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 symphysisal 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...
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), microcomputed-tomography (CT) scans (19, 33) and quantitative CT (qCT) (32, 36) based on bone mineral density measurement (Hounsfield 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 radiovisography (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 (BPM) (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 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), NBMM (9, 20), TA (35), BCP (31, 32, 39) and BMSCs (19, 36), while, in the other studies, mixtures of L-PRF with TCP (37)
L-PRF in bone regeneration

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

<table>
<thead>
<tr>
<th>Number and type of animals</th>
<th>Defect location &amp; size</th>
<th>Used materials</th>
<th>Evaluatio n methods</th>
<th>Bone gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pripatnanont et al. (30)</td>
<td>12, rabbit</td>
<td>Periosteal distraction (mandible)</td>
<td>Hyrax device (A) Hyrax device + L-PRF (B)</td>
<td>HA Micro-CT</td>
</tr>
<tr>
<td>Yuanzheng et al. (36)</td>
<td>20, dog</td>
<td>Unilateral alveolar cleft</td>
<td>ABG + BMSCs+ L-PRF (A) ABG+BMSCs(B) ABG+L-PRF (C) ABG (D)</td>
<td>Quantitati ve CT Histologic</td>
</tr>
<tr>
<td>Oliviera et al. (20)</td>
<td>48 rats</td>
<td>cranium, 5mm</td>
<td>Bio-Oss* L-PRF Comb.</td>
<td>HA</td>
</tr>
<tr>
<td>Acar et al. (31)</td>
<td>20 rabbits</td>
<td>Calvarium, 6mm</td>
<td>HAp/BCP L-PRF Comb.</td>
<td>HA Micro-CT</td>
</tr>
<tr>
<td>Nacopoulos et al. (32)</td>
<td>15 rabbits</td>
<td>Femoral condyle</td>
<td>L-PRF L-PRF+BCP</td>
<td>Histologic Quantitative CT</td>
</tr>
<tr>
<td>Yilmaz et al. (37)</td>
<td>3 pigs</td>
<td>Tibia, 5mm</td>
<td>β-TCP L-PRF Comb.</td>
<td>Stereology</td>
</tr>
<tr>
<td>Kim et al. (21)</td>
<td>12 rabbits</td>
<td>Calvarium, oval 10mm+15mm</td>
<td>PRP L-PRF CGF</td>
<td>HA</td>
</tr>
<tr>
<td>Li et al. (18)</td>
<td>A rat</td>
<td>Cranium CSBD</td>
<td>LPRF L-PRF: Fibrin gel</td>
<td>HA</td>
</tr>
<tr>
<td>Yoon et al. (22)</td>
<td>10 rabbits</td>
<td>Calvarium 7mm</td>
<td>Bio-Oss*+ L-PRF Bio-Oss*</td>
<td>HA</td>
</tr>
<tr>
<td>Xuan (9)</td>
<td>6 dogs</td>
<td>Sinus,-</td>
<td>Bio-Oss*+ Tissel* Bio-Oss*+ L-PRF</td>
<td>HA</td>
</tr>
<tr>
<td>Srisurang et al. (38)</td>
<td>6 minipigs, Dental socket,-</td>
<td>L-PRF FGG (control) Comb.</td>
<td>HA OD</td>
<td>After 12 weeks: NBF was higher in PRF than others, NS OD in L-PRF: 158.57±30.74*, FGG:108.39±29.99, Comb.: 111.69±21.36 &amp; empty: 91.31±37,33</td>
</tr>
<tr>
<td>Hatakeyama et al. (33)</td>
<td>12 dogs</td>
<td>Dental socket,-</td>
<td>PPP PRP L-PRF</td>
<td>Micro-CT</td>
</tr>
<tr>
<td>Jeong S. et al. (34)</td>
<td>6 dogs</td>
<td>Sinus 1+ 1.5 cm2</td>
<td>L-PRF</td>
<td>HA CT scan</td>
</tr>
<tr>
<td>Pripatnanont et al. (23)</td>
<td>10 rabbits</td>
<td>Calvarium 10+10 mm</td>
<td>ABG (A) DBB (B) L-PRF (C) ABG+DBB (D) ABG+ L-PRF (E) DBB+L-PRF (F) ABG+ DBB +PRF (G)</td>
<td>HA</td>
</tr>
<tr>
<td>Tunali et al. (24)</td>
<td>6 rabbits</td>
<td>Calvarium 7mm</td>
<td>T-PRF</td>
<td>Histology</td>
</tr>
<tr>
<td>Honda et al. (19)</td>
<td>27 rat</td>
<td>Calvarium CSBD</td>
<td>LPRF L-PRF+ BMSCs</td>
<td>Micro-CT</td>
</tr>
</tbody>
</table>

