Use of Leukocyte-and Platelet-Rich Fibrin for Bone Regeneration: A Systematic Review

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Introduction: Leukocyte- and platelet- rich fibrin (L-PRF) is a fibrin matrix in which the platelet cytokines, growth factors and cells are trapped and this material has been recruited in reconstruction of various defects. The aim of this study was to systematically review of the published data on the effectiveness of using L-PRF on regeneration of bone defects in oral and maxillofacial surgeries. **Materials and Methods:** Medline and Cochrane Central databases were searched for related articles up to and including August 2015. Being English, having ≥ four weeks follow-up, and clinical, radiographic, histological and histomorphometric assessments were the inclusion criteria. **Results:** Twenty-four animal studies and 45 human trials were included that reported the rate of new bone formation (NBF). Also, 38 human reports with low levels of evidence to list evaluating various applications of L-PRF in oral and maxillofacial reconstructions were assessed. Using L-PRF either solely or mixed in human trials was evaluated and divided into six groups of sinus floor augmentation and guided bone regeneration (GBR) technique, socket preservation, periodontal intra-bony defects (PID) regeneration, peri-apical and endo-periodontal defects treatment, peri-implant bone regeneration and treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Moreover, other uses of L-PRF with bone regeneration purposes in oral and maxillofacial surgeries were discussed. **Conclusion:** As a consequence, although L-PRF either solely or mixed showed challengeable outcomes in animal studies, it was shown to be effective used to accelerate and enhance new bone formation in human studies. However, future clinical trials in some treatment areas are needed with larger sample sizes and long follow-ups to arrive at an evidence-based conclusion.

Keywords: Leukocyte- and platelet- rich fibrin; Guided bone regeneration; Bone tissue engineering; Bone defects; Sinus floor augmentation

Introduction

Reconstruction of bone defects is challenging in oral and maxillofacial surgery (1, 2). One of the challenges facing clinical researchers in this field is the development of bioactive additives like platelet concentrates to regulate inflammation and enhance the healing process (3, 4). Choukroun *et al.*, introduced leukocyte- and platelet- rich fibrin (L-PRF) as a bioactive surgical additive to regulate inflammation and reduce the healing time (3). L-PRF is a new generation of platelet concentrates that is not only inexpensive and natural, but also does not require any biochemical modifications (anticoagulant, bovine thrombin or calcium chloride are not required) compared to other platelet concentrations (4-6). L-PRF is a fibrin matrix in which the platelet cytokines, growth factors and cells are trapped and can be released during a certain period of time (7). Also, it may be used as a resorbable membrane (8).

According to the literature, L-PRF has been employed to improve the rate of bone regeneration in sinus floor augmentations (11), ridge augmentation and guided bone regeneration (GBR) (12), socket preservation (13) and treatment of periodontal defects (15) and endodontic lesions (15).

Xuan *et al.,* revealed that L-PRF membrane had a significant effect on new bone formation (NBF) in sinus floor augmentation in dogs (9). L-PRF clots reduced probing depths and gained significantly greater clinical attachment in periodontal defects (10). However, Tatullo *et al.,* demonstrated that sinus floor augmentation of 60 patients using mixture of L-PRF and natural bovine bone mineral (NBBM) had less NBF histologically compared to the use of NBBM alone (11). Knapen *et al.*, showed less NBF by the application of L-PRF alone or mixed with NBBM in calvarial defects in rabbits compared to empty defects (12). Closure of alveolar clefts with symphyseal bone graft (13), closure of bone exposure in bisphosphonate-related osteonecrosis of the jaw (14), bone healing in combined endodontic periodontal lesion (15) and regeneration of aggressive periodontitis lesions (16) are

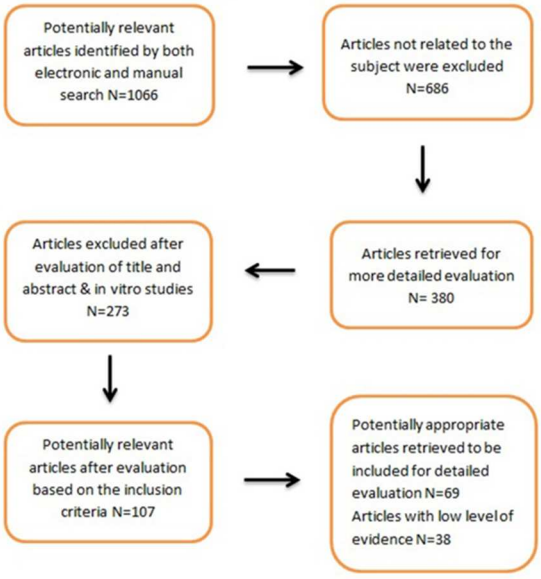

Figure 1. Flow diagram of study selection

other applications of L-PRF reported in the literature; but reports are contradictory and inconclusive (24). Therefore, that the use of L-PRF either solely or mixed with other bone grafts in every oral and maxillofacial bone defects can be an effective approach was our hypothesis. So that, the purpose of this study was to systematically review the effects of L-PRF on bone regeneration, first in animal models which are developed for preclinical studies on bone regeneration, and then in various human oral and maxillofacial surgeries which have been categorized for the current study.

Materials and Methods

Search strategy

This systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (17). Electronic search for published papers up to and including August 2015 was done in Medline (accessed through PubMed) and Cochrane Central databases. The following terms were searched alone and in combination using Boolean operators: "platelet rich fibrin", "bone", "bone substitute material", "bone transplantation", "bone regeneration", "bone augmentation", "periodontal defect", "apical lesion", and "maxillofacial surgery" (Figure. 1). Online studies which were published electronically were also considered in case of accordance to our criteria of this study. Besides, we have manually searched the below listed journals: Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, Journal of Oral and Maxillofacial Surgery, The International Journal of Oral & Maxillofacial Implants, Journal of Periodontology and Journal of Clinical Periodontology.

Study selection

Bone defects in which L-PRF was used as a membrane or clot for reconstruction, were considered as the test group. Bone defects in which bone graft or bone substitute materials without L-PRF were used were considered as the positive controls, and defects that were left empty were considered as the negative controls. The inclusion criteria were: 1) English papers 2) follow-up period of four weeks or more and 3) reporting clinical, radiographic and histological findings. Authors had tried to do not miss any papers of using L-PRF regarding bone regeneration purposes related to inclusion criteria. Also, studies with few cases were included as studies with low level of evidence.

Data extraction

A data extraction form was designed to collect data on the type of materials used, membranes, number of patients and samples, data evaluation methods, the follow-up periods, and the outcomes. Descriptive results of selected studies were extracted and collected in tables separately according to the technique applied for using L-PRF in surgeries with different indications for bone regeneration.

Results

Animal trials

Table 1 shows 24 studies conducted on rats (18-20), rabbits (12, 21-32), dogs (9, 33-36) , pigs (37, 38) and sheep (39). Defects were created in calvarium in 12 studies (12, 18-25, 27, 29, 31), in the tibia in four (26, 28, 37, 39), in the sinus in two (9, 34), in dental sockets in two (33, 38), in femur in two (32, 35), in mandible in one (30) and as an alveolar cleft in one study (36). The sacrificing times had started from one week (22) and finished to six months (9, 36) post-operatively. In 15 studies, L-PRF was used as a mixture with tricalcium phosphate (TCP) (27, 37), biphasic calcium phosphate (BCP) (32, 39), hydroxyapatite (31), NBBM (12, 20, 22), autologous bone graft (ABG) (36), deproteinized bovine bone (DBB) (23), tooth ash (TA) (35), silk fibroin powder (SFP) (28, 29), bone marrow stromal cells (BMSCs) (19, 36), and epithelialized palatal free graft (FGG) as an autologous membrane (38). In six studies, L-PRF was used as a sole grafting material (21, 25, 26, 30, 33, 34). One study used L-PRF membrane in conjunction with titanium barriers for GBR (25). Furthermore, one study compared L-PRF membrane with a commercial one (9). With regard to the preparation methods, Tunali *et al.*, evaluated titanium-prepared PRF (T-PRF) membranes prepared in titanium tubes in comparison with Chouckroun's preparation method in glass tubes (24) (Table 1). In terms of storage of L-PRF, Li *et al.,* compared lyophilized PRF with fresh PRF for use in calvarium defects in rats (18) (Table 1).

In 18 studies, the rate of NBF was reported mainly based on histomorphometric analysis (HA), while others performed histological (24) and stereology assessments (37), micro computed-tomography (CT) scans (19, 33) and quantitative CT (qCT) (32, 36) based on bone mineral density measurement (Hunsfield unit). According to HA, the lowest percentage of NBF was observed in L-PRF mixed with NBBM and reported to be 5.00 ±3.74% after one week in calvarial defects of rabbit model (22), whereas the highest percentage was 87.5±9.15% and observed after eight weeks in peri-implant bone defects created in the femur of dog model receiving a mixture of L-PRF and tooth ash powder (35). Moreover, when L-PRF clots were used as the sole grafting materials, the lowest percentage of NBF was demonstrated to be 7.4±0.7% after 10 days in tibial defects of sheep (39) , while the highest rate was 50.70±4.60% and observed after 12 weeks in calvarial defects of rabbits (21). According to qCT analysis, while subcortical and cortical area of defects treated with L-PRF alone was significantly more when compared to using mixture of L-PRF and BCP three months postoperatively, subcortical and cortical density of L-PRF sole grafting which were measured 982.66 ± 61.78 and 1028.27 ± 44.12 , respectively, showed non-significant difference (32).

Human trials

Maxillary sinus floor augmentation and GBR technique

Thirteen studies were aimed at evaluating the rate of bone regeneration in sinus floor augmentation (8, 11, 40-50) (Table 2). Follow-up appointments were between 106 days (11) and 1 year (47). HA was used in eight studies (11, 40, 42, 46, 48-51), while the evaluation methods of the other ones were both clinical and radiological (43-45, 47) or CT scan evaluations (41). Five studies used L-PRF clots mixed with NBBM (11, 42, 45), deproteinized bovine bone mineral (DBBM) (50) and FDBA(48). Five studies used L-PRF in sinus lift surgeries as the sole graft material (41, 43, 44, 46, 47), two of which used it with osteotome-mediated sinus floor elevation (OMSFE) technique (44, 47). Also, L-PRF membrane was compared with collagen membrane in three studies (8, 40, 49).

NBF of L-PRF was reported to be 33±5% after six months used as the sole graft material (46), but 37.06% after 150 days or 18.35%±5.62% after six months when mixed with NBBM (11, 42), 34.5 ± 5.7% after 7-10 months mixed with DBBM and 31.24% after four months mixed with FDBA (48). NBF by using L-PRF membrane varied from 17.0 (7.8-27.8)% after five months (8), 35.0±8.60% after six months (49) and 28.6±6.90% after seven to 11 months (40). There were no statistically significant differences between them and control groups; furthermore, the rate of residual graft material (RGM) was not significant between the two groups.

After sinus floor augmentation, dental implants were inserted immediately in six studies (41, 43-47, 52), but in the other seven studies it was performed in second surgeries (8, 11, 40, 42, 48, 50). Nine studies reported survival rates of inserted dental implants about 97.1% (47), 97.8% (44) and 100% (40, 41, 43, 45, 46, 49, 51) at least after 12 weeks (40) up to 6 years (43) postoperatively.

Eleven articles reported GBR techniques (53-58), sinus floor augmentation (52, 59, 60), 3-D augmentation of alveolar ridge using titanium mesh and bone morselizer (61) and vertical alveolar distraction technique (62) with low level of evidence (Table 3). For instance, a new minimally invasive GBR was reported for using L-PRF mixed with bone substitute materials in 11 patients and showed 2.4 to 5.1 mm vertical and 1.3 to 3.9 mm horizontal gain (57).

Socket preservation

Eleven studies evaluated the effectiveness of L-PRF on socket preservation (63-71) (Table 4); two of them had low level of evidence (67, 71) (Table 5). Socket preservation was performed in molar sites (66, 68-70, 72, 73), non-molar sites (64, 65, 69), and buccal bone plate dehiscence of the anterior maxilla (63). Methods of evaluation were clinical and radiographic (63, 65, 68-70, 73), serial radiovisiography (RVG) (66), technetium-99m methylene diphosphonate uptake(72) and both micro CT scans and histology (64). L-PRF was used as a sole graft material in eight articles in which the results of L-PRF group were not significantly better than controls (64-66, 68-70, 72, 73) (Table 4). According to a prospective randomized controlled study, even though a significant effect on intrinsic bone quality was observed, bone volume/ total volume (BV/TV) ratio gathered from micro-CT scans after eight weeks in L-PRF group was not significantly greater than L-PRF with mucosal flap or sham group (64). When L-PRF was mixed with corticocancellous porcine bone (CCPB) and collagen membrane (74), bone level significantly improved after five months in the distal sites (63) (Table 4).

Periodontal intra-bony defects regeneration

Seventeen studies were found regarding regeneration of periodontal intra bony defects (PID) (10, 75-87), horizontal defects(88) and grade II mandibular furcation involvement (89, 90) (Table 5). L-PRF was applied alone (10, 76, 78, 79, 82, 85-90) or mixed with DFDBA (77, 81), bovine porous bone mineral (BPBM) (75), nanocrystalline hydroxyapatite (NcHA)(83), bioactive glass (BG) (91) and 1% metformin (92). Follow-up

appointments were six months (75, 77, 83, 85-87, 91), nine months (76, 78, 79, 82, 88-90, 92), and one year (10, 81). Probing depth reduction (PDR), clinical attachment gain (CAG), radiologic bone fill (RBF) and defect depth reduction (DDR) were investigated. In 12 studies, the parameters significantly improved in follow-ups than base-line evaluations (10, 77, 81-83, 85-90, 92). Both PDR and CAG were significantly greater in case than in control groups in nine studies (10, 75, 77, 79, 81, 88-90, 92). In three studies, sole use of L-PRF was compared to using ABG(85), DFDBA(86) and enamel matrix derivatives (EMD) (87) in which both PDR and CAG were not significant between the understudy groups. All studies in which the RBF was evaluated showed a significant filling of defects radiographically using L-PRF compared to control groups (75, 76, 78, 79, 81, 89, 90, 92). DDR, also had significant enhancement in the L-PRF group (Table 5) (10).

