



XENOGRAFT VERSUS PRF ALONE OR MIXED WITH METFORMIN IN HORIZONTAL RIDGE AUGMENTATION WITH SPLIT-CREST TECHNIQUE FOR IMPLANT INSTALLATION

Abd Al-Aziz Kamal Mohamed Aboamo ^{1*}, Usama Mohammed Madany², Mahmoud Taha Eldestawy ³

ABSTRACT

Objective: To evaluate and compare the efficacy of xenograft and PRF alone, or mixed with metformin, in horizontal ridge augmentation with split-crest technique, for implant placement. **Patients & Methods:** Eighteen patients with narrow ridges were divided into Group 1: Patients received a split crest technique (SCT) with implant placement and xenograft. Group 2: Patients received an SCT with implant placement and PRF only. Group 3: Patients received an SCT with implant placement and metformin mixed with PRF. Implant stability was recorded immediately after implant placement, and at loading. Modified gingival index (mGI), modified plaque index (mPI), and probing depth (PD) were recorded and repeated after one, 3, and 6 months of prostheses. Alveolar crest width (ACW), crestal bone loss (CBL) as well as relative bone density (RBD) evaluated immediately after surgery, at the time of loading, and 6 months after loading. **Results:** The mean Alveolar Crest Width (ACW) measurements of the present study showed significantly higher ACW in (SCT / PRF) and (SCT / metformin / PRF) than (SCT / xenograft). CBL at loading and 6 months in favor of xenograft and metformin mixed with PRF groups. **Conclusion:** Compared to PRF alone, xenograft and 1% MF gel mixed with PRF might provide better implant stability, and less CBL. Both xenograft and 1%MF mixed with PRF may be used as peri-implant graft materials with expected comparable clinical outcomes.

KEYWORDS: PRF, metformin, ridge augmentation, split-crest, implant.

INTRODUCTION

Dental rehabilitation of edentulous patients with implants has become a common practice in the last few decades. Unfortunately, local conditions of some alveolar ridges such as a relevant horizontal deficit may be a challenge for implant placement. Several solutions were presented to overcome this challenge including the split crest technique (SCT)⁽¹⁾.

Crest split is used in cases of minimum ridge width of 2 mm to leave minimally 1 mm thickness of intact alveolar bone around the dental implant⁽²⁾. After completion of osteotomy, the facial and lingual walls are separated apart by using osteotomes, chisels, microsaws, and more recently piezoelectric devices. To make space for placement of the implant vertical osteotomy may be required. Then the implant is placed submerged at least 1 mm apical to the alveolar ridge crest⁽³⁾.

1. Assistant Lecturer, Dental Medicine, Periodontology, Oral Radiology and Diagnosis, Faculty of Oral and Dental Medicine, Cairo, Boys, Al-Azhar University.
2. Professor, Department of Oral Medicine, Periodontology, Oral Diagnosis, and Oral Radiology, Faculty of Dental Medicine, Cairo, Boys, Al-Azhar University.
3. Assistant Professor, Department of Oral Medicine, Periodontology, Diagnosis and Oral Radiology Faculty of Dental Medicine, Boys, Cairo, Al-Azhar University

• **Corresponding author:** abdel-azizabo-ammo.209@azhar.edu.eg

To enhance healing, the remaining voids of the expanded ridge are treated as in socket preservation to preserve and maintain the expanded ridge. These voids can be filled with bone graft or substitute⁽⁴⁾, as well as, autologous biological therapies such as plasma rich in growth factors⁽⁵⁾.

Autologous bone grafts are considered the gold standard, but unfortunately, site morbidity, as well as, utilizing more than one surgical site may limit its application. Xenografts are known to be osteoconductive, readily available, and risk-free of disease transmission⁽⁶⁾. Numerous studies have reported the effects of xenograft in crest split surgical procedures with immediate implant placement which showed long-term alveolar ridge width stability⁽⁷⁾.

Platelet-Rich Fibrin (PRF), in which, platelets have a higher concentration above the baseline level can regulate inflammation and stimulate the immune process of chemotaxis. This natural material seems to accelerate the physiological wound healing with or without bone grafts to accelerate new bone formation⁽⁸⁾. In clinical practice, it has already been largely applied as an inexpensive carrier and way to obtain many growth factors (GFs) in physiological proportions. The use of PRF as a sole filling material during a simultaneous split-crest augmentation technique and implantation stabilized a high volume of natural regenerated bone in the spaces unoccupied by the implants⁽⁹⁾.

