT scans were taken (for the segment which includes the implant site to reduce the patient's exposure dose as possible.) immediately after surgery, at the time of loading, and 6 months after loading to evaluate alveolar crest width (ACW), crestal bone loss (CBL) as well as relative bone density (RBD). The gray values of the relative bone density around the implant were measured immediately after surgery, immediately after implant insertion, at the time of loading, and 6 months after loading.

Statistical Analysis

All data were expressed as mean ± SD of 6 patients. The statistical significance was evaluated by two-ways analysis of variance (ANOVA) using SPSS statistical software package version 21 and the post-hoc individual comparisons were obtained by Duncan test. Differences were considered statistically significant at $p<0.05$.

Results

MGI and MPI: There was a statistically non-significant difference between groups. (table 1).

PD: there was a statistically non-significant difference between groups except after 6 months. PRF/metformin showed a lower PD than PRF alone (table 1).

Osstell ISQ Measurement: After surgery, there was a statistically a significant difference between groups. PRF/metformin showed a lower Osstell ISQ measurement than PRF alone (table 1). After 6 months, there was a statistically non-significant difference between groups.

RBD: At loading, there was a statistically a significant difference between groups. PRF/metformin showed a higher RBD measurement than PRF alone (table 2).

CBL in mm: At loading and at 6 months, there was a statistically a significant difference between groups. PRF/metformin a lower CBL measurement than PRF alone (table 2).

ACW: at loading and After 6 months, there was a statistically non-significant difference between groups.

Table 1: *Clinical parameters*

	Group 1		Group 2		p
	Mean	±SD	Mean	±SD	
Modified gingival index (MGI)					
1M after loading	.4700	.20575	.4900	.11972	1.000
3M after loading	.2900	.14491	.2500	.15811	0.529
6M after loading	.3600	.21705	.3700	.18886	0.912
Modified Plaque Index (MPI)					
1M after loading	.5100	0.1853	.5400	.08433	0.971
3M after loading	.3500	.15811	.3500	.15811	1.000
6M after loading	.4400	.1776	.4100	.19120	0.796
Probing Depth (PD)					
1M after loading	1.5300	.39735	1.4600	.29515	0.660
3M after loading	1.6900	.58013	1.7000	.44472	0.966
6M after loading	2.7300	.24967	2.0300	.35606	<0.001*
Osstell ISQ measurement					
After surgery	64.7000	5.43752	59.5000	2.50555	0.017*
At loading	69.5000	4.67262	74.1000	5.15213	0.051

p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

Group I: PRF

Group II: PRF/metformin

Table 2: *Radiographic parameters*

	Group 1		Group 2		p
	Mean	**±SD**	**Mean**	**±SD**	
Relative Bone density (RBD)					
after surgery	565.8000	147.92175	632.6000	110.89555	0.268
At loading	617.7000	112.28738	721.3000	104.59345	0.047*
6M after loading	669.9000	112.10159	744.2000	108.21152	0.149
Crestal Bone Loss (CBL) in mm					
At loading	.7100	.21318	.4100	.11972	0.001*
6 m after loading	1.4600	.27968	.8000	.21082	<0.001*
Alveolar Crest Width (ACW)					
Preoperative	3.5700	.55187	3.2400	.32387	0.120
After s.	6.0700	.62902	6.4500	.69001	0.214
At loadng	5.7500	.62048	6.0100	.52164	0.324
After 6m of loading	5.5800	.52662	5.7530	.55104	0.482

p: p value for comparing between the studied groups
*: Statistically significant at $p \leq 0.05$