Moreover, four studies with low level of evidence investigated the application of L-PRF according to the treatment of labial-cervical-vertical groove (LCVG) (93), generalized aggressive periodontitis (GAgP) (16) and intra-bony defects (Table 6) (94, 95).

Peri-apical and endo-periodontal defects treatment

Two clinical trials were conducted on using L-PRF as a sole material to manage periapical lesions and apico-marginal defects (Table 7) (96, 97). Singh *et al.,* reported complete bone regeneration of periapical lesions after six months (96). Also, Dhiman *et al.*, showed significant PDR but not CAG using sole L-PRF in treatment of apico-marginal defects after one year (97).

Fourteen studies reported some cases in which L-PRF was used for treatment of endodontic-periodontal lesions (15, 98-103), apical lesions (104, 105) and radicular cysts (106-110) with a low level of evidence (Table 8). For this purpose, L-PRF was used as the sole material (100, 102-104, 108), or mixed with iliac bone graft (110), hydroxyapatite (105), DFDBA (106), BG (15, 107) or β-TCP (109).

Peri-implant bone regeneration

Three randomized clinical trial used L-PRF alone in treatment of peri-implant bone defects (111), prevention of bone loss after dental implant insertion (112) and increasing stability of inserted dental implants in a drilled hole filled with L-PRF (Table 9) (113). One study reported healing of retrograde peri-implantitis using a mixture of a xenograft with L-PRF(114). Another study used L-PRF in immediate implant insertion after extraction of a fractured central incisor (Table 9) (115).

Treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ)

Three studies were found on the effect of L-PRF on the treatment of bisphosphonate-related osteonecrosis of the jaw (BRONJ) (14, 115-117) (Table 10). Two studies used L-PRF clot (116) and membrane(14) alone, and another study mixed with recombinant human bone morphogenetic protein 2 (rh-BMP2) (117).

Other uses of L-PRF for bone regeneration

According to bone regeneration purposes, three other studies were found. L-PRF mixed with DFDBA was used in a novel technique of ridge augmentation with long palatal connective tissue rolled pedicle graft (118) and auto-transplantation of an impacted central incisor (Table 11) (119). Moreover, a mixture of L-PRF and autogenous symphyseal graft was used in alveolar cleft treatment (13).

Discussion

Recently, applications of L-PRF have been presented in various studies for different purposes like regeneration of both hard and soft tissues (74), dental pulp revitalization (120) , tooth root regeneration (121), wound healing (122), treatment of articular cartilage defects (123), rejuvenating media for avulsed teeth (124), chronic lower-extremity ulcers (125), etc. The present study was a systematic review designed to appraise the available evidences regarding the effectiveness of L-PRF on regeneration of different bone defects in oral and maxillofacial surgeries. In this study, the effectiveness of L-PRF was discussed at first in animal models, then, was categorized and discussed in treatment of six different human bone defects according to the various surgeries and techniques finally the results of three studies with other bone defects and techniques were reviewed. Although Shah *et al.*, (126) have recently systematically reviewed the effect of sole L-PRF on periodontal intra bony defects, the current study has systematically reviewed the studies in which L-PRF was used either sole (n=12) or in combination with other bone grafts (n=5) in periodontal defects, in addition to six recent published clinical studies in 2015. Furthermore, we have discussed the results of a recent systematic review on application of L-PRF in sinus floor augmentation by Sherif *et al.,* (127) although due to the main aim of our study, the data were extracted differently and the results of five other clinical studies were also considered. However, due to co-application of L-PRF with various bone grafts and various quality of included studies, it was not feasible to meta-analyze the included studies.

Using L-PRF in animal models

Fourteen studies evaluated the L-PRF mixed with different bone grafts, but eight studies were conducted on using L-PRF alone. Among studies which evaluated mixtures of L-PRF, 12 indicated significant effect of adding L-PRF to ABG (23, 36), SFP (28, 29), TCP (27), NBBM (9, 20), TA (35), BCP (31, 32, 39) and BMSCs (19, 36), while, in the other studies, mixtures of L-PRF with TCP (37)

Table 1. Included animal studies, which used PRF in bone regeneration

	Number and type of animals	Defect location & size	Used materials	Evaluation methods	Bone gain
Pripatnanont *et al.* (30)	12, rabbit	Periosteal distraction (mandible)	Hyrax device (A) Hyrax device + L-PRF (B)	HA Micro-CT	NBF After 4 weeks: A: 23.21 ± 11.00%, B: 41.37 ± 7.57%* After 8 weeks: A: 33.25 ± 5.46%, B: 55.46 ± 10.67%*
Yuanzheng *et al.* (36)	20, dog	Unilateral alveolar cleft	ABG + BMSCs+ L-PRF (A) ABG+BMSCs(B) ABG+L-PRF (C) ABG (D)	Quantitative CT Histologic	Graft resorption after 6 mo.: A* vs. B,C,D B* vs. D & C* vs. D HA does not performed to report the NBF rate
Oliviera *et al.* (20)	48 rats	cranium, 5mm	Bio-Oss® L-PRF Comb.	HA	NBF After 30 days: L-PRF: 21.77% Bio-Oss®: 26.15% Comb.: 54.05%* After 60 days: L-PRF: 23.03% Bio-Oss®: 57.34%* Comb.: 63.58%*
Acar *et al.* (31)	20 rabbits	Calvarium, 6mm	HAp/BCP L-PRF Comb.	HA Micro-CT	NBF After 4 weeks: L-PRF: 13.86±5.26%, HAp/BCP: 14.81±4.72% , Comb.: 27.40±7.33%* After 8 weeks: L-PRF: 24.51±7.71%**, HAp/BCP: 24,50±3,87%**, Comb.: 39,10±8,10%*,**
Nacopoulos *et al.* (32)	15 rabbits	Femoral condyle	L-PRF L-PRF+BCP	Histologic Quantitative CT	After 3 mo.: Bone density : L-PRF+BCP* vs. L-PRF Cortical and subcortical areas: L-PRF+BCP* vs. L-PRF
Yilmaz *et al.* (37)	3 pigs	Tibia, 5mm	β-TCP L-PRF Comb.	Stereology	NBF after 12 weeks: β-TCP: 21.1 ±2.8µm2* L-PRF: 18.2 ±5.1 µm2*, β-TCP +PRF: 22.1±7.4 µm2*
Kim *et al.* (21)	12 rabbits	Calvarium, oval 10mm+15mm	PRP L-PRF CGF	HA	NBF: After 6 weeks: PRP: 36.86±4.86%* , L-PRF: 37.85±3.40%*, CGF: 39.18±2.46%* After 12 weeks: PRP:52.69±2.16%, L-PRF: 50.70±4.60%, CGF:57.52±2.48%
Li *et al.* (18)	A rat	Cranium CSBD	LPRF L-PRF: Fibrin gel	HA	After 6 weeks*: LPRF: 62.13±1.89%*, L-PRF: 43.91±1.35%*, Fibrin gel: 31.65±5.84%*
Yoon *et al.* (22)	10 rabbits	Calvarium 7mm	Bio-Oss®+ L-PRF Bio-Oss®	HA	NBF at 1st week: test: 5.00 ±3.74 control: 6.50±3.11 NS at 2nd week: test: 30.00±10.00 control: 40.00±10.00 NS at 4th week: test: 63.33±23.09 control: 51.67±12.58 NS
Xuan (9)	6 dogs	Sinus,-	Bio-Oss®+ Tisseel® Bio-Oss®+ L-PRF	HA	After 6 mo.: NBF: L-PRF: 41.8±5.9%*, Tisseel®: 31.3±6.4% OR: L-PRF: 43.5 ± 12.4% *, Tisseel®: 30.7 ± 7.9%
Srisurang *et al.* (38)	6 minipigs,	Dental socket,-	L-PRF FGG (control) Comb.	HA OD	After 12 weeks: NBF was higher in PRF than others. NS OD in L-PRF: 158.57±30.74*, FGG:108.59±29.99, Comb.: 111.69±21.36 & empty: 91.31±37.33
Hatakeyama *et al.* (33)	12 dogs	Dental socket,-	PPP PRP L-PRF	Micro-CT	Median area of NBF at 4th week (mm2): PPP: 5.85*, PRP: 3.66, L-PRF: 5.22* & control: 3.55. At 8th week: PPP: 7.52*, PRP: 4.50, L-PRF: 5.98 & control: 5.93
Jeong S. *et al.* (34)	6 dogs	Sinus 1+ 1.5 cm2	L-PRF	HA CT scan	The height of NBF around the implants in the sinus after 6 mo.: Buccal side:2.6±2.0 mm & Palatal side:1.3±1.8 mm
Pripatnanont *et al.* (23)	10 rabbits	Calvarium 10+10 mm	ABG (A) DBB (B) L-PRF (C) ABG+DBB (D) ABG+ L-PRF (E) DBB+ L-PRF (F) ABG+ DBB +PRF (G)	HA	NBF after 8 weeks: E: 38.03 ± 4.23%* was significantly higher from F: 13.067 ± 3.64%* & G: 22.63 ± 3.6%* and C: 18.81 ± 9.27%* And D: 21.29 ± 3.52% was significantly higher than B: 9.63 ± 5.47%
Tunali *et al.* (24)	6 rabbits	Calvarium 7mm	T-PRF	Histology	NBF were noted on the 15th day, 3 aspects on 30th day: inflammation (remaining membrane), granulation tissue & remodeling areas.
Knapen *et al.* (12)	18 rabbits	Calvarium 8mm	L-PRF Bio-Oss® Comb.	HA	NBF after 12 weeks: L-PRF: 24.11±6.57%**, Bio-Oss®: 21.15±7.24%**, Comb.: 21.42±7.37%** Empty: 25.77± 8.41%**
Honda *et al.* (19)	27 rat	Calvarium CSBD	L-PRF L-PRF+ BMSCs	Micro-CT	NBF in all the times: L-PRF+BMSCs*> L-PRF > empty

Bolukbasi *et al.* (39)	6 sheep	Tibia 5mm	BCP L-PRF Comb.	HA	NBF in Comb. after 10days:11.4±0.7*, 20days: 42.2±0.9* & 40days: 54.9±0.8* was significantly higher than BCP and L-PRF groups in that times.
Jeong K. *et al.* (35)	6 dogs	Femur (around implants), 8mm	TA (A) TA+ L-PRP (B) TA+PRF (C)	HA	NBF at 4th week (%): A: 57.9±22.79 B: 52.8±26.85, C: 78_8±6.95*, control: 38.3±15.84 NBF at 8th week (%): A: 70.8±11.11, B: 65.8±27.03, C: 87.5±9.15*, control: 59.5±9.24
Ozdemir *et al.* (25)	24 rabbits	Calvarium ,-	L-PRF Bio-Oss® 4BoneTM	HA	after 3 month, NBF in test : was significantly higher than 1 month & control group NBF at both times: L-PRF> Bio-Oss®>4BoneTM NS
Lee *et al.* (26)	8 rabbits	Tibia width:3.0mm, length:5.0mm	L-PRF	HA	After 8 weeks NBF in L-PRF:29.30%±7.50%* & in control :11.06%±8.94%
Kim *et al.* (27)	36 rabbits	Calvarium , 8mm	TCP+rhBMP2(A) TCP+ L-PRF (B) TCP (C)	HA	NBF at 2nd week: A: 4.8%, B: 11.4%*, C: 0% At 4th week: A: 22.3%, B: 27.3%*, C: 17.1% At 6th week: A: 28.0%, B: 37.4%*, C: 19.6% At 8th week: A: 30.3%, B: 41.5%*, C: 29.9%
Jang *et al.* (28)	10 rabbits	Tibia (around implants), 7mm	SFP+ L-PRF	HA	After 8 weeks NBF in test: 51.93 ± 27.90%* & in control : 11.67 ± 15.12% BIC in test: 43.07. 21.96%* & in control: 15.37. 23.84%
Lee *et al.* (29)	10 rabbits	Calvarium , 9mm	SFP+ L-PRF	HA	After 6 weeks NBF in test: 44.38 ± 17.00% & control: 36.59 ± 6.11 NS & after 12 weeks : 59.83 ± 10.92%* In control: 49.86 ± 7.49%

CT: Clinical trial, CR: Case report, RS: Retrospective study, RSMD: randomized split-mouth design, CS: Case series, NR: Not reported, HA: Histomorphometric analysis, NBF: new bone formation, NS: not significant, RGM: residual graft material, DBBM: deproteinized bovine bone mineral, ABG: autologous bone graft, CT scan: computed tomographic scan, HU: Hounsfield units, L-PRF: Leukocyte- and platelet-rich fibrin, BBG: Bovine bone graft, RCM: Resorbable collagen membrane, OMSFE: osteotome-mediated sinus floor elevation, BAOSFE: bone-added osteotome sinus floor elevation