Lately, metformin (MF), an antidiabetic agent, has been successfully used as a local drug delivery agent in chronic periodontitis patients. Literature has suggested that MF possesses the osteogenic potential and induces the growth of osteoblast precursor cells. Therefore, several human studies have reported the use of metformin alone or combined with PRF in the treatment of bony defects⁽¹⁰⁾.

Short time stability of PRF may not give it superiority over a commonly used bone graft like xenograft in promoting bone formation⁽¹¹⁾. Adding a medical formula with osteogenic

potential such as metformin to PRF may potentiate its therapeutic performance and may present a graft material comparable to bone substitutes, with the additional benefit of being cost-effective. Testing this hypothesis constituted the primary aim of work in the present clinical study.

PATIENTS AND METHODS

In this study a total of 30 implants were inserted in 18 patients, 8 males, and 10 females, ranging in age from 23 to 45 years with an average of 38.7 years. 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 Proface™ 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) were used, 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 divided into three groups using a random number table and each group was dedicated after receiving an SCT by ultrasonic bone surgery with implant placement and use of xenograft (**Group 1**), PRF only (**Group 2**), and metformin mixed with PRF. (**Group 3**) as gap-filling materials.

Preparation of 1% metformin gel: MF gel was prepared as described by Mohapatra et al⁽¹²⁾ 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 $\geq 80^\circ\text{C}$, and mannitol was added to the solution formed. 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, Smithkline Beecham), one day before surgery as prophylactic. One tablet from Ibuprofen 400mg (ibuprofen 400 mg tab. SEDICO) and Paracetamol 500mg (Panadol Alexandria, GLAXO Smithkline) 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 2-3 mm shorter in-depth than the full length of the planned implant to ensure primary stability with a clearance of 1 mm 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 pre-implant size. Then the implant (J dental care

two-stage implant system) was placed submerged at least 1 mm apical to the alveolar ridge crest. The gaps between or around dental implants were filled with Xenograft in group 1, PRF in group 2 and 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⁽¹³⁾ (MGI), modified plaque index⁽¹³⁾ (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 ridge width, crestal bone loss as well as

bone density. The gray values of the 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 \pm SD of 6 patients. The statistical significance was evaluated by two-way 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

Demographics:

In this study a total of 39 implants were inserted in 24 patients, 10 males, and 14 females, ranging in age from 23 to 45 years with the average of 38.7 years. The patients were divided into three groups using a random number table and each group was dedicated to xenograft (group 1), PRF grafting (group 2), MF mixed with PRF (group 3).

The group 1 included 4 males and 4 females, 6 implants in mandible, and 7 implants in the maxilla. Group 2 included 3 males and 5 females, 5 implants in the mandible, and 8 implants in the maxilla. Group 3 included 3 males and 5 females, 7 implants in the mandible, and 6 implants in the maxilla.

Modified gingival index (MGI)

The intragroup differences reached the statistically significant level ($p < 0.05$) at the last follow-up period only. On the contrary, the intergroup differences of the three groups were statistically insignificant (Table 1).

Modified Plaque Index (MPI)

Each group showed a statistically significant decrease ($p < 0.05$) from 1 to 6 months. In contrast, the intergroup differences were statistically insignificant (Table 1).

Probing Depth (PD)

All intragroup differences were statistically significant ($p < 0.05$). 6 months after loading, group 2 showed higher and statistically significant ($p < 0.05$) PD compared to the other two groups that exhibited almost close values (table 1).

Osstell ISQ measurement

All groups showed a statistically significant ($p < 0.05$) increase in the mean Osstell ISQ measurements at baseline and loading. The differences were non-statistically significant between group 1 and group 3. On the other hand, in group 2, Osstell ISQ mean values were significantly less than in group 1 and group 3 (table 1).

Relative Bone density (RBD)

The intragroup differences reached a statistically significant value ($p < 0.05$) at baseline and 6M after loading time intervals of the study. On contrary, the intergroup differences were non statistically significant at baseline and 6M after loading between group 1, and group 2 but it was statistically significant between group 2 and the other two groups in favor of group 2 (table 2).

Crestal Bone Loss (CBL) in mm

The intergroup differences reached the statistically significant level ($p < 0.05$) between group 2 and the other two groups, at time intervals in favor of group 1 and group 3. On contrary, the intergroup differences were non-statistically significant between-group 1, and group 3 at different time intervals (table 2).