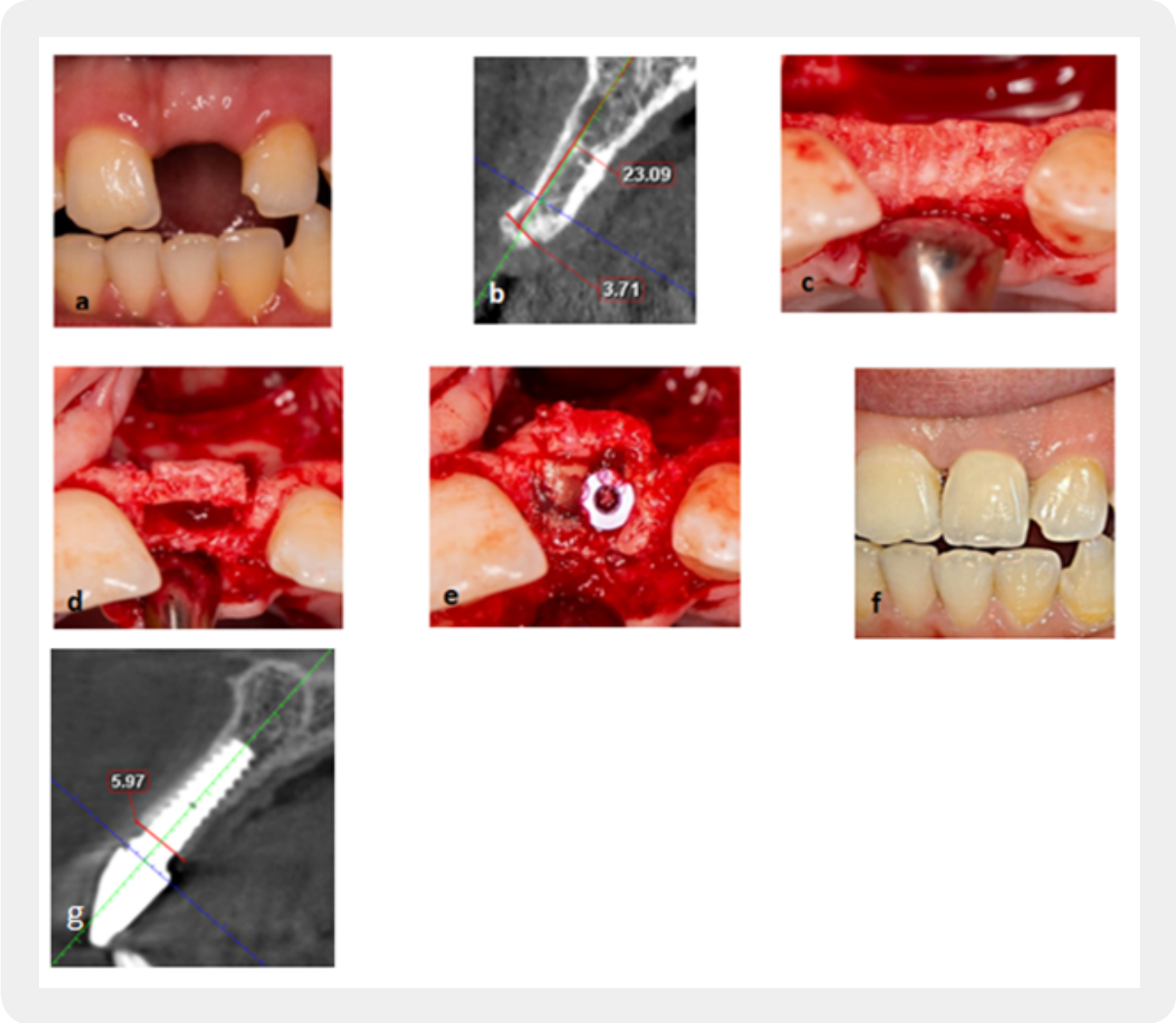

Figure 1: *SCT for tooth No. 21: (a) Preoperative situation before treatment, (b) CBCT sagittal section with vertical and horizontal measurements of available bone, (c) Available bone width after flap reflection, (d) Alveolar after splitting, (e) Implant and mixture of metformin and PRF filling peri-implant gap, (f) Final restoration after cementation. (g) CBCT sagittal section of implant in between the splitted cortical plates after 6 months of loading.*