Table 2. Included human studies using PRF in sinus floor augmentation

	Type of study	**Number of patients, sites, implants**	**Type of surgery**	**Used materials**	**Evaluation methods**	**Bone gain**	**Survival rate of implants (follow-up point)**
Tanaka *et al.* (50)	Preliminary study	4,4,-	Two stage	DBBM/L-PRF	HA	After 7-10 mo.: 34.5 ± 5.7%	-
Bosshardt *et al.* (40)	CT	12, 16, 16	Two stage	NanoBone + L-PRF NanoBone +RCM	HA	After 7-11 mo.: NBF in L-PRF (%): 28.6±6.90 RCM: 28.7±5.4 NS RGM in L-PRF (%): 25.7±8.8 RCM: 25.5±7.6 NS	100%, 12 weeks
Gassling *et al.* (8)	RSMD	6, 12 , 32	Two stage	Bio-Oss® +ABG+ L-PRF Bio-Oss® +ABG+ RCM	HA	After 5 mo. NBF in L-PRF:17.0 (7.8-27.8)% & RCM : 17.2 (8.5-24.2) % NS RGM in L-PRF(%): 15.9 (0.9-33.4)% & in RCM: 17.3 (0.7-33.5)% NS	100%,12 mo.
Tajima *et al.* (41)	CS	6, 9, 17	One stage	L-PRF (sole material)	CT scan	After 6 mo., the mean density of NBF around the implants : 323 ± 156.2 HU (185 to 713 HU)	100% , 6 mo.
Bölükbaşı *et al.* (49)	RS	25,32,66	Two stage	Bio-Oss®+ L-PRF BioOss®+RCM	HA	After 6 mo.: NBF in PRF (%):35.0±8.60 RCM: 32.97±9.71 NS RGM in L-PRF (%): 33.05±6.29, RCM: 33.79±8.57 NS	100%, 30 mo.
Tatullo *et al.* (11)	CS	60, 72, 240	Two stage	Bio-Oss®+ L-PRF Bio-Oss®	Histologic & clinical	Trabecular bone after 106 days in test : 22.79% & in control: 26.44% NS after 120days in test: 26.15% in control: 28.7% NS ater 150 days in test: 37.06% in control:38.97 NS	NR

Zhang *et al.* (42)	CS	10, 11, NR	Two stage	Bio-Oss®+ L-PRF Bio-Oss®	HA	After 6 mo., NBF in L-PRF vs. control: 18.35%±5.62% vs. 12.95%±5.33% NS RGM: 19.16%±6.89% vs. 28.54%±12.01% NS	NR
Simonpieri *et al.* (43)	CS	20, 23, 32	One stage	L-PRF (sole material)	Radiographic &clinical	After 6 mo., vertical bone gain was 10.4 ± 1.2 (range, 8.5 to 12 mm) & periimplant crestal bone height was stable.	100%, 6 year
Toffler *et al.* (44)	CS	110,138,138	One stage	L-PRF (sole material)	Radiographic &clinical	The mean increase in the height of implant sites by OMSFE/PRF was 3.4 mm (range, 2.5 to 5 mm).	97.8%
Inchingolo *et al.* (45)	CS	23,31,95	One stage	Bio-Oss®+ L-PRF	Radiographic &clinical	presence of an optimal PS of inserted implants & significant increase in the peri-implant bone density	100%, 6-9 mo.
Mazor (46)	CS	20,25,41	One stage	L-PRF(sole material)	Radiographic & HA	After 6 mo. all biopsies showed well organized and vital bone, NBF: 33±5%.	100%, 6 mo.
Diss *et al.* (47)	CS	20,-,35	One stage	L-PRF/ BAOSFE	Radiographic	The mean endosinus gain: mesial side: 3.5 ± 1.4 mm (max: 5.8, min:0.9) & distal side: 2.9 ± 1.6 mm (max:5.2, min:0.1)	97.1%, 1year
Choukroun *et al.* (48)	CS	NR, 9, NR	Two stage	FDBA+L-PRF FDBA	HA	Trabecular bone after 4 mo. in test: 31.24% & after 8 mo. in control: 30.36%	NR

L-PRF: Leukocyte- and platelet-rich fibrin, PeSPTT: Piezotome enhanced subperiosteal tunnel technique, GBR: Guided-bone regeneration, OMSFE: osteotome-mediated sinus floor elevation, VAD: Vertical alveolar distraction , NR: Not reported, PLGA: polylactic-co-glycolic acid, BCP: Biphasic calcium phosphate, TCP: Tricalcium phosphate, ABG: Aoutogenous bone graft, BHA: Bone hydroxyapatite, ASG: autogenous symphseal graft, CBCT: cone-beam computed tomography scan, BSM: Bone substitute material

Table 3. Included studies using L-PRF in GBR technique and bone augmentation

	Number of cases	Used material	Technique	Evaluation method	Bone gain	Survival rate of implants (follow-up point)
Angelo *et al.* (58)	82	PLGA coated BCP PLGA coated TCP PLGA coated TCP+ L-PRF	PeSPTT	Clinical (insertion torque value) CBCT	Superior biomechanical stability in PLGA coated TCP alone or combined with L-PRF	
Zhao *et al.* (60)	One	L-PRF	Two stage sinus lift	Clinical, radiographic & histologic	NBF observation and dental implants insertion after 6 months	
Toffler *et al.* (53)	Two	L-PRF membranes	GBR + Allogeneic cortical bone pins (2 mm in diameter in customized lengths)	CBCT	Provide both horizontal &vertical ridge augmentation at severely compromised implant sites	NR
Kanayama *et al.* (52)	Two	L-PRF (sole material)	One stage sinus augmentation & implantation	CT scan	HU valu at final follow-up was increased in case 1 to 1240 (corresponding to cortical Bone) & in case 2 to 675 (corresponding to porous cortical and fine trabecular bone)	100% ,12mo.
Montanari *et al.* (54)	One	L-PRF+ ABG+ BHA	GBR with 5 PRF membrane	CBCT	A predictable method of augmenting deficient alveolar ridges after 4 mo.	NR
Gowda *et al.* (61)	One	ASG+L-PRF	3-D augmentation of alveolar ridge using	Clinical	An increase in a ridge width of 2 mm and	NR

			titanium mesh and bone morselizer		height by 4-5mm after 4 mo.	
Kim *et al.* (55)	Two	L-PRF + BioCera®	GBR+ Double J technique	Histology	After 16 weeks: Presence of a substantial amount of osteoid tissues & vital bone, & infiltration of new bone to the grafted materials. Good esthetic &functional results after 6 mo. & 1year in both cases.	100%, 1year
Gupta *et al.* (67)	One	L-PRF+ BCP	Compromised extraction sockets preservation	Clinical & radiographic	satisfactory and successful regeneration after 6 mo.	
Vijayalakshmi *et al.* (56)	One	L-PRF+ BG+ resorbable membrane	GBR (fenestration around an implant)	Clinical	After 6 mo, buccolingual width of the ridge was 7 mm.	NR
Peck *et al.* (59)	Two	L-PRF	OMSFE	Clinical & radiographic	No pain or movement of implants was reported & NBF was observed	No report
Kocyigit *et al.* (62)	One	ASG+ L-PRF (at first step)	VAD to maintain the suitable bony height 3 months after first step	Clinical & radiographic	A total of 11 mm vertical height was gained with VAD & Sufficient bone volume and height were observed after 12-month follow-up period	NR
Peck *et al.* (59)	Two	L-PRF	Compromised extraction sockets preservation OMSFE	Clinical & radiographic	Successful alveolar ridge preservation & sinus floor augmentation	
Peck *et al.* (71)	One	L-PRF	Compromised extraction sockets preservation	Clinical & radiographic	Successful implant placement 6 weeks after tooth extraction	
Kfir *et al.* (57)	11	BSM+L-PRF	A new minimally invasive GBR	CT scan, 5 to 6 mo.	vertical gain: 2.4 to 5.1 mm & horizontal gain: 1.3 to 3.9 mm.	NR

L-PRF: Leukocyte- and platelet-rich fibrin, PeSPTT: Piezotome enhanced subperiosteal tunnel technique, GBR: Guided-bone regeneration, OMSFE: osteotome-mediated sinus floor elevation, VAD: Vertical alveolar distraction , NR: Not reported, PLGA: polylactic-co-glycolic acid, BCP: Biphasic calcium phosphate, TCP: Tricalcium phosphate, ABG: Aoutogenous bone graft, BHA: Bone hydroxyapatite, ASG: autogenous symphseal graft, CBCT: cone-beam computed tomography scan, BSM: Bone substitute material

Table 4. Included studies using L-PRF in socket preservation

	Type of study	Number of patients & involved location	Used materials	Evaluation methods	Bone gain
Baslarli *et al.* (72)	CT & SMD	20, 40 3rd MMs	L-PRF	technetium-99m methylene diphosphonate uptake	No significant different between PRF-treated and non-PRF-treated sockets after 30 and 90 days postoperatively
Kumar *et al.* (73)	RCT	31,31 3rd MMs	L-PRF	Clinical & radiographic	After 3 mo.: Significantly mean pocket depth reduction after 1 and 3 months in both test and control groups Increased radiographic factors non-significantly in L-PRF group
Barone *et al.* (63)	CS	33, anterior of maxilla, BBD	CCPB+ L-PRF+ CM	Radiographic	Improvement of vertical bone level after 5 months: 0.8 ± 0.1 mm (mesial site)* 0.7 ± 0.1 mm (distal site)*
Hauser *et al.* (64)	RCT	23, premolar site	L-PRF L-PRF+ mucosal flap	Micro-CT & histologic	BV/TV after 8 weeks: PRF: 0.281±0.037, PRF+ flap: 0.197±0.027, control: 0.249±0.037 A significant effect on intrinsic bone quality & preservation of the alveolar width was observed using PRF vs. L-PRF+ flap

Srisurang *et al.* (65)	CT & SMD	10, 20 premolar sites	L-PRF	Clinical	First week: HR on buccal aspect of PRF (1.07 ± 0.31 mm) control (1.81 ± 0.88 mm)* PRF had faster bone healing than control: NS
Girish Rao *et al.* (66)	CT	22, 44 3rd MMs	L-PRF	Serial RVG at 0 & 1 day & 1,3 & 6 m.	The mean pixels recorded between test and control groups: NS
Singh *et al.* (68)	CT	20, 40 3rd MMs	L-PRF	Clinical & radiographic	After 12 weeks: TBF was seen in all of both groups GSV for L-PRF: 146.9* and for control: 123
Simon *et al.* (69)	CT	21, 6 molar&15 premolar sites	L-PRF	Clinical & radiographic	After 4 months: Mean WR for L-PRF (mm): 0.32 (4.71%) & control: 0.57 (7.38%): NS
Ruga *et al.* (70)	CT	NR, 28 3rd MMs	L-PRF	Clinical	After 6 months: Sufficient and adequate socket fulfillment In all L-PRF cases PDR in L-PRF: 0.86mm & control: 0.5 mm NS

CS: Cohort study, CT: Clinical trial, RCT: Randomized controlled trial, SMD: split mouth design, NR: Not reported, BBD: buccal bone plate dehiscence, L-PRF: Leukocyte- and platelet-rich fibrin, CM: Collagen membrane, CCPB: Corticocancellous porcine bone, HA: Histomorphometric analysis, HR: horizontal resorption, WR: width resorption, *significant difference regarding base line, NS: Not significant, MMs: Mandibular molars, RVG: radiovisiography, TBF: trabecular bone formation, PCT: periodontally compromised tooth , GSV: gray scale value, PDR: probing depth reduction

Table 5. Included studies using L-PRF in periodontal intra bony defect regeneration

	Type of Study	Number of cases, problem	Used materials	Evaluation method	Bone gain
Agrawal *et al.* (81)	SMD	60, PID with CP	L-PRF+ DFDBA (A) DFDBA(B)	Clinical & radiographic	After 12 months**: PDR in A (mm): 4.15 ± 0.84* & B: 3.60 ± 0.51 CAG in A (mm): 3.73 ± 0.74* & B: 2.61 ± 0.68 Defect fill in A (mm): 3.50 ± 0.67* & B:2.49 ± 0.64
Ajwani *et al.* (82)	SMD	40, PID	L-PRF+OFD OFD	Clinical & radiographic	After 9 months**: Mean PDR in L-PRF vs. control: 1.90mm vs. 1.60mm Mean CAG in L-PRF vs. control: 1.80mm vs. 2mm
Elgendy & Shady (2015)(83)	SMD	40, PID	L-PRF+ NcHA NcHA	Clinical & radiographic	After 6 months**: Mean PDR in L-PRF+ NcHA: 3.33mm & NcHA: 3.30mm Mean CAG in L-PRF+ NcHA vs. & NcHA: 3.55mm vs. 3.50mm Mean RBD changes: L-PRF+ NcHA* vs. NcHA: 34.45 vs. 16.86
Pradeep *et al.* (92)	RCT	120, PID with CP	1%MF+L-PRF+OFD (A) 1%MF+OFD (B) L-PRF+OFD (C) OFD (D)	Clinical & radiographic	After 9 months**: PDR in A (mm):4.90±0.30*, B:3.93±0.25*, C:4.00±0.18* & D:3.00±0.18 CAG in A (mm):4.90±0.30*, B:3.93±0.25*, C:4.03±0.18* & D:2.96±0.18 RBF in A (%): 52.65±0.04*, B:48.69±0.026*, C:48% ± 0.029%* & D:9.14% ± 0.04%
Mathur *et al.* (85)	CT	38, PID	OFD+L-PRF OFD+ABG		After 6 months** : PDR in L-PRF vs. ABG:2.67± 1.29mm vs. 2.4± 1.06mm Mean CAG in L-PRF vs. ABG: 2.53± 1.06mm vs. 2.67± 1.63mm
Shah *et al.* (86)	SMD	40,PID	OFD+L-PRF OFD+DFDBA		After 6 months** : PDR in L-PRF vs. DFDBA: 3.67± 1.48 mm vs. 3.70 ± 1.78 mm CAG in L-PRF vs. DFDBA: 2.97± 1.42 mm vs. 2.97 ± 1.54 mm
Rosamma *et al.* (88)	SMD	45, horizontal defects	L-PRF+OFD (A) L-PRF+ L-PRF membrane+ OFD (B) OFD (C)	Clinical & radiographic	After 9 months**: PDR in A (mm):1.73±0.53*, B:1.7±0.45* & C: 1.1±0.38 CAG in A (mm):1.56±0.62*, B:1.7±0.52* & C:0.86±0.58
Gupta *et al.* (87)	RCT	44, PID with CP	L-PRF EMD	Clinical & CBCT	After 6 months**: PDR in L-PRF vs. EMD: NS CAG in L-PRF vs. EMD : NS Defect resolution in L-PRF: 32.41 ± 14.6% & EMD: 43.07% ± 12.2*
Bansal *et al.*	SMD	20, PID	DFDBA+	Clinical &	After 6 months**:

(77)			L-PRF DFDBA	radiographic	PDR in L-PRF (mm): 4.0±0.856* & control: 3.1±0.738 CAG in L-PRF (mm): 3.4±0.606* & control: 2.3±0.099 Defect fill in L-PRF (mm): 2.42±1.111 & control: 1.97±1.155
Bajaj *et al.* (89)	RCCT	72, degree II MFI	L-PRF+OFD PRP+OFD OFD	Clinical & radiographic	After 9 months** : PDR in L-PRF (mm): 4.29±1.04* & PRP: 3.92±0.93* RVCAG (mm): in L-PRF: 2.87± 0.85 * & PRP: 2.71±1.04* RHCAG (mm): in L-PRF: 2.75±0.94* & PRP: 2.5±0.83* RBF (%): in L-PRF: 44.01±9.98* & PRP: 42.83±11.15*
Rosamma *et al.* (10)	CCT & SMD	30, PID	L-PRF+OFD OFD	Clinical & radiographic	After 1 year in test** : PDR: 2.27±0.29mm * CAG: 3.33±0.35mm* DDR:1.29±0.32mm *
Pradeep *et al.* (76)	CT	90, PID with CP	L-PRF+OFD PRP+OFD OFD	Clinical & radiographic	After 9 months: PDR (mm): L-PRF (3.77 ± 1.19) & PRP (3.77 ± 1.07) CAG (mm): L-PRF (3.17 ± 1.29) & PRP (2.93 ± 1.08) RBF (%): L-PRF (55.41±11.39)* & PRP (56.85 ±14.01) *
Lekovic *et al.* (75)	SMD	34, PID	L-PRF+ BPBM L-PRF (control)	Clinical & radiographic	After 6 months: PDR in test (mm): 4.47±0.78 on B & 4.29±0.82 on L sites * CAG in test (mm): 3.82±0.78 on B & 3.71±0.75 on L sites* RBF in test: 4.06±0.87 on B & 3.94±0.73 on L sites*
Thorat *et al.* (79)	CCT	32, PID with CP	L-PRF OFD	Clinical & radiographic	After 9 months: PDR in PRF vs. OFD (mm): 4.56 ± 0.37 vs. 3.56 ± 0.27 * CAG in L-PRF vs. OFD (mm): 3.69 ± 0.44 vs. 2.13 ± 0.43 * RBF in L-PRF vs. OFD(%): 46.92 vs. 28.66*
Sharma *et al.* (78)	RCCT	56, PID with CP	L-PRF+OFD OFD	Clinical & radiographic	After 9 months: PDR in test vs. control (mm): 4.55 ± 1.87 vs. 3.21 ± 1.64 CAG in test vs. control (mm): 3.31 ± 1.76 vs. 2.77 ± 1.44 RBF in test vs. control: 48.26 ± 5.72* vs. 1.80 ±1.56
Sharma *et al.* (90)	DBRS	36, degree II MFI	L-PRF+OFD OFD	Clinical & radiographic	After 9 months**: PDR in test vs. control (mm): 4.056±0.416* vs. 2.889±0.676 RVCAG in test vs. control (mm): 2.333±0.485* vs. 1.278±0.461, RHCAG in test vs. control (mm): 2.667±0.594* vs. 1.889±0.758 RBF in test vs. control (%): 50.8±6.24* vs. 16.7±6.42
Chang *et al.* (91)	RS	6, PID	L-PRF+BG	Clinical & radiographic	After 6 months: PDR (mm): 2.83 ± 1.70 CAG (mm): 2.25 ± 1.76

CT: Clinical trial, SMD: split mouth design, CCT: controlled clinical trial , RCCT: Randomized controlled clinical trial, RS: Retrospective study, DBRS: double-blind randomized study, PID: Periodontal intra bony defect, CP: chronic periodontitis MFI: Mandibular furcation involvement, CBCT: Cone beam computed tomography, OFD: Open flap debridement, L-PRF: Leukocyte- and platelet-rich fibrin, EMD: enamel matrix derivative, MF: Metformin, PD: Probing depth, PDR: Probing depth reduction, CAG: Clinical attachment gain, RVCAG: Relative vertical clinical attachment gain, RHCAG: Relative horizontal clinical attachment gain, RBF: Radiographic bone fill, DR: Defect resolution, GML: gingival margin level, DDR: Defect depth reduction, RBD: Radiographic bone density, DFDBA: Demineralized freeze-dried bone allograft, NcHA: Nanocristaline hydroxyapatite, ABG: Autogenous bone graft, BPBM: Bovine porous bone mineral, BG: Bioactive glass *Statistically significant difference with control group, ** Statistically significant difference with base line evaluation, NS: Non significant

Table 6. Case reports using L-PRF in advanced periodontal defects regeneration

	Number of cases & Problem	Used materials	Evaluation methods	Bone gain
Shah *et al.* (93)	1, LCVG	L-PRF	Clinical	PD before surgery: mesial: 11mm, midbuccal: 8mm PD after surgery: mesial: 2mm, midbuccal: 1mm
Anuroopa *et al.* (94)	2,IBD	L-PRF	Clinical	After 6 months: PDR: 5mm (distal) & 6mm (mesial) for #12 & 3mm (distal) for #13 CAG: 9mm for #12 & 5 mm for #13

Panda *et al.* (95)	1,IBD	L-PRF+xenograft	Clinical	After 6 months: PDR: 5mm CAG: 6mm
Desarda *et al.* (16)	2, GAgP	L-PRF	Clinical & radiographic	Bone fill of 60-75% in case1 & 70-80% in case2 after 4 mo. radiographically After 9 mo. decreased PD & increased CA in both cases was observed.

Table 7. Included clinical trials using L-PRF in endodontic surgery

	Type of study	Number of cases, problem	Used materials	Evaluation methods	Bone gain
Dhiman et al (99)	RCT	30, Apico-marginal lesions	L-PRF	Clinical and radiographic	After 12 months**: PDR in L-PRF vs. control: 8± 0.92* vs. 7.27±0.96 CAL in L-PRF vs. control: 7±0.92 vs. 6.6±1.18 SPLR in L-PRF vs. control: 93.41±7.00 vs. 94.57±5.87
Singh et al (15)	CT	15, peri-apical lesions	L-PRF	Radiographic	CBR after 6 months

RCT: Randomized clinical trial, CT: clinical trial, L-PRF: Leukocyte- and platelet-rich fibrin, PDR: Probing depth reduction, CAG: Clinical attachment gain, SPLR: Size of pri-apical lesion reduction, CBR: Complete bone regeneration, *Statistically significant difference with control group, ** Statistically significant difference with base line evaluation

Table 8. Case reports using L-PRF for healing of peri-apical or endo-periodontal lesions

	No of cases	problem	Used materials	Evaluation methods	Bone gain
Vidhale et al(2015)(112)	3	RC	L-PRF+ Iliac bone graft	Radiographic	After 3 months: Increased radiopacity as compared to earlier radiographs
Nagaveni et al (2015)(102)	1	PID with EI (immature tooth)	L-PRF	Clinical & radiographic	After 6 months: PDR: 2mm CBR
Varughese et al (2015)(103)	1	PID with EI	L-PRF+ bone graft+ membrane	Clinical & radiographic	After 12 months: PDR: 4mm (distal) & 3mm (mesial) CBR
Karunakar et al (2014)(104)	2	PID with EI	L-PRF	Clinical & radiographic	After 9 months: PDR: 6mm & 5mm CBR
Panda et al (2014)(100)	1	PID with EI	PRF+ bone graft	Clinical & radiographic	After 6 months: PDR: 6mm CAG: 7mm
Goyal et al (2014)(22)	1	EPL	L-PRF+BG	Clinical & radiographic	PDR, CAG & RBF after 18 months follow-ups
Sam and Shivashankar (2014)(105)	1	PID+EI	L-PRF	Clinical & radiographic	After 6 months: Healthy gingiva and probing pocket depth of 3 mm

Mazumdar et al (2013)(106)	1	AL	L-PRF	Radiographic	CBR after 1 year
Shivashankar et al (2013)(107)	2	AL	L-PRF+HA	Radiographic	CBR after 2 year follow-ups
Patil et al (2013)(108)	1	RC	L-PRF+ DFDBA	Radiographic	Favorable bone regeneration after 6 months
Zhao et al (2012)(109)	2	RC	L-PRF+ BG	Radiographic & CBCT scan	satisfactory healing & bone regeneration after 4 mo.
Bambal et al (2012)(110)	2	RC	L-PRF	3-D X-ray	Test had better healing than the the other side.
Jayalakshmi et al (2012)(111)	1	Anterior maxilla, RC	L-PRF+ β-TCP	Clinical & radiographic	Faster bone healing in 1 year follow-ups than literature
Anilkumar et al (2009)(101)	1	PID with EI	PRF+ bone graft	Clinical & radiographic	Radiologic complete bone regeneration after 1year

CR : Case report, EPL: Endo-perio lesion, L-PRF: Leukocyte- and platelet-rich fibrin, PDR: Probing depth reduction, CAG: Clinical attachment gain, RBF: Radiographic bone fill, HA: Hydroxyapatite, PID: Periodontal intra bony defect, EI: Endodontic involvement, AL: Apical lesion, CBR: Complete bone regeneration, RC: Radicular cyst, DFDBA: demineralized freeze-dried bone allograft, CBCT scan: Cone- beam computed tomography scan, BG: Bioactive glass, β-TCP: tricalcium phosphate

Table 9. Included studies on peri-implant bone defects treated by L-PRF

	Type of study	Aim	Number of cases	Used materials	Evaluation method	Results
Boora et al (2015)(114)	RCT	Pri-implant bone loss after insertion	20	L-PRF	Clinical & radiographic	BL in L-PRF: After 1 month vs. base line**: mesial*: 0.13±0.04 & distal*: 0.15±0.04 After 3 months vs. base line**: mesial*: 0.25±0.06 & distal*: 0.27±0.07 After 3 months vs. 1 month**: mesial*: 0.11±0.04 & distal*: 0.11±0.05
Hamzacebi et al (2014)(113)	RCT	Pri-implant bone defect healing	19	L-PRF	Clinical	After 6 months**: PDR in L-PRF* vs. control: 2.82 ± 1.03 mm vs. 2.05 ± 0.77 mm CAG in L-PRF* vs. control: 3.31 ± 1.08 mm vs. 1.84 ± 0.81 mm
Oncu et al (2014)(115)	RCT	Implant stability	20	L-PRF	Clinical	ISQs of L-PRF vs. control: After 1 week: 69.3 ± 10.5 vs. 64.5 ± 12.2 After 4 weeks: 77.1 ± 7.1 vs. 70.5 ± 7.7
Mohamed et al (2012)(116)	CR	Retrograde peri-implantitis healing	1	Xenograft+ L-PRF	Clinical & radiographic	After 1 year, health & function of the implant was restored
Del Corso et al (2012)(117)	CR	Immediate implant insertion	1	L-PRF	Clinical & radiographic	Restoration & esthetic results were stable after 2 years.

RCT: Randomized clinical trial, CR1: Case report, L-PRF: Leukocyte- and platelet-rich fibrin, BL: Bone loss, PDR: Probing depth reduction, CAG: Clinical attachment gain, ISQs: implant stability quotients, * Significant difference compared to control, **Significant difference regarding understudy times

Table10. Included studies using L-PRF in treatment of bisphosphonate-related osteonecrosis of the jaw

	Type of study	Number of cases	Used materials	Evaluation method	Results
Kim et al (2015)(119)	CR	1	L-PRF+rhBMP2	Clinical	After 11 weeks, total bone closure was observed.
Kim et al (2014)(118)	CS	34	L-PRF	Clinical	26 complete and 6 delayed healing after 4 months
Soydan et al (2014)(21)	CR	1	Double-layered PRF membrane	Clinical	Total bone closure after 1 month No gingival loss, inflammation, or infection after 6 months

CS: Case series, CR: Case report, rhBMP2: recombinant human bone morphogenetic protein-2

Table 11. Case reports using L-PRF with the aim of bone regeneration

	Number of cases	Problem	Used materials	Evaluation method	Results
Reddy et al (120)	3	Ridge augmentation	L-PRF+DFDBA	Clinical	After 2 months: increased ridge dimensions
Chaudhary et al (121)	1	Auto-transplantation of an impacted incisor	L-PRF+DFDBA	Clinical & radiographic	After 1 year: no complications
Findik et al (20)	3	Alveolar cleft	L-PRF+ ASG	Radiographic	Initiating the orthodontic tooth movement in 3 to 4 months later. Graft in 1 case was exposed but recovered smoothly by hygiene recommendations

L-PRF: Leukocyte- and platelet-rich fibrin, BRONJ: Bisphosphonate-related osteonecrosis of the jaw, DFDBA: demineralized freeze-dried bone allograft, ASG: Autogenous symphyseal graft

and NBBM (22) did not increase bone healing significantly. For instance, Kim *et al.*, demonstrated promising results by application of L-PRF mixed with TCP in sinus floor augmentation of rabbits (27); however, Yilmaz *et al.*, showed that adding L-PRF to TCP had approximately equal NBF with sole use of TCP in pig tibial defects (37). Moreover, the highest NBF was shown in mixture of L-PRF with TA around dental implants inserted in the femur of dogs (78_8±6.95% and 87.5±9.15% after 4 and 8 weeks, respectively), which was significantly higher than empty defects, but not significantly more than TA and TA+PRP groups (35).