Alveolar Crest Width (ACW)

The intergroup differences were non statistically significant at the different time intervals of the study, only, at loading, as well as 6 months thereafter, group 2 showed significantly less ACW than the other 2 groups. On the other hand, the intragroup differences were statistically significant at loading only for group 1 and group 3. Then, at 6 months after loading, the three groups revealed an insignificant decrease and were still maintaining the significant gain in ACW (table 2).

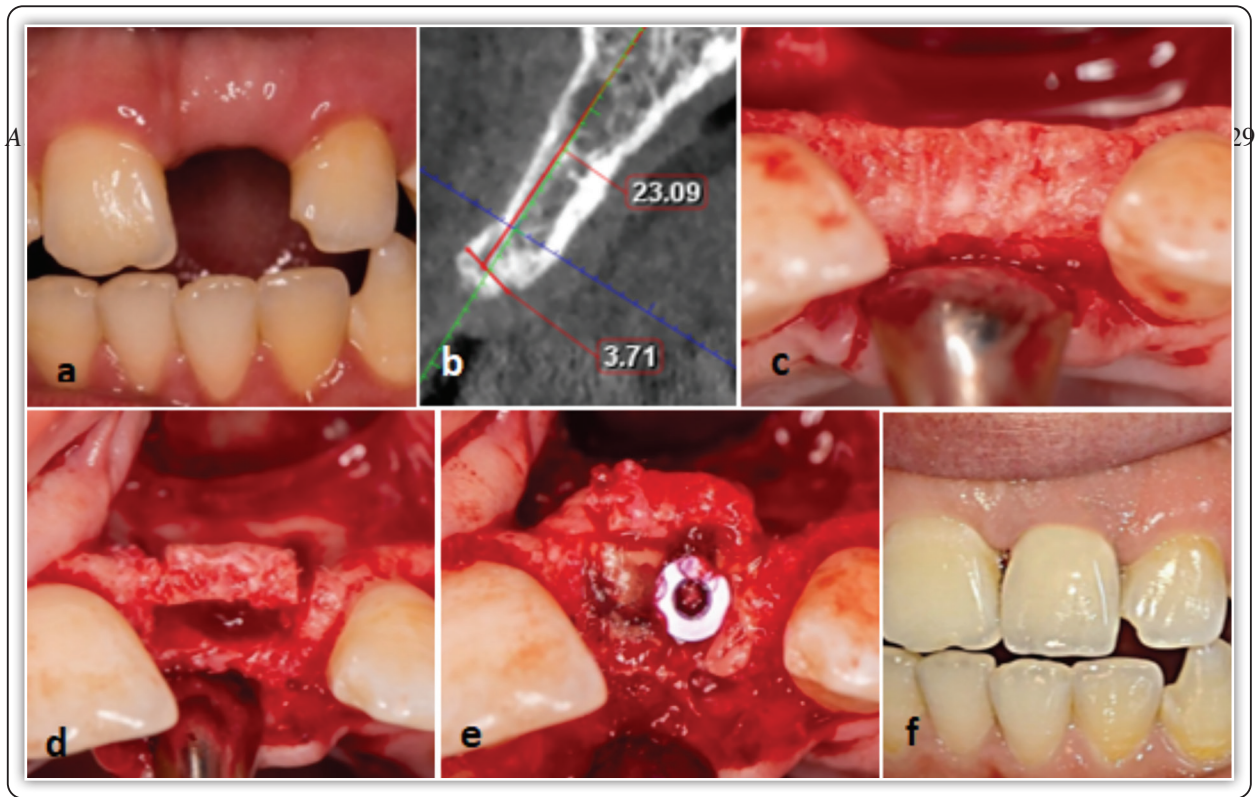


FIG (1) SCT for tooth No. 21: (a) Preoperative situation before treatment, (b) CBCT sagittal section with vertical and horizontal measurements of available bone, (c) Available bone width after flap reflection, (d) Alveolar ridge after splitting, (e) Implant and mixture of MF + PRF filling peri-implant defect, (f) Final restoration after cementation.