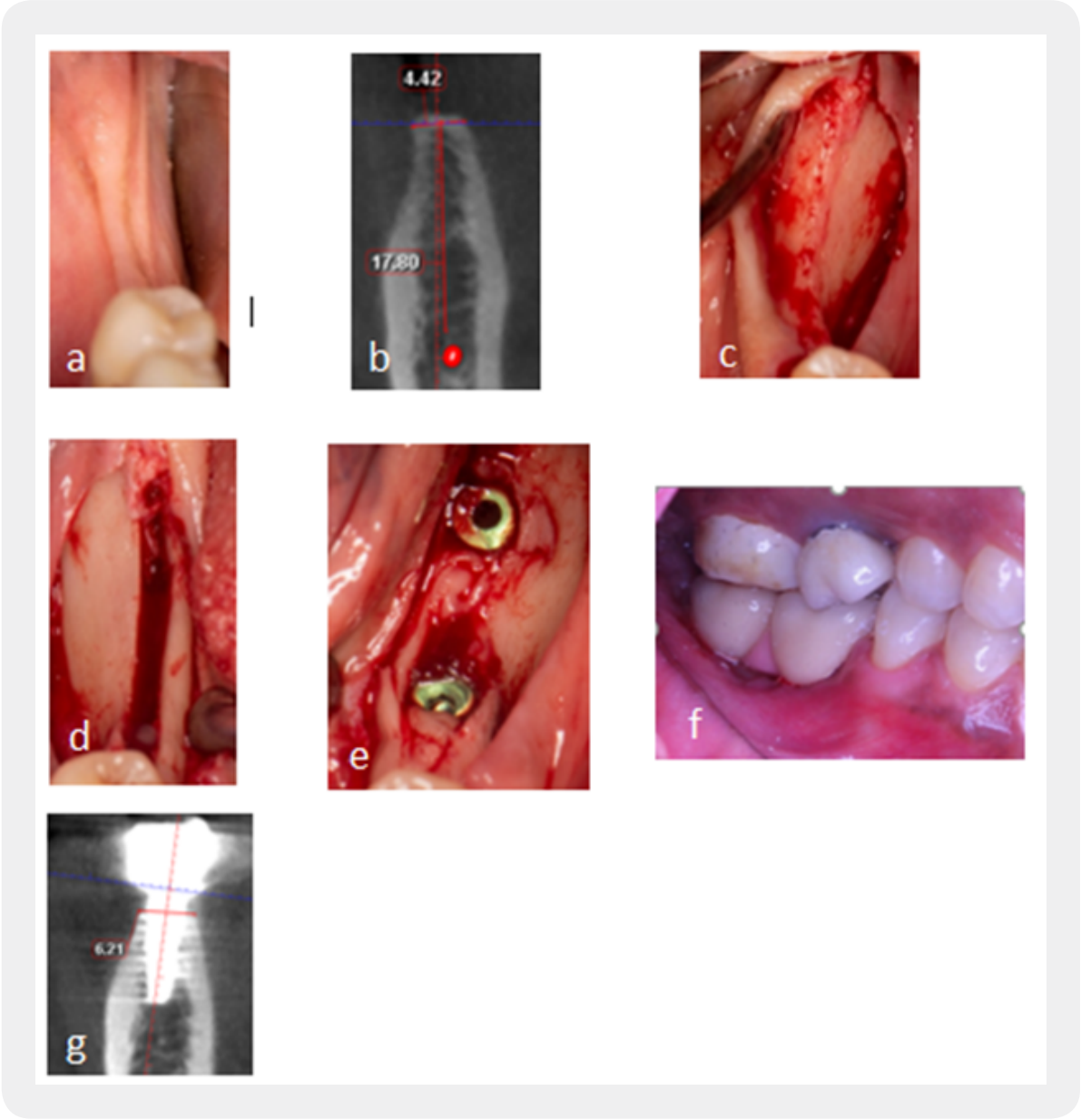

Figure 2: *SCT for tooth No. 46, and 47: (a) Preoperative situation before treatment, (b) CBCT sagittal section with vertical and horizontal measurements of available bone, (c) Available bone width after flap reflection, (d) Alveolar ridge after splitting, (e) Implant and PRE filling peri-implant gap, (f) Final restoration after cementation, (g) CBCT coronal section of implant in-between the splitted cortical plates after 6 months of loading*

Discussion

Many *in vitro* studies have pointed to bone anabolic effects of MF; increasing the bone-forming capacity of osteoblasts and decreasing the recruitment and bone-resorbing activity of osteoclasts [19,20]. It can protect osteoblasts against hypoxia-induced oxidative stress and alleviate hypoxia-enhanced apoptosis [21].