Eight studies were conducted to evaluate L-PRF as the sole material. Two of them demonstrated its significant effect on calvarial defects in rabbits (21, 26), while three studies showed it did not significantly affect it (25, 33, 38). For example, Srisurang *et al.*, showed positive effects of L-PRF on both hard and soft tissues in early phases of healing though NBF by L-PRF after 12 weeks was not significantly higher than in controls (38). Also, the effectiveness of using L-PRF with titanium barriers was similar to using NBBM or BCP alone (25). However, Knapen *et al.,* reported that L-PRF did not have additional effects on bone regeneration in calvarium defects of rabbits (12). Jeong *et al.*, reported that use of L-PRF in sinus floor augmentation and immediate implantation was not a reproducible and predictable procedure (34). In order to evaluate osteogenic periosteal distraction, Pripatnanont *et al.,* demonstrated that NBF was significantly greater when L-PRF was added when a modified Hyrax device was used in rabbits' mandible (30).

Two studies evaluated other aspects of L-PRF (Table 1). Li *et al.*, showed that NBF of lyophilized L-PRF, which has the improved storage capacity, was more than fresh PRF in critical-sized bone defect (CSBD) of rats (18). Using titanium tubes to prepare L-PRF membrane led to bone regeneration after 15 days (24).

Although rabbits used in 13 studies provides a suitable model to investigate regenerative potential of bone substitute materials (128), according to Dohan Ehrenfest *et al.,* human protocols which were performed on rabbits produced L-PRF-like material which was not actual L-PRF, and accurate results were not produced by rabbit studies (129). However, Tunali *et al,.* reported that rabbits could be used as a suitable model for titanium prepared PRF studies (24).

According to the definition of CSBD (130), three studies investigated L-PRF in CSBD (18, 19, 21). Two of them showed significantly greater NBF in L-PRF groups after 6 weeks, and Honda *et al.*, reported excellent healing of CSBD by combination of L-PRF with BMSCs. Since other sources of mesenchymal stem cells (MSCs) than bone marrow such as adipose tissues, dental tissues and induced pluripotent stem cells (iPSCs) (131-134), etc. have been introduced in recent years, evaluation of L-PRF and MSCs combination therapy may be considered in future studies.

Most studies evaluated the rate of NBF by HA analysis; nonetheless, some studies used radiologic assessments like CT (30, 36, 135) and micro CT (19, 30, 31, 33) alone or beside histological evaluations. Bone mineral density (BMD) measurement is one of the most important factors to assess bone quality (136). Recently, it is demonstrated that using both CT and micro CT scans are reliable for BMD measurements (137). Moreover, using CT scans has gained popularity in BMD measurements, and BMD derived from Hunsfield units has been highly reliable in the human jaws (138).

Sole grafting of L-PRF

According to the literature, platelet-derived epidermal growth factor (PD-EGF), platelet-derived growth factor A and B (PDGF), transforming growth factor beta1 (TGF-ß1), insulin like growth factor 1 and 2 (IGF), vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), and basic fibroblast growth factor (bFGF) are released from L-PRF even after seven days (7, 69), some of which play an important role in bone regeneration (139-141). Due to the 3-D structure of fibrin network and slow release of growth factors for at least 7-10 days (7), use of sole L-PRF may cover two key factors of bone tissue engineering.

In order to evaluate the effectiveness of using L-PRF as the sole material in bone defects, NBF of L-PRF groups in eight studies was significantly greater than empty defects after four weeks in dogs (33) or rabbits (25), six weeks in rats (18) and rabbits (21), eight weeks in rabbits (23, 26), and 12 weeks in pigs (37) or rabbits (25); moreover, it was not significantly greater than empty defects after ten and 20 days in sheeps (39), eight weeks in dogs (33), and 12 weeks in rats (19), rabbits (21) and guinea pigs (38). Consequently, although the rate of NBF with use of L-PRF in some studies was significantly greater compared to empty defects 12 weeks or three months postoperatively, it was reported in other studies almost equal between two groups in this time. However, L-PRF groups had insignificantly lower NBF than empty defects in two studies after 40 days in sheeps (39) and 12 weeks in rabbits (12).

Comparison of sole application with mixtures of L-PRF, L-PRF groups showed significantly lower NBF than L-PRF mixed with ABG after 8 weeks (23) and BCP after 10 , 20 and 40 days (39), but insignificant BMSCs (19), TCP (37) and ABG+DBB (23). However, NBF of L-PRF was more than mixing it with DBB (23) and NBBM (12) though it was not significant. Therefore, using mixtures of L-PRF may have better results than L-PRF as the sole graft especially with ABG or BCP, and further research is essential to identify the best mixture of L-PRF.

When L-PRF was compared with PRP, the difference was not significant and even after four, six and eight weeks L-PRF showed higher NBF, but after 12 weeks NBF by PRP was greater (21, 33). However, Hatakeyama *et al.*, reported that platelet-poor plasma (PPP) had more NBF than both PRP and L-PRF groups after four and eight weeks (33).

Using sole L-PRF had higher NBF than other bone grafts in four studies; to illustrate, it was higher than BCP after 10 and 20 days (39) and three months (25), NBBM after one month (25) and 12 weeks (25), DBB after eight weeks (23), and using FGG alone after 12 weeks (38). However, the NBF by mixing ABG and DBB after eight weeks (23), BCP after 40 days (39), and TCP after 12 weeks (37) was greater than that of using sole L-PRF. This may indicate that using sole L-PRF can affect bone regeneration as well as various bone grafts.

Two studies reported that the NBF of L-PRF was significantly increased in calvarial defects of rabbits among understudied times (12, 25). To illustrate, at 12 weeks, the NBF by both L-PRF and L-PRF mixed with NBBM was more than one and five weeks (12). Also, Ozdemir *et al.,* reported that at three months after using L-PRF, NBF was greater than at one month (25).

Mixtures of L-PRF

When the effect of adding L-PRF to bone grafts were compared, L-PRF clots mixed with ABG after eight weeks (23) and six months (36),TCP after two, four, six and eight weeks (27) BCP after ten, 20 and 40 days (39), four and eight weeks (31) and three months (32) and NBBM after one and two months (20) , and L-PRF membrane with NBBM after six months (9) showed significantly higher NBF than bone grafts alone; moreover, NBF of L-PRF clots mixed with NBBM after four and 12 weeks (12, 22), DBB and DBB with ABG after eight weeks (23), TA after four and eight weeks (35), and TCP after 12 weeks (37) were more than bone grafts alone, but not significantly. However, mixtures of L-PRF with NBBM just after one and two weeks showed lower NBF than NBBM group (22). Also, application of FGG with L-PRF was approximately equal to FGG groups (38).

Mixing L-PRF with DBB, ABG and both of them after eight weeks (23), SFP after eight weeks around dental implants (28) and after 12 weeks in calvarium defects (29), TA after both four and eight weeks (35), TCP after 12 weeks (37), and BCP after ten, 20 and 40 days (39) revealed significant NBF compared to empty defects. However, NBF by L-PRF mixed with SFP after six weeks was not significantly greater compared to empty defects (29); furthermore, L-PRF mixed with NBBM showed lower NBF than empty non critical-sized calvarial defects after 12 weeks (12). This result shows the effectiveness of adding L-PRF to bone graft materials.

Using L-PRF in humans

The effect of L-PRF on Maxillary sinus floor augmentation and GBR techniques

L-PRF membranes

Three studies reported the use of L-PRF membranes in sinus floor augmentation (Table 2). Using it with NcHA embedded

in a highly porous silica gel matrix (NanoBone) (40), NBBM alone (49) or mixture of NBBM with ABG (8) indicated reletive efficiency of both NBF and RGM with resorbable collagen membrane groups (2). It is noticeable that survival rate of dental implants inserted in second surgery of these studies was 100% after 12 weeks (40), 12 months (8) and 30 months follow-ups (49). Also, effectiveness of L-PRF membranes was reported in GBR technique for both horizontal and vertical ridge augmentation used with allogenic cortical bone pins (53), ABG (61), ABG mixed with bovine hydroxyapatite (54) or ABG with using vertical alveolar distaction (62) with low level of evidence (Table 3). The choice of bone graft is one of the key factors in alveolar augmentation for GBR (142).

Sole grafting of L-PRF

Sole grafting of L-PRF was used in five studies. Simultaneous sinus lift, lateral window approach, and implantation using L-PRF as the sole grafting material showed 100% survival rate of dental implants after six months (41, 46) and six years follow-ups (43) (Table 2). In contrast to the results obtained in dogs (34), these studies indicated that L-PRF could be an adequate adjuvant to this technique and promote new bone regeneration around dental implants.

Two studies reported 100% one-year survival rate of dental implants inserted immediately after either sinus floor augmentation for atrophic maxilla (residual bone hights: 3.7 and 1.4 milimeter) by crestal aproach (52) or using both GBR and double J technique in atrophic ridges (55) with low level of evidence (Table 3).

Moreover, OMSFE/PRF technique was presented in two studies in which survival rate of dental implants inserted immediately after sinus lift was 97.1% (n=35) after one year (47)and 97.8% (n=138) (44) (Table 2). Implant failures occurred in early phase; for example, according to Toffler *et al.*, two implants failed four weeks after insertion because of infection. Perforation of sinus membrane and less than five milimeter residual subantral bone hight were also observed. Also, Peck *et al.*, demonstrated successful use of OMSFE/PRF technique for immediate implant insertion in maxillary second premolar site with less than four mm residual vertical bone hight (Table 3) (59).

Mixtures of L-PRF

Histological and histomorphometric analyses of biopsies obtained after sinus floor augmentation during second surgery demonstrated that NBF of using L-PRF mixed with NBBM had no significant difference than using NBBM alone (11, 42). These results confirmed animal studies investigating mixtures of L-PRF and NBBM in calvarium defects of rabbits (12, 22). Moreover, dental implants (n=95) inserted immediately after sinus lift of severe atrophy of maxilla using a mixture of L-PRF and NBBM showed 100% survival rate at six to nine months after loading (45). However, it was observed that five-year survival rate of dental implants (n=84) inserted with one-stage sinus lift using just bovine bone grafts was 100% (143).

Choukroun *et al.*, reported shorter healing period of L-PRF mixed with DFDBA after sinus lift (four months) than DFDBA alone (eight months) (48). In other words, addition of L-PRF to DFDBA may positively affect acceleration of healing process after sinus lift.

The effect of L-PRF on socket preservation

Sole grafting of L-PRF

According to the results (Table 4), the positive effect of using L-PRF to preserve both molar sites (66, 68-70, 72, 73), and nonmolar sites (64, 69) immediately after dental extraction was shown. However, Suttapreyasri *et al.*, reported limited efectiveness of L-PRF for both bone formation enhancement and socket preservation in 20 premolar sites (65), in which there were no statistically significant differences in either width or hight reduction between using L-PRF and empty defects in the literature except for a study by Hauser *et al.*, in which using L-PRF showed significantly less width reduction than controls (64). In fact, the surgical prucedure may be as important as choosing the grafting material since using L-PRF with mucosal flap showed more width reduction vs. L-PRF alone. However, piezoelectric surgery with L-PRF use revealed sufficient and adequate socket filling, and it may be a safe technique to preserve the alveolar ridge (70). Furthermore, Peck *et al.*, reported uneventful use of L-PRF in a maxillary molar socket after removing a failed dental implant or extraction of a poor prognosis tooth, and successful new dental implant insertion was demonstrated three months or six weeks later, respectively (Table 4) (59, 71).

Mixtures of L-PRF

According to Barone *et al.,* the mixture of L-PRF and CCPB used with collagen membrane in fresh extraction sockets in the maxillary esthetic zone which had partial or complete deficiency of the buccal bone plate showed significant vertical bone level improvement after five months. Also, delayed insertion of dental implants demonstrated favorable outcomes after one year follow-up (63). Gupta *et al.*, evaluated mixture of L-PRF and BCP in a compromised extraction socket, and successful regeneration was gained after six months (Table 3) (67).