TABLE (I) Comparison between studied groups according to Clinical parameters

	Group I		Group II		Group III		p
	Mean	±SD	Mean	±SD	Mean	±SD	
Modified gingival index (MGI)							
1M after loading	0.5200	0.19322	0.4700	0.20575	0.4900	0.11972	0.818
3M after loading	0.2800	0.17512	0.2900	0.14491	0.2500	0.15811	0.845
6M after loading	0.3700	0.18886	0.3600	0.21705	0.3700	0.18886	0.992
Modified Plaque Index (MPI)							
1M after loading	0.5400	0.05164	0.5100	0.18529	0.5400	0.08433	0.817
3M after loading	0.3500	0.15811	0.3500	0.15811	0.3500	0.15811	1.000
6M after loading	0.4300	0.17029	0.4400	0.17764	0.4100	0.19120	0.931
Probing Depth (PD)							
1M after loading	1.3700	0.22632	1.5300	.39735	1.4600	0.29515	0.529
3M after loading	1.6600	0.23190	1.6900	.58013	1.7000	0.44472	0.978
6M after loading	1.9800	0.56135	2.7300	.24967	2.0300	0.35606	0.000
Osstell ISQ measurement							
After surgery	60.2000	2.29976	64.7000	5.43752	59.5000	2.50555	0.008
At loading	74.8000	5.59365	69.5000	4.67262	74.1000	5.15213	0.060

Group I: xenograft Group II: PRF Group III: PRF/metformin

p: p-value for comparison between the three groups

TABLE (2) Comparison between studied groups according to Radiographic parameters

	Group I		Group II		Group III		p
	Mean	±SD	Mean	±SD	Mean	±SD	
Relative Bone density (RBD)							
after surgery	643.3000	168.20758	565.8000	147.92175	632.6000	110.89555	0.440
At loading	645.1000	144.60556	617.7000	112.28738	721.3000	104.59345	0.163
6M after loading	749.5000	169.63638	669.9000	112.10159	744.2000	108.21152	0.341
Crestal Bone Loss (CBL) in mm							
At loading	0.4600	0.15055	0.7100	0.21318	0.4100	0.11972	0.001
6 m after loading	0.7900	0.22828	1.4600	0.27968	0.8000	0.21082	0.000
Alveolar Crest Width (ACW)							
Preoperative	3.2100	0.27669	3.5700	0.55187	3.2400	0.32387	0.104
After.	6.5900	0.69514	6.0700	0.62902	6.4500	0.69001	0.220
At loading	6.0700	0.40565	5.7500	0.62048	6.0100	0.52164	0.362
After 6m of loading	5.7730	0.53827	5.5800	0.52662	5.7530	0.55104	0.682

Group I: xenograft Group II: PRF Group III: PRF/metformin

p: p-value for comparison between the three groups

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. It can protect osteoblasts against hypoxia-induced oxidative stress and alleviate hypoxia-enhanced apoptosis⁽¹⁴⁾. 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⁽¹⁵⁾. 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 xenograft (group1), PRF (group2) alone, or mixed with MF (group3).

All implants were successfully placed and the mean ISQs measurements were reasonable and almost close in all groups at the time of surgery 60.20,

64.70, and 59.50 for group 1, group 2, and group 3 respectively). At loading, mean ISQs increased but were still higher in group1 (74.80) and G3 (74.10) than in group 2 (69.50), possibly denoting a relatively better osseointegration process. Concerning xenograft, the results of the present study agree with the results of Gonzalez et. al.⁽¹⁶⁾, Demetriades et. al.⁽¹⁷⁾, and Jang et al⁽¹⁸⁾. Concerning the encountered results of MF, they agree with the results of Sharma et al⁽¹⁹⁾ who inserted MF gel around 2 cases with good secondary stability, suggesting the potential role of metformin 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 objective clinical differences with the other investigated groups. This agrees with Oncu et al⁽⁹⁾ who suggested that simple application of this material seemed to provide faster osseointegration.

Group 1 and group 3 compared to group 2 showed significantly higher relative bone density (RBD) as revealed by CBCT. This may be due to higher densities of xenograft particles and the materials used to manufacture MF gel which gave 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 finding of Shaarawy and Fahmy⁽²⁰⁾ 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. On the other hand, the debatable issue, whether xenograft is truly resorbable or not⁽²¹⁾ may give an advantage for MF mixed with PRF as a graft material over xenograft, as both components seem to be completely biodegradable⁽²²⁾.

All studied groups showed a statistically significant increase in mean CBL at loading and 6 months after loading. The differences were almost close and non-statistically significant between the Xenograft group and MF mixed with the PRF group, and statistically significant among both groups and PRF group. 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⁽²²⁻²⁵⁾ or systemic administration⁽²⁶⁾ of MF. The CBL values in this study in all groups were less than those recorded in the study of Tang et al⁽²⁷⁾ and Garcez et al⁽⁷⁾, 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⁽²⁸⁾ who used the advantage of SCT with the use of autologous PRF around immediate implant placement in flapless SCT.