Regeneration, Reconstruction & Restoration 2016;1(2):47-68
Bolukbasi et al. (39)  | 6 sheep | Tibia 5mm | BCP, L-PRF Comb. | HA | NBF in Comb. after 10 days: 11.4±0.7%, 20 days: 42.±0.9* & 40 days: 54.±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-PRF (B) TA+PRF (C) | HA | NBF at 4th week (%): A: 59.±22.79 B: 52.±26.85, C: 78.±6.95*, control: 38.±15.84. NBF at 8th week (%): A: 70.±±11.1, B: 65.8±27.03, C: 87.±9.15*, control: 59.±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:3mm, length:5mm | L-PRF | HA | After 8 weeks NBF in: L-PRF:29.30%±7.50%* & control:11.06%±8.94%.

Kim et al. (27)  | 36 rabbits | Calvarium , 8mm | TCP+rhBMP,(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: 51.9±27.90%* & control: 11.67±15.2%.

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%.


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

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number of patients, sites, implants</th>
<th>Type of surgery</th>
<th>Used materials</th>
<th>Evaluation methods</th>
<th>Bone gain</th>
<th>Survival rate of implants (follow-up point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka et al. (50)</td>
<td>Preliminary study</td>
<td>4,4,-</td>
<td>Two stage</td>
<td>DBBM/L-PRF</td>
<td>HA</td>
<td>After 7-10 mo.: 43.±5.7%</td>
</tr>
<tr>
<td>Bosshardt et al. (40)</td>
<td>CT</td>
<td>12, 16, 16</td>
<td>Two stage</td>
<td>NanoBone + L-PRF NanoBone + RCM</td>
<td>HA</td>
<td>After 7-11 mo.: NBF in L-PRF (%): 28.6±6.90 RCM: 28.7±6.54 NS RGM in L-PRF (%): 25.7±8.8 RCM: 25.5±7.6 NS 100%, 12 weeks</td>
</tr>
<tr>
<td>Gassling et al. (8)</td>
<td>RSMD</td>
<td>6, 12, 32</td>
<td>Two stage</td>
<td>Bio-Oss* +ABG+ L-PRF Bio-Oss* +ABG+ RCM</td>
<td>HA</td>
<td>After 5 mo. NBF in L-PRF:17.0 (7.8-27.8)% &amp; RCM : 17.2 (8.5-24.2) % NS RGM in L-PRF(%): 15.9 (0.9-33.4)% &amp; in RCM: 17.3 (0.7-33.5)% NS 100%,12 mo.</td>
</tr>
<tr>
<td>Tajima et al. (41)</td>
<td>CS</td>
<td>6, 9, 17</td>
<td>One stage</td>
<td>L-PRF (sole material)</td>
<td>CT scan</td>
<td>After 6 mo., the mean density of NBF around the implants: 323 ± 156.2 HU (185 to 713 HU) 100%, 6 mo.</td>
</tr>
<tr>
<td>Bülükbaşı et al. (49)</td>
<td>RS</td>
<td>25,32,66</td>
<td>Two stage</td>
<td>Bio-Oss* + L-PRF BioOss*+RCM</td>
<td>HA</td>
<td>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.</td>
</tr>
<tr>
<td>Tatullo et al. (11)</td>
<td>CS</td>
<td>60, 72, 240</td>
<td>Two stage</td>
<td>Bio-Oss* + L-PRF Bio-Oss*</td>
<td>Histologic &amp; clinical</td>
<td>Trabecular bone after 106 days in test : 22.79% &amp; in control: 26.44% NS after 120days in test: 26.15% in control: 28.7% NS after 150 days in test: 37.06% in control:38.97 NS NR</td>
</tr>
</tbody>
</table>
**Table 3.** Included studies using L-PRF in GBR technique and bone augmentation