The effect of L-PRF on periodontal intra-bony defects regeneration

Sole grafting of L-PRF

Comparison of the use of both L-PRF and conventional open flap debridement (OFD) with OFD alone according to the results showed better outcomes in the test groups (Table 5). To illustrate, in the treatment of mandibular grade II defects, significant differences in the parameters of PDR, CAG and RBF between tests and controls, and after 9 months to base line were

observed (89, 90). In the treatment of PID, in two split mouth design and randomized clinical studies, not only was probing depth reduced significantly but clinical attachment was also gained in the test than the control (10, 88, 92), but it was not significant in other clinical trials (76, 78, 82). Moreover, significant RBF and radiologic defect depth reduction was observed in the test groups compared to controls (10, 76, 78, 92). However, the measured parameters improved significantly after nine months (82, 88, 92) and one year (10) compared to base-line, but it was not significant after nine months in two studies (76, 78). Thorat *et al.*, evaluated the treatment of periodontal intra bony defects either with L-PRF or OFD alone, and presented significant improvement of the parameters in L-PRF group though no significant difference was reported after nine months compared to base-line (79). Recently, Shah *et al.*, conducted a meta-analysis showing mean standard difference of 2.33 (1.43, 3.23) for intra-bony defect reduction, 0.95 mm (0.20, 1.71) for CAG and 1.10 mm (0.56, 1.64) for PDR (126). Furthermore, adding 1% metformin to L-PRF revealed significant effects on PIDs (92). For future studies, it can be noticed that the parameters should be evaluated in various follow-ups like both nine months and one year in one study to better understand the effect of L-PRF on time for PID treatment.

L-PRF has been used for treatment of a labial-cervical-vertical groove, and displayed significant PDR (93). Moreover, L-PRF showed considerable RBF after four months, PDR and CAG after nine months in two generalized aggressive periodontitis patients (16) (Table 6).

Mixtures of L-PRF

In the treatment of PID (Table 5), two studies demonstrated that using L-PRF mixed with DFDBA significantly enhanced both PDR and CAG compared to DFDBA alone after six months (77) and one year(81). Furthermore, Lekovic *et al.*, presented significant improvement of PDR, CAG and RBF regarding the use of L-PRF mixed with BPBM than L-PRF alone after six months(75). According to a retrospective study, the effectiveness of L-PRF mixed with bio-active glass was, also, demonstrated (91). However, although the outcomes of adding L-PRF to NcHA showed significant difference compared to base-line, both PDR and CAG was not significant between mixture of NcHA with L-PRF and NcHA after six months (83). Regarding split mouth design and randomized clinical studies, it was no significant difference between using L-PRF and each DFDBA(86), ABG(85) and EMD (87). Consequently, L-PRF may be an appropriate replacement for other grafts in PID regeneration.

The effect of L-PRF on peri-apical and endo-periodontal defects treatment

For regeneration of defects after root-end surgery, Singh *et al.*, found compelete bone regeneration after six months of filling the defects with the sole L-PRF in 15 patients (96). Also, Dhiman *et al.*, revealed significant effects of using sole L-PRF in the treatment of endo-periodontal lesions in a randomized clinical trial (97). Studies with low level of evidence, also, demonstrated satisfactory outcomes and bone regeneration after periapical defects treatment using L-PRF as either the sole material (100, 102-104, 108)or the mixture with iliac bone graft (110), bio-active glass (15, 107), hydroxyapatite (105), tri-calcium phosphate (109) and DFDBA (106) after different follow-up times like four, 12, 18 or 24 months (Table 8). Also, treatment of PID with endodontic involvement by using mixture of L-PRF and a bone graft was favorable after six months (98) and one year (99, 101).

The effect of L-PRF on peri-implant bone

Applying L-PRF around dental implants after insertion showed significantly less bone loss one and three months postoperatively (112). For peri-implant bone defects regeneration, significant PDR and CAG were revealed after six months using sole L-PRF (111). In other randomized clinical trial, stability of dental implants was investigated, and implant stability quotients (ISQs) for L-PRF group were reported more than control group after four weeks post-operatively though there was not a significant difference (113). Furthermore, a retrograde peri-implantitis was treated by using a xenograft and coverage by L-PRF (114). Also, two-year favorable results were observed after immediate insertion of a dental implant in post extraction site of a fractured maxillary central incisor with the labial gap between implant and residual buccal plate filled with mixture of L-PRF clots and CCPB, and covered with L-PRF membrane.

The effect of L-PRF on treatment of BRONJ

Kim *et al.*, reported a case series of the BRONJ treatment using L-PRF alone in a prospective study (116). They revealed promising results of using L-PRF in treatment of a large group of patients (n=32). There were no significant association between response to L-PRF and both low C-terminal crosslinked telopeptide of type I collagen (sCTX) concentration and presence of actinomycosis, the biomarkers for risk of BRONJ prediction. Also, healing of bone exposures of BRONJ using double-layered L-PRF membrane after one month(14) and a mixture of L-PRF and rh-BMP2 after 11 weeks (117) was demonstrated in the literature.

Other uses of L-PRF for bone regeneration

Findik *et al.*, reported successful reconstruction of unilateral alveolar cleft by using L-PRF and autologous symphyseal graft in young patients (13). Furthermore, Chaudhary *et al.*, replanted an impacted central incisor in a prepared socket and splinted (119). L-PRF mixed with DFDBA placed in the defect and L-PRF membrane covered the defect from edge to edge.

They observed no complication like root resorption or ankylosis after 1 year follow-up. Moreover, Reddy *et al.*, demonstrated a novel technique of ridge augmentation in maxillary anterior region, and revealed a favorable use of a mixture of L-PRF with DFDBA with long palatal connective tissue rolled pedicle graft (118).

Conclusion

In conclusion, in animal studies, using the mixtures of L-PRF with ABG, NBBM and synthetic grafts has demonstrated significant bone regeneration; however, using L-PRF alone showed some challengeable results comparing to defects either grafted without L-PRF or left empty. Moreover, the rate of new bone formation was almost equal in both L-PRF and PRP groups with regard to the results of two animal studies.

According to the human studies, L-PRF either solely or mixed demonstrated favorable results in sinus floor augmentation. With the aim of socket preservation, using L-PRF solely showed non-significant results even though adding it to other grafts may have better effect on bone regeneration in dental socket. Using sole L-PRF in IBD revealed significant results when compared to OFD groups; also, it had similar effects on bone regeneration to use of other grafts without L-PRF. Furthermore, using L-PRF showed appropriate outcomes in the treatment of peri-apical and endo-periodontal defects, peri-implant bone defects and BRONJ though further clinical studies are required for arriving at an evidence-based conclusion.

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References

1. Khojasteh A. Regenerative medicine in oral and maxillofacial surgery: is it a valuable modality? Int J Oral Maxillofac Surg. 2013;42(10):1374-.
2. Khojasteh A, Soheilifar S, Mohajerani H, Nowzari H. The effectiveness of barrier membranes on bone regeneration in localized bony defects: a systematic review. Int J Oral Maxillofac Implants. 2012;28(4):1076-89.
3. Choukroun J, Adda F, Schoeffler C, Vervelle A. Une opportunité en paro-implantologie: le PRF. Implantodontie. 2001;42(55):e62.
4. Behnia H, Khojasteh A, Kiani MT, Khoshzaban A, Mashhadi Abbas F, Bashtar M, et al. Bone regeneration with a combination of nanocrystalline hydroxyapatite silica gel, platelet-rich growth factor, and mesenchymal stem cells: a histologic study in rabbit calvaria. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2013;115(2):e7-e15.
5. Khojasteh A, Eslaminejad MB, Nazarian H. Mesenchymal stem cells enhance bone regeneration in rat calvarial critical size defects more than platelete-rich plasma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(3):356-62.
6. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(3):e37-e44.
7. Dohan Ehrenfest DM, de Peppo GM, Doglioli P, Sammartino G. Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies. Growth Factors. 2009;27(1):63-9.
8. Gassling V, Purcz N, Braesen JH, Will M, Gierloff M, Behrens E, et al. Comparison of two different absorbable membranes for the coverage of lateral osteotomy sites in maxillary sinus augmentation: a preliminary study. J Craniomaxillofac Surg. 2013;41(1):76-82.
9. Xuan F, Lee CU, Son JS, Jeong SM, Choi BH. A comparative study of the regenerative effect of sinus bone grafting with platelet-rich fibrin-mixed Bio-Oss(R) and commercial fibrin-mixed Bio-Oss(R): an experimental study. J Craniomaxillofac Surg. 2014;42(4):e47-50.
10. Rosamma Joseph V, Raghunath A, Sharma N. Clinical effectiveness of autologous platelet rich fibrin in the management of infrabony periodontal defects. Singapore Dent J. 2012;33(1):5-12.
11. Tatullo M, Marrelli M, Cassetta M, Pacifici A, Stefanelli LV, Scacco S, et al. Platelet Rich Fibrin (P.R.F.) in reconstructive surgery of atrophied maxillary bones: clinical and histological evaluations. Int J Med Sci. 2012;9(10):872-80.
12. Knapen M, Gheldof D, Drion P, Layrolle P, Rompen E, Lambert F. Effect of Leukocyte-and Platelet-Rich Fibrin (L-PRF) on Bone Regeneration: A Study in Rabbits. Clin Implant Dent Relat Res. 2015;17(S1):e143-e52.
13. Findik Y, Baykul T. Secondary closure of alveolar clefts with mandibular symphyseal bone grafts and with platelet-rich fibrin under local anesthesia: three case reports. J Contemp Dent Pract. 2013;14(4):751-3.
14. Soydan SS, Uckan S. Management of bisphosphonate-related osteonecrosis of the jaw with a platelet-rich fibrin membrane: technical report. J Oral Maxillofac Surg. 2014;72(2):322-6.
15. Goyal L. Clinical effectiveness of combining platelet rich fibrin with alloplastic bone substitute for the management of combined endodontic periodontal lesion. Restor Dent Endod. 2014;39(1):51-5.
16. Desarda HM, Gurav AN, Gaikwad SP, Inamdar SP. Platelet rich fibrin: A new hope for regeneration in aggressive periodontitis patients: Report of two cases. Indian J Dent Res. 2013;24(5):627.

17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151(4):W-65-W-94.
18. Li Q, Reed DA, Min L, Gopinathan G, Li S, Dangaria SJ, et al. Lyophilized Platelet-Rich Fibrin (PRF) Promotes Craniofacial Bone Regeneration through Runx2. Int J Mol Sci. 2014;15(5):8509-25.
19. Honda H, Tamai N, Naka N, Yoshikawa H, Myoui A. Bone tissue engineering with bone marrow-derived stromal cells integrated with concentrated growth factor in Rattus norvegicus calvaria defect model. J Artif Organs. 2013;16(3):305-15.
20. Oliveira M, Ferreira S, Avelino C, Garcia I, Mariano R. Influence of the association between platelet-rich fibrin and bovine bone on bone regeneration. A histomorphometric study in the calvaria of rats. Int J Oral Maxillofac Surg 2015;44(5):649-55.
21. Kim T-H, Kim S-H, Sádor GK, Kim Y-D. Comparison of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) in rabbit-skull defect healing. Arch Oral Biol. 2014;59(5):550-8.
22. Yoon J-S, Lee S-H, Yoon H-J. The influence of platelet-rich fibrin on angiogenesis in guided bone regeneration using xenogenic bone substitutes: A study of rabbit cranial defects. J Craniomaxillofac Surg. 2014;42(7):1071-7.
23. Pripatnanont P, Nuntanaranont T, Vongvatcharanon S, Phurisat K. The primacy of platelet-rich fibrin on bone regeneration of various grafts in rabbit's calvarial defects. J Craniomaxillofac Surg. 2013;41(8):e191-e200.
24. Tunalı M, Özdemir H, Küçükodacı Z, Akman S, Fıratlı E. In vivo evaluation of titanium-prepared platelet-rich fibrin (T-PRF): a new platelet concentrate. Br J Oral Maxillofac Surg. 2013;51(5):438-43.
25. Ozdemir H, Ezirganli S, Isa Kara M, Mihmanli A, Baris E. Effects of platelet rich fibrin alone used with rigid titanium barrier. Arch Oral Biol. 2013;58(5):537-44.
26. Lee JW, Kim SG, Kim JY, Lee YC, Choi JY, Dragos R, et al. Restoration of a peri-implant defect by platelet-rich fibrin. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(4):459-63.
27. Kim BJ, Kwon TK, Baek HS, Hwang DS, Kim CH, Chung IK, et al. A comparative study of the effectiveness of sinus bone grafting with recombinant human bone morphogenetic protein 2-coated tricalcium phosphate and platelet-rich fibrin-mixed tricalcium phosphate in rabbits. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(5):583-92.
28. Jang ES, Park JW, Kweon H, Lee KG, Kang SW, Baek DH, et al. Restoration of peri-implant defects in immediate implant installations by Choukroun platelet-rich fibrin and silk fibroin powder combination graft. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(6):831-6.
29. Lee EH, Kim JY, Kweon HY, Jo YY, Min SK, Park YW, et al. A combination graft of low-molecular-weight silk fibroin with Choukroun platelet-rich fibrin for rabbit calvarial defect. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109(5):e33-8.
30. Pripatnanont P, Balabid F, Pongpanich S, Vongvatcharanon S. Effect of osteogenic periosteal distraction by a modified Hyrax device with and without platelet-rich fibrin on bone formation in a rabbit model: A pilot study. Int J Oral Maxillofac Surg. 2015;44(5):656-63.
31. Acar AH, Yolcu Ü, Gül M, Keleş A, Erdem NF, Kahraman SA. Micro-computed tomography and histomorphometric analysis of the effects of platelet-rich fibrin on bone regeneration in the rabbit calvarium. Arch Oral Biol. 2015;60(4):606-14.
32. Nacopoulos C, Dontas I, Lelovas P, Galanos A, Vesalas A-M, Raptou P, et al. Enhancement of Bone Regeneration With the Combination of Platelet-Rich Fibrin and Synthetic Graft. J Craniofac Surg. 2014;25(6):2164-8.
33. Hatakeyama I, Marukawa E, Takahashi Y, Omura K. Effects of platelet-poor plasma, platelet-rich plasma, and platelet-rich fibrin on healing of extraction sockets with buccal dehiscence in dogs. Tissue Eng Part A. 2014;20(3-4):874-82.
34. Jeong S-M, Lee C-U, Son J-S, Oh J-H, Fang Y, Choi B-H. Simultaneous sinus lift and implantation using platelet-rich fibrin as sole grafting material. J Craniomaxillofac Surg. 2014.
35. Jeong K-I, Kim S-G, Oh J-S, Lee S-Y, Cho Y-S, Yang S-S, et al. Effect of platelet-rich plasma and platelet-rich fibrin on peri-implant bone defects in dogs. J Biomed Nanotechnol. 2013;9(3):535-7.
36. Yuanzheng C, Yan G, Ting L, Yanjie F, Peng W, Nan B. Enhancement of the Repair of Dog Alveolar Cleft by an Autologous Iliac Bone, Bone Marrow–Derived Mesenchymal Stem Cell, and Platelet-Rich Fibrin Mixture. Plast Reconstr Surg. 2015;135(5):1405-12.
37. Yilmaz D, Dogan N, Ozkan A, Sencimen M, Ora BE, Mutlu I. Effect of platelet rich fibrin and beta tricalcium phosphate on bone healing. A histological study in pigs. Acta Cirurgica Brasileira. 2014;29(1):59-65.
38. Srisurang S, Kantheera B, Narit L, Prisana P. Socket preservation using platelet-rich fibrin in conjunction with epithelialized palatal free graft in minipigs. J Oral Maxillofac Surg Med Pathol. 2014;26(2):108-17.
39. Bölükbaşı N, Yeniyol S, Tekkesin MS, Altunatmaz K. The use of platelet-rich fibrin in combination with biphasic calcium phosphate in the treatment of bone defects: a histologic and histomorphometric study. Curr Ther Res Clin Exp. 2013;75:15-21.
40. Bosshardt DD, Bornstein MM, Carrel JP, Buser D, Bernard JP. Maxillary sinus grafting with a synthetic, nanocrystalline hydroxyapatite-silica gel in humans: histologic and histomorphometric results. Int J Periodontics Restorative Dent. 2014;34(2):259-67.