Peri-implant probing around the implant was a good predictor of crestal bone loss in the present study, as the results of pocket depths almost followed the same results of CBL in the three 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 M et al⁽²⁹⁾, and Bragger U. et al⁽³⁰⁾.

The three groups in the present study acquired significant ACW. The results at the time of loading were nearly equal to those of Waechter et al⁽³¹⁾, de Souza et al⁽³²⁾, and Anitua et al⁽³³⁾. At all evaluation periods of the present study, patients in the three 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 the used materials including 1% metformin gel.

CONCLUSION

The results of the present study may provide clinical evidence for the possible osteogenic potential of MF, indicating that, adding it as 1% gel to PRF, which is known with short time stability, may increase its therapeutic performance and may present a graft material comparable to a commonly used bone substitute as xenograft.

REFERENCES

1. Tolstunov L. Classification of the alveolar ridge width: implant-driven treatment considerations for the horizontally deficient alveolar ridges. *Oral Implantology J.* 2014;40:365-70.
2. Goyal M, Mittal N, Krishan Gupta G, Singhal M. Ridge augmentation in implant dentistry 2015. 94-112 p.
3. Tolstunov L, Hicke B. Horizontal augmentation through the ridge-split procedure: a predictable surgical modality in implant reconstruction. *Clinical oral implants research J.* 2013;39:59-68.
4. Sethi A, Kaus T. Maxillary ridge expansion with simultaneous implant placement: 5-year results of an ongoing clinical study. *International Journal of Oral Maxillofacial Implants.* 2000;60:37-42.
5. Shibuya Y, Yabase A, Ishida S, Kobayashi M, Komori TJKJMS. Outcomes and treatments of mal fractures

- caused by the split-crest technique in the mandible. 2014;60(2):E37-42.
6. Sheikh Z, Hamdan N, Ikeda Y, Grynypas M, Ganss B, Glogauer M. Natural graft tissues and synthetic biomaterials for periodontal and alveolar bone reconstructive applications: a review. *Biomaterials research J.* 2017;21:1-20.
 7. Garcez-Filho J, Tolentino L, Sukekava F, Seabra M, Cesar N, Araújo M. Long-term outcomes from implants installed by using split-crest technique in posterior maxillae: 10 years of follow-up. *Clinical Oral Implants Research J.* 2015;26:326-31.
 8. Jang E, Park J, Kweon H, Lee K, Kang S, Baek D, et al. Restoration of peri-implant defects in immediate implant installations by Choukroun platelet-rich fibrin and silk fibroin powder combination graft. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, Endodontology J.* 2010;109(6):831-6.
 9. Oncu E, Alaaddinoglu E. The effect of platelet-rich fibrin on implant stability. *International Journal of Oral Maxillofacial Implants J.* 2015;30:578-82.
 10. Pradeep A, Nagpal K, Karvekar S, Patnaik K, Naik S, Guruprasad C. Platelet-rich fibrin with 1% metformin for the treatment of intrabony defects in chronic periodontitis: a randomized controlled clinical trial. *Journal of periodontology.* 2015;86:729-37.
 11. Sam G, Vadakkekuttikal R, Amol N. In vitro evaluation of mechanical properties of platelet-rich fibrin membrane and scanning electron microscopic examination of its surface characteristics. *Indian Society of Periodontology J.* 2015;19:32-6.
 12. Mohapatra M, Parikh R, Gohel M. Formulation, development and evaluation of patient friendly dosage forms of metformin, part-II: Oral soft gel formulation, development and evaluation of patient friendly dosage forms of metformin. *Pharm J.* 2008;2:172-6.
 13. Mombelli A, Van M, Schurch E, Lang N. The microbiota associated with successful or failing osseointegrated titanium implants. *Oral microbiology immunology J.* 1987;2:145-51.
 14. Lai E, Yang C, Lin S, Wang H, Kok S, Hong C, et al. Metformin Ameliorates Periapical Lesions through Suppression of Hypoxia-induced Apoptosis of Osteoblasts. *Journal of endodontics.* 2018;44:1817-25.
 15. Ma L, Wu X, Ling E, Wang D, Liu H. The transmembrane transport of metformin by osteoblasts from rat mandible. *Archives of Oral Biology J.* 2009;54:951-62.
 16. Gonzalez G, Monje F, Moreno C. Alveolar split osteotomy for the treatment of the severe narrow ridge maxillary atrophy: a modified technique. *International journal of oral maxillofacial surgery* 2011;40:57-64.
 17. Demetriades N, Park Ji, Laskarides CJJoOI. Alternative bone expansion technique for implant placement in atrophic edentulous maxilla and mandible. *Journal of Oral Implantology.* 2011;37(4):463-71.
 18. Jang E-S, Park J-W, Kweon H, Lee K-G, Kang S-W, Baek D-H, et al. Restoration of peri-implant defects in immediate implant installations by Choukroun platelet-rich fibrin and silk fibroin powder combination graft. 2010;109(6):831-6.
 19. Sharma H, Sharma A. Soft tissue complications associated with the application of 1% metformin gel around dental implants: A report of two cases. *The Pharma Innovation J.* 2018;7:694-6.
 20. Shaarawy M, Fahmy A. Evaluation of two different grafting materials used during immediate post-extraction implant placement for retaining mandibular overdentures. *Egyptian dental journal.* 2013;59:1631-41.
 21. Piattelli M, Favero GA, Scarano A, Orsini G, Piattelli A. Bone reactions to anorganic bovine bone (Bio-Oss) used in sinus augmentation procedures: a histologic long-term report of 20 cases in humans. *The International journal of oral & maxillofacial implants.* 1999;14(6):835-40.
 22. Rao NS, Pradeep A, Kumari M, Naik SB. Locally delivered 1% metformin gel in the treatment of smokers with chronic periodontitis: A randomized controlled clinical trial. *Journal of periodontology.* 2013;84(8):1165-71.
 23. Pradeep A, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad CJJop. Platelet-rich fibrin with 1% metformin for the treatment of intrabony defects in chronic periodontitis: a randomized controlled clinical trial. 2015;86(6):729-37.
 24. Mushtaq I, Shukla P, Malhotra G, Dahiya V, Kataria P, Joshi CSJIJoOC, et al. Comparative evaluation of 1% metformin gel as an adjunct to scaling and root planing in the treatment of chronic periodontitis with scaling and root planing alone: a randomized controlled clinical trial. 2018;6(2):79-88.
 25. Kurian IG, Dileep P, Ipshita S, Pradeep ARJJoi, dentistry c. Comparative evaluation of subgingivally-delivered 1% metformin and Aloe vera gel in the treatment of intrabony defects in chronic periodontitis patients: A randomized, controlled clinical trial. 2018;9(3):e12324.