Moreover, upon local administration, osteoblasts can transport MF intracellularly, yet, decreasing drug dosage, increasing drug concentration, and at the same time avoiding adverse systemic side effects [22]. In the present study, narrow alveolar ridges were managed using crest split (Piezo-electric) and simultaneous implant placement while, the resultant peri-implant gaps were filled with PRF (group1) alone or mixed with 1% MF (group2).

All implants were successfully placed, and the mean ISQs measurements were reasonable and almost close in both tested groups at the time of surgery. On the other hand, at loading, mean ISQs increased in group 2 (74.80) more than in group 1 (69.50). This might denote relatively better osseointegration process around and on the implant surfaces in group 2. The results of the present study agree with the results Gonzalez *et. al.* [1], Demetriades *et al* [23] and Jang *et al*. [6] , who measured implant stability in alveolar ridge expansion. Concerning the encountered results of MF, there is agreement between the current results and the results of Sharma *et al*. [14] who inserted MF gel around 2 implants in 2 cases. Both implants achieved good secondary stability, suggesting the potential role of MF in enhancing osseointegration around dental implants.

Although, PRF showed less numerical values of implant ISQ, the implants in this group succeeded and there were no clinically significant differences of results among the investigated groups. This is in accordance with and Oncu *et al.* [9] who compared the stability of dental implants inserted in a one-stage surgical protocol with or without PRF application. In that study, PRF application increased implant stability during the early healing period, as evidenced by higher ISQ values. The authors suggested that, simple application of this material seemed to provide faster osseointegration

Group 2 compared to group1 showed significantly higher RBD as revealed by CBCT. This may be due to added densities of materials used to manufacture MF gel, which possibly resulted in false higher RBD measurements at the baseline, with little difference between the baseline and 6 months of loading measurements. The present study also agrees with the findings of Shaarawy and Fahmy [24], and Oncu *et al*. [9], who demonstrated that PRF enlarged both the amount and rate of new bone creation and enhanced bone-to-implant contact throughout the initial stages of healing.

Both studied groups showed a statistically significant increase in mean CBL at loading and 6 months after loading. The differences were statistically significant among both groups in favor of group 2. This may be interpreted clinically as the possible combined enhancement of efficacy of growth factors released by PRF and osteogenic potential of MF. Furthermore, these results may provide support for other studies that reported a reduction of bone resorption due to either topical [11,14,25] or systemic administration [26,27] of MF. The CBL values in this study in both groups were less than those recorded in the study of Tang *et al*. [28] and Garcez *et al* [29], who used chisels, drills, and a specific Extension Crest device for crest splitting. Mean CBL of the PRF group in the present study matches well with the results of Cortese *et al*. [30] who used flapless SCT with autologous PRF around placed implants.

Peri-implant probing around the implant was a good predictor of CBL in the present study, as the results of PD almost followed the same results of CBL in both groups. In the PRF group that had greater CBL, there was a greater and statistically significant increase in PD at 6 months after loading compared to the other groups. This supports the findings of Quirynen *et al* [31], and Bragger *et al.* [32].

It has been considered that any gain of ACW represents success of the SCT and depends on many factors including the diameter of the placed implants [33]. Both groups in the present study acquired significant ACW. The results at the time of loading were nearly equal to those of Waechter *et al.* [33], de Souza *et al.* [34], and Anitua *et al.* [5].

At all evaluation periods of the present study, patients in the two groups showed generally good oral hygiene habits, and a healthy state of the soft tissue around the implants, as well as no statistically significant difference in mean gingival and plaque indices scores. This may further emphasize the excellent biocompatibility of 1% metformin gel.

Conclusion

The results of the present study may provide a clinical evidence for the possible osteogenic potential of MF, indicated that, adding it to PRF which is known with short time stability may increase its therapeutic performance.

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