41. Tajima N, Ohba S, Sawase T, Asahina I. Evaluation of sinus floor augmentation with simultaneous implant placement using platelet-rich fibrin as sole grafting material. Int J Oral Maxillofac Implants. 2013;28(1):77-83.
42. Zhang Y, Tangl S, Huber CD, Lin Y, Qiu L, Rausch-Fan X. Effects of Choukroun's platelet-rich fibrin on bone regeneration in combination with deproteinized bovine bone mineral in maxillary sinus augmentation: a histological and histomorphometric study. J Craniomaxillofac Surg. 2012;40(4):321-8.
43. Simonpieri A, Choukroun J, Del Corso M, Sammartino G, Ehrenfest DMD. Simultaneous sinus-lift and implantation using microthreaded implants and leukocyte-and platelet-rich fibrin as sole grafting material: a six-year experience. Implant Dent. 2011;20(1):2-12.
44. Toffler M, Toscano N, Holtzclaw D. Osteotome-mediated sinus floor elevation using only platelet-rich fibrin: an early report on 110 patients. Implant Dent. 2010;19(5):447-56.
45. Inchingolo F, Tatullo M, Marrelli M, Inchingolo AM, Scacco S, Inchingolo AD, et al. Trial with Platelet-Rich Fibrin and Bio-Oss used as grafting materials in the treatment of the severe maxillar bone atrophy: clinical and radiological evaluations. Eur Rev Med Pharmacol Sci. 2010;14(12):1075-84.
46. Mazor Z, Horowitz RA, Del Corso M, Prasad HS, Rohrer MD, Dohan Ehrenfest DM. Sinus floor augmentation with simultaneous implant placement using Choukroun's platelet-rich fibrin as the sole grafting material: a radiologic and histologic study at 6 months. J Periodontol. 2009;80(12):2056-64.
47. Diss A, Dohan DM, Mouhyi J, Mahler P. Osteotome sinus floor elevation using Choukroun's platelet-rich fibrin as grafting material: a 1-year prospective pilot study with microthreaded implants. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105(5):572-9.
48. Choukroun J, Diss A, Simonpieri A, Girard M-O, Schoeffler C, Dohan SL, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part V: histologic evaluations of PRF effects on bone allograft maturation in sinus lift. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(3):299-303.
49. Bölükbaşı N, Ersanlı S, Keklikoğlu N, Başeğmez C, Özdemir T. Sinus augmentation with platelet-rich fibrin in combination with bovine bone graft versus bovine bone graft in combination with collagen membrane. J Oral Implantol. 2013.
50. Tanaka H, Toyoshima T, Atsuta I, Ayukawa Y, Sasaki M, Matsushita Y, et al. Additional Effects of Platelet-Rich Fibrin on Bone Regeneration in Sinus Augmentation With Deproteinized Bovine Bone Mineral: Preliminary Results. Implant Dent. 2015.
51. Gassling V, Douglas TE, Purcz N, Schaubroeck D, Balcaen L, Bliznuk V, et al. Magnesium-enhanced enzymatically mineralized platelet-rich fibrin for bone regeneration applications. Biomed Mater. 2013;8(5):055001.
52. Kanayama T, Sigetomi T, Sato H, Yokoi M. Crestal approach sinus floor elevation in atrophic posterior maxilla using only platelet rich fibrin as grafting material: A computed tomography evaluation of 2 cases. J Oral Maxillofac Surg Med Pathol. 2013.
53. Toffler M. Guided bone regeneration (GBR) using cortical bone pins in combination with leukocyte- and platelet-rich fibrin (L-PRF). Compend Contin Educ Dent. 2014;35(3):192-8.
54. Montanari M, Callea M, Yavuz I, Maglione M. A new biological approach to guided bone and tissue regeneration. BMJ case reports. 2013;2013:bcr2012008240.
55. Kim J-S, Jeong M-H, Jo J-H, Kim S-G, Oh J-S. Clinical application of platelet-rich fibrin by the application of the Double J technique during implant placement in alveolar bone defect areas: case reports. Implant Dent. 2013;22(3):244-9.
56. Vijayalakshmi R, Rajmohan CS, Deepalakshmi D, Sivakami G. Use of platelet rich fibrin in a fenestration defect around an implant. J Indian Soc Periodontol. 2012;16(1):108-12.
57. Kfir E, Kfir V, Eliav E, Kaluski E. Minimally invasive guided bone regeneration. J Oral Implantol. 2007;33(4):205-10.
58. Angelo T, Marcel W, Andreas K, Izabela S. Biomechanical Stability of Dental Implants in Augmented Maxillary Sites: Results of a Randomized Clinical Study with Four Different Biomaterials and PRF and a Biological View on Guided Bone Regeneration. Biomed Res Int. 2015;2015.
59. Peck MT, Marnewick J, Stephen LX, Singh A, Patel N, Majeed A. The use of leukocyte- and platelet-rich fibrin (L-PRF) to facilitate implant placement in bone-deficient sites: a report of two cases. SADJ. 2012;67(2):54-6, 8-9.
60. Zhao J-H, Tsai C-H, Chang Y-C. Clinical application of platelet-rich fibrin as the sole grafting material in maxillary sinus augmentation. J Formos Med Assoc. 2015.
61. Gowda VS, Priya BM. An Innovative Combined Three Dimensional Augmentation of Alveolar Ridge using Titanium Mesh, PRF and Autogenous Bone Graft with Implant Placement. Chettinad Health City. 2013:137.
62. Kocyigit ID, Tuz HH, Alp YE, Atil F, Tekin U, Coskunses FM. Correction of postsurgical alveolar ridge defect with vertical alveolar distraction of the onlay block graft. J Craniofac Surg. 2012;23(5):1550-2.
63. Barone A, Ricci M, Romanos GE, Tonelli P, Alfonsi F, Covani U. Buccal bone deficiency in fresh extraction sockets: a prospective single cohort study. Clin Oral Implants Res. 2014.
64. Hauser F, Gaydarov N, Badoud I, Vazquez L, Bernard J-P, Ammann P. Clinical and histological evaluation of postextraction platelet-rich fibrin socket filling: a prospective randomized controlled study. Implant Dent. 2013;22(3):295-303.
65. Suttapreyasri S, Leepong N. Influence of Platelet-Rich Fibrin on Alveolar Ridge Preservation. J Craniofac Surg. 2013;24(4):1088-94.

66. Girish Rao S, Bhat P, Nagesh KS, Rao GH, Mirle B, Kharbhari L, et al. Bone regeneration in extraction sockets with autologous platelet rich fibrin gel. J Maxillofac Oral Surg. 2013;12(1):11-6.
67. Gupta HS, Chowdhary KY, Pathak TS, Kini VV, Pereira R, Mistry A. Socket Preservation at Molar Site using Platelet Rich Fibrin and Bioceramics for Implant Site Development. Development. 2013;3(2):102-7.
68. Singh A, Kohli M, Gupta N. Platelet rich fibrin: a novel approach for osseous regeneration. J Maxillofac Oral Surg. 2012;11(4):430-4.
69. Simon BI, Gupta P, Tajbakhsh S. Quantitative evaluation of extraction socket healing following the use of autologous platelet-rich fibrin matrix in humans. Int J Periodontics Restorative Dent. 2011;31(3):285-95.
70. Ruga E, Gallesio C, Boffano P. Platelet-rich fibrin and piezoelectric surgery: a safe technique for the prevention of periodontal complications in third molar surgery. J Craniofac Surg. 2011;22(5):1951-5.
71. Peck MT, Marnewick J, Stephen L. Alveolar ridge preservation using leukocyte and platelet-rich fibrin: a report of a case. Case Rep Dent. 2011;2011:345048.
72. Baslarli O, Tumer C, Ugur O, Vatankulu B. Evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. Med Oral Patol Oral Cir Bucal. 2015;20(1):e111.
73. Kumar N, Prasad K, Ramanujam L, Ranganath K, Dexith J, Chauhan A. Evaluation of Treatment Outcome After Impacted Mandibular Third Molar Surgery With the Use of Autologous Platelet-Rich Fibrin: A Randomized Controlled Clinical Study. J Oral Maxillofac Surg. 2015;73(6):1042-9.
74. Marrelli M, Tatullo M. Influence of PRF in the healing of bone and gingival tissues. Clinical and histological evaluations. Eur Rev Med Pharmacol Sci. 2013;17(14):1958-62.
75. Lekovic V, Milinkovic I, Aleksic Z, Jankovic S, Stankovic P, Kenney EB, et al. Platelet-rich fibrin and bovine porous bone mineral vs. platelet-rich fibrin in the treatment of intrabony periodontal defects. J Periodontal Res. 2012;47(4):409-17.
76. Pradeep AR, Rao NS, Agarwal E, Bajaj P, Kumari M, Naik SB. Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of 3-wall intrabony defects in chronic periodontitis: a randomized controlled clinical trial. J Periodontol. 2012;83(12):1499-507.
77. Bansal C, Bharti V. Evaluation of efficacy of autologous platelet-rich fibrin with demineralized-freeze dried bone allograft in the treatment of periodontal intrabony defects. J Indian Soc Periodontol. 2013;17(3):361.
78. Sharma A, Pradeep AR. Treatment of 3-wall intrabony defects in patients with chronic periodontitis with autologous platelet-rich fibrin: a randomized controlled clinical trial. J Periodontol. 2011;82(12):1705-12.
79. Thorat M, Pradeep AR, Pallavi B. Clinical effect of autologous platelet-rich fibrin in the treatment of intra-bony defects: a controlled clinical trial. J Clin Periodontol. 2011;38(10):925-32.
80. Chang IC, Tsai CH, Chang YC. Platelet-rich fibrin modulates the expression of extracellular signal-regulated protein kinase and osteoprotegerin in human osteoblasts. J Biomed Mater Res A. 2010;95(1):327-32.
81. Agarwal A, Gupta ND, Jain A. Platelet rich fibrin combined with decalcified freeze-dried bone allograft for the treatment of human intrabony periodontal defects: a randomized split mouth clinical trail. Acta Odontol Scand. 2016;74(1):36-43.
82. Ajwani H, Shetty S, Gopalakrishnan D, Kathariya R, Kulloli A, Dolas R, et al. Comparative evaluation of platelet-rich fibrin biomaterial and open flap debridement in the treatment of two and three wall intrabony defects. J Int Oral Health. 2015;7(4):32-7.
83. Elgendy EA, Shady TEA. Clinical and radiographic evaluation of nanocrystalline hydroxyapatite with or without platelet-rich fibrin membrane in the treatment of periodontal intrabony defects. J Indian Soc Periodontol. 2015;19(1):61.
84. Pradeep A, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad C. Platelet Rich Fibrin with 1% Metformin for the Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Controlled Clinical Trial. J Periodontol. 2015(0):1-14.
85. Mathur A, Bains VK, Gupta V, Jhingran R, Singh G. Evaluation of intrabony defects treated with platelet-rich fibrin or autogenous bone graft: A comparative analysis. Eur J Dent. 2015;9(1):100.
86. Shah M, Patel J, Dave D, Shah S. Comparative evaluation of platelet-rich fibrin with demineralized freeze-dried bone allograft in periodontal infrabony defects: A randomized controlled clinical study. J Indian Soc Periodontol. 2015;19(1):56.
87. Gupta S, Jhingran R, Gupta V, Bains V, Madan R, Rizvi I. Efficacy of platelet-rich fibrin vs. enamel matrix derivative in the treatment of periodontal intrabony defects: a clinical and cone beam computed tomography study. J Int Acad Periodontol. 2014;16(3):86-96.
88. Rosamma Joseph V, Sam G, Amol NV. Clinical evaluation of autologous platelet rich fibrin in horizontal alveolar bony defects. J Clin Diagn Res. 2014;8(11):ZC43.
89. Bajaj P, Pradeep A, Agarwal E, Rao NS, Naik SB, Priyanka N, et al. Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of mandibular degree II furcation defects: a randomized controlled clinical trial. J Periodontal Res. 2013;48(5):573-81.
90. Sharma A, Pradeep AR. Autologous platelet-rich fibrin in the treatment of mandibular degree II furcation defects: a randomized clinical trial. J Periodontol. 2011;82(10):1396-403.