26. Losada E, Soldevila B, Ali MS, Martínez-Laguna D, Nogués X, Puig-Domingo M, et al. Real-world antidiabetic drug use and fracture risk in 12,277 patients with type 2 diabetes mellitus: a nested case-control study. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*. 2018;29(9):2079-86.
27. Tang YL, Yuan J, Song YL, Ma W, Chao X, Li DHJCOIR. Ridge expansion alone or in combination with guided bone regeneration to facilitate implant placement in narrow alveolar ridges: a retrospective study. 2015;26(2):204-11.
28. Cortese A, Pantaleo G, Amato M, Howard CM, Pedicini L, Claudio PP. Platelet-Rich Fibrin (PRF) in Implants Dentistry in Combination with New Bone Regenerative Flapless Technique: Evolution of the Technique and Final Results. *Open medicine (Warsaw, Poland)*. 2017;12:24-32.
29. Quirynen M, Naert I, S V. Fixture design and overload influence marginal bone loss and future success in the Brånemark® system. *Clinical oral implants research J*. 1992;3(3):104-11.
30. Bragger U, Hafeli U, Huber B, Hämmerle C, Lang N. Evaluation of postsurgical crestal bone levels adjacent to non-submerged dental implants. *Clinical Oral Implants Research J*. 1998;9(4):218-24.
31. Waechter J, Leite F, Nascimento G, Carmo F, Faot F. The split crest technique and dental implants: a systematic review and meta-analysis. *International Journal of Oral Maxillofacial Surgery J*. 2017;46(1):116-28.
32. de Souza CSV, de Sá BCM, Goulart D, Guillen GA, Macêdo FGC, Nória CFJJoM, et al. Split Crest Technique with Immediate Implant to Treat Horizontal Defects of the Alveolar Ridge: Analysis of Increased Thickness and Implant Survival. 2020:1-8.
33. Anitua E, Begona L, Orive G. Two-stage split-crest technique with ultrasonic bone surgery for controlled ridge expansion: a novel modified technique. *Oral Surgery, Oral Medicine, Oral Pathology Oral Radiology, and Endodontology J*. 2011;112(6):708-10.