91. Chang YC, Zhao JH. Effects of platelet-rich fibrin on human periodontal ligament fibroblasts and application for periodontal infrabony defects. Aust Dent J. 2011;56(4):365-71.
92. Pradeep A, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad C. Platelet Rich Fibrin with 1% Metformin for the Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Controlled Clinical Trial. J Periodontol. 2015(0):1-14.
93. Shah MP, Gujjari SK, Shah KM. Labial-cervical-vertical groove: A silent killer-Treatment of an intrabony defect due to it with platelet rich fibrin. J Indian Soc Periodontol. 2014;18(1):98.
94. Anuroopa P, Padmavathi Patil VKR. Role and Efficacy of L-PRFmatrix in the Regeneration of Periodontal Defect: a New Perspective. J Clin Diagn Res. 2014;8(12):ZD03.
95. Panda S, Jayakumar N, Sankari M, Varghese SS, Kumar DS. Platelet rich fibrin and xenograft in treatment of intrabony defect. Contemp Clin Dent. 2014;5(4):550.
96. Singh S, Singh A, Singh S, Singh R. Application of PRF in surgical management of periapical lesions. National J Maxial Surg. 2013;4(1):94.
97. Dhiman M, Kumar S, Duhan J, Sangwan P, Tewari S. Effect of Platelet-rich Fibrin on Healing of Apicomarginal Defects: A Randomized Controlled Trial. J Endod. 2015.
98. Panda S, Ramamoorthi S, Jayakumar ND, Sankari M, Varghese SS. Platelet rich fibrin and alloplast in the treatment of intrabony defect. J Pharm Bioallied Sci. 2014;6(2):127-31.
99. Anilkumar Kanakamedala GA, Sudhakar U, Vijayalakshmi R, Ramakrishnan T, Emmadi P. Treatment of a furcation defect with a combination of platelet-rich fibrin (PRF) and bone graft–a case report. ENDO (Lond Engl). 2009;3(2):127-35.
100. Nagaveni N, Kumari K, Poornima P, Reddy V. Management of an endo-perio lesion in an immature tooth using autologous platelet-rich fibrin: a case report. J Indian Soc Pedod Prev Dent. 2015;33(1):69.
101. Varughese V, Mahendra J, Thomas AR, Ambalavanan N. Resection and Regeneration–A Novel Approach in Treating a Perio-endo Lesion. J Clin Diagn Res. 2015;9(3):ZD08.
102. Karunakar P, Prasanna JS, Jayadev M, Shravani GS. Platelet-rich fibrin,"a faster healing aid" in the treatment of combined lesions: A report of two cases. J Indian Soc Periodontol. 2014;18(5):651.
103. Sam G, Shivashankar VY. Management of a pathologically migrated upper anterior tooth using platelet-rich fibrin and a modified crown preparation technique. J Indian Soc Periodontol. 2014;18(6):786.
104. Mazumdar P, Nag D, Bhunia S. Treatment of Periapical Lesion with Platelet Rich Fibrin. Ind Med Gaz. 2013:28-33.
105. Shivashankar VY, Johns DA, Vidyanath S, Sam G. Combination of platelet rich fibrin, hydroxyapatite and PRF membrane in the management of large inflammatory periapical lesion. J Conserv Dent. 2013;16(3):261-4.
106. Patil VA, Desai MH, Patil VS, Reddy Kaveti H, Ganji KK, Danappanavar PM. A novel approach for treatment of an unusual presentation of radicular cysts using autologous periosteum and platelet-rich fibrin in combination with demineralized freeze-dried bone allograft. Case Rep Dent. 2013;2013:893791.
107. Zhao J-H, Tsai C-H, Chang Y-C. Management of radicular cysts using platelet-rich fibrin and bioactive glass: a report of two cases. J Formos Med Assoc. 2012.
108. Bambal D, Manwar NU, Chandak M, Rudagi K. A comparative evaluation of the healing ability of bilateral periapical lesions treated with and without the use of platelet-rich fibrin. Todays FDA. 2012;24(6):54-7.
109. Jayalakshmi KB, Agarwal S, Singh MP, Vishwanath BT, Krishna A, Agrawal R. Platelet-Rich Fibrin with beta-Tricalcium Phosphate-A Noval Approach for Bone Augmentation in Chronic Periapical Lesion: A Case Report. Case Rep Dent. 2012;2012:902858.
110. Vidhale G, Jain D, Jain S, Godhane AV, Pawar GR. Management of Radicular Cyst Using Platelet-Rich Fibrin & Iliac Bone Graft-A Case Report. J Clin Diagn Res. 2015;9(6):ZD34.
111. Hamzacebi B, Oduncuoglu B, Alaaddinoglu EE. Treatment of Peri-implant Bone Defects with Platelet-Rich Fibrin. Int J Periodontics Restorative Dent. 2014;35(3):415-22.
112. Boora P, Rathee M, Bhoria M. Effect of Platelet Rich Fibrin (PRF) on Peri-implant Soft Tissue and Crestal Bone in One-Stage Implant Placement: A Randomized Controlled Trial. J Clin Diagn Res. 2015;9(4):ZC18-21.
113. Öncü E, Alaaddinoğlu EE. The effect of platelet-rich fibrin on implant stability. Int J Oral Maxillofac Implants. 2014;30(3):578-82.
114. Mohamed JB, Alam MN, Singh G, Chandrasekaran SC. The management of retrograde peri-implantitis: a case report. J Clin Diagn Res. 2012;6(9):1600-2.
115. Del Corso M, Mazor Z, Rutkowski JL, Dohan Ehrenfest DM. The use of leukocyte- and platelet-rich fibrin during immediate postextractive implantation and loading for the esthetic replacement of a fractured maxillary central incisor. J Oral Implantol. 2012;38(2):181-7.
116. Kim J-W, Kim S-J, Kim M-R. Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study. Br J Oral Maxillofac Surg. 2014;52(9):854-9.
117. Kim JW, Kim SJ, Kim MR. Simultaneous Application of Bone Morphogenetic Protein-2 and Platelet-Rich Fibrin for the Treatment of Bisphosphonate-Related Osteonecrosis of Jaw. J Oral Implant. 2016;42(2):205-8.
118. Reddy PK, Bolla V, Koppolu P, Srujan P. Long palatal connective tissue rolled pedicle graft with demineralized freeze-dried bone allograft plus platelet-rich fibrin combination: A novel technique for ridge augmentation-Three case reports. J Indian Soc Periodontol. 2015;19(2):227.

119. Chaudhary Z, Kumar YR, Mohanty S, Khetrapal A. Amalgamation of allogenic bone graft, platelet-rich fibrin gel, and PRF membrane in auto-transplantation of an impacted central incisor. Contemp Clin Dent. 2015;6(2):250.
120. Shivashankar VY, Johns DA, Vidyanath S, Kumar MR. Platelet rich fibrin in the revitalization of tooth with necrotic pulp and open apex. J Conserv Dent. 2012;15(4):395.
121. Ji B, Sheng L, Chen G, Guo S, Xie L, Yang B, et al. The Combination Use of Platelet-Rich Fibrin and Treated Dentin Matrix for Tooth Root Regeneration by Cell Homing. Tissue Eng Part A. 2015;21(1-2):26-34.
122. Kulkarni MR, Thomas BS, Varghese JM, Bhat GS. Platelet-rich fibrin as an adjunct to palatal wound healing after harvesting a free gingival graft: A case series. J Indian Soc Periodontol. 2014;18(3):399.
123. Kazemi D, Fakhrjou A, Dizaji VM, Khanzadeh M. Effect of autologous platelet rich fibrin on the healing of experimental articular cartilage defects of the knee in an animal model. Biomed Res Int. 2014.
124. Hiremath H, Kulkarni S, Sharma R, Hiremath V, Motiwala T. Use of Platelet-rich fibrin as an autologous biologic rejuvenating media for avulsed teeth–an in vitro study. Dent Traumatol. 2014;30(6):442-6.
125. O'Connell SM, Impeduglia T, Hessler K, Wang XJ, Carroll RJ, Dardik H. Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic lower-extremity ulcers. Wound Repair Regen. 2008;16(6):749-56.
126. Shah M, Deshpande N, Bharwani A, Nadig P, Doshi V, Dave D. Effectiveness of autologous platelet-rich fibrin in the treatment of intra-bony defects: A systematic review and meta-analysis. J Indian Soc Periodontol. 2014;18(6):698.
127. Ali S, Bakry SA, Abd-Elhakam H. Platelet rich fibrin in maxillary sinus augmentation: A systematic review. J Oral Implantol. 2015;41(6):746-53.
128. Castaneda S, Largo R, Calvo E, Rodriguez-Salvanes F, Marcos M, Diaz-Curiel M, et al. Bone mineral measurements of subchondral and trabecular bone in healthy and osteoporotic rabbits. Skeletal Radiol. 2006;35(1):34-41.
129. Dohan Ehrenfest DM, Lemo N, Jimbo R, Sammartino G. Selecting a relevant animal model for testing the in vivo effects of Choukroun's platelet-rich fibrin (PRF): rabbit tricks and traps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110(4):413-6; author reply 6-8.
130. Bastami F. Letter to the Editor: Critical-sized bone defect in sheep model. Bone. 2014;68:162.
131. Semyari H, Rajipour M, Bastami F, Semyari H. Isolation and Culture of Mesenchymal Stem Cells From Rabbit Scapular Subcutaneous Adipose Tissue and Their Ability to Differentiate Into Osteoblasts. Avicenna J Dent Res. 2015;7(2).
132. Khojasteh A, Sadeghi N. Application of buccal fat pad-derived stem cells in combination with autogenous iliac bone graft in the treatment of maxillomandibular atrophy: a preliminary human study. Int J Oral Maxillofac Surg. 2016.
133. Ishiy FA, Fanganiello RD, Griesi-Oliveira K, Suzuki AM, Kobayashi GS, Morales AG, et al. Improvement of In Vitro Osteogenic Potential through Differentiation of Induced Pluripotent Stem Cells from Human Exfoliated Dental Tissue towards Mesenchymal-Like Stem Cells. Stem Cells Int. 2015;2015:249098.
134. Kang R, Zhou Y, Tan S, Zhou G, Aagaard L, Xie L, et al. Mesenchymal stem cells derived from human induced pluripotent stem cells retain adequate osteogenicity and chondrogenicity but less adipogenicity. Stem Cell Res Ther. 2015;6(1):144.
135. Jeong S-M, Lee C-U, Son J-S, Oh J-H, Fang Y, Choi B-H. Simultaneous sinus lift and implantation using platelet-rich fibrin as sole grafting material. J Craniomaxillofac Surg. 2014;42(6):990-4.
136. Celenk C, Celenk P. Relationship of mandibular and cervical vertebral bone density using computed tomography. Dentomaxillofac Radiol. 2014.
137. Parsa A, Ibrahim N, Hassan B, Stelt P, Wismeijer D. Bone quality evaluation at dental implant site using multislice CT, micro-CT, and cone beam CT. Clin Oral Implants Res. 2015;26(1):e1-e7.
138. Shapurian T, Damoulis PD, Reiser GM, Griffin TJ, Rand WM. Quantitative evaluation of bone density using the Hounsfield index. Int J Med Sci. 2005;21(2):290-7.
139. Houshmand B, Behnia H, Khoshzaban A, Morad G, Behrouzi G, Dashti SG, et al. Osteoblastic differentiation of human stem cells derived from bone marrow and periodontal ligament under the effect of enamel matrix derivative and transforming growth factor-Beta. Int J Oral Maxillofac Implants. 2012;28(6):e440-50.
140. Khojasteh A, Dashti SG, Dehghan MM, Behnia H, Abbasnia P, Morad G. The osteoregenerative effects of platelet-derived growth factor BB cotransplanted with mesenchymal stem cells, loaded on freeze-dried mineral bone block: A pilot study in dog mandible. J Biomed Mater Res B Appl Biomater. 2014.
141. Khojasteh A, Behnia H, Naghdi N, Esmaeelinejad M, Alikhassy Z, Stevens M. Effects of different growth factors and carriers on bone regeneration: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2013;116(6):e405-e23.
142. Khojasteh A, Behnia H, Shayesteh YS, Morad G, Alikhasi M. Localized bone augmentation with cortical bone blocks tented over different particulate bone substitutes: a retrospective study. Int J Oral Maxillofac Implants. 2011;27(6):1481-93.
143. Özkan Y, Akoglu B, Kulak-Özkan Y. Maxillary sinus floor augmentation using bovine bone grafts with simultaneous implant placement: a 5-year prospective follow-up study. Implant Dent. 2011;20(6):455-9.

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