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

Gupta et al. (67)  One  L-PRF+ BCP  Compromised extraction sockets preservation  Clinical & radiographic  satisfactory and successful regeneration after 6 mo.  NR

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

Kocygigit 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


<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number of patients &amp; involved location</th>
<th>Used materials</th>
<th>Evaluation methods</th>
<th>Bone gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baslarli et al. (72)</td>
<td>20, 40 3rd MMs</td>
<td>L-PRF</td>
<td>technetium-99m methylene diphosphonate uptake</td>
<td>No significant different between PRF-treated and non-PRF-treated sockets after 30 and 90 days postoperatively</td>
</tr>
<tr>
<td>Kumar et al. (73)</td>
<td>31, 31 3rd MMs</td>
<td>L-PRF</td>
<td>Clinical &amp; radiographic</td>
<td>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</td>
</tr>
<tr>
<td>Barone et al. (63)</td>
<td>33, anterior of maxilla, BBD</td>
<td>CCPB+ L-PRF+ CM</td>
<td>Radiographic</td>
<td>Improvement of vertical bone level after 5 months: 0.8 ± 0.1 mm (mesial site)* 0.7 ± 0.1 mm (distal site)*</td>
</tr>
<tr>
<td>Hauser et al. (64)</td>
<td>23, premolar site</td>
<td>L-PRF L-PRF+ flap</td>
<td>Micro-CT &amp; histologic</td>
<td>BV/TV after 8 weeks: PRF: 0.28±0.037, PRF+ flap: 0.197±0.027, control: 0.249±0.037. A significant effect on intrinsic bone quality &amp; preservation of the alveolar width was observed using PRF vs. L-PRF+ flap</td>
</tr>
</tbody>
</table>
Regeneration, Reconstruction & Restoration 2016;1(2):47-68

L-PRF in bone regeneration

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 (1.61 ± 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

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

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Number of cases, problem</th>
<th>Used materials</th>
<th>Evaluation method</th>
<th>Bone gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrawal et al. (81) SMD</td>
<td>60, PID with CP</td>
<td>L-PRF+ DFDBA (A) DFDBA(B)</td>
<td>Clinical &amp; radiographic</td>
<td>After 12 months**:</td>
</tr>
<tr>
<td>Ajwani et al. (82) SMD</td>
<td>40, PID</td>
<td>L-PRF+OFD OFD</td>
<td>Clinical &amp; radiographic</td>
<td>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</td>
</tr>
<tr>
<td>Elgendy &amp; Shady (2015)(83) SMD</td>
<td>40, PID</td>
<td>L-PRF+ NcHA NcHA</td>
<td>Clinical &amp; radiographic</td>
<td>After 6 months**: Mean PDR in L-PRF+ NcHA: 3.33mm &amp; 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</td>
</tr>
<tr>
<td>Pradeep et al. (92) RCT</td>
<td>120, PID with CP</td>
<td>1%MF+L-PRF+OFD (A) 1%MF+OFD (B) L-PRF+OFD (C) OFD (D)</td>
<td>Clinical &amp; radiographic</td>
<td>After 9 months**: PDR in A (mm): 4.90±0.30*, B:3.93±0.25*, C:4.00±0.18* &amp; D:3.00±0.18 CAG in A (mm): 4.90±0.30*, B:3.93±0.25*, C:4.03±0.18* &amp; D:2.96±0.18 RBF in A (%): 52.65±0.04*, B:48.69±0.026*, C:48% ± 0.029% &amp; D:9.14% ± 0.04%</td>
</tr>
<tr>
<td>Mathur et al. (85) CT</td>
<td>38, PID</td>
<td>OFD+L-PRF OFD+ABG</td>
<td>Clinical &amp; radiographic</td>
<td>After 6 months**: Mean 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</td>
</tr>
<tr>
<td>Shah et al. (86) SMD</td>
<td>40,PID</td>
<td>OFD+L-PRF OFD+DFDBA</td>
<td>Clinical &amp; radiographic</td>
<td>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</td>
</tr>
<tr>
<td>Rosamma et al. (88) SMD</td>
<td>45, horizontal defects</td>
<td>L-PRF+OFD (A) L-PRF+L-PRF membrane+ OFD (B) OFD (C)</td>
<td>Clinical &amp; radiographic</td>
<td>After 9 months**: PDR in A (mm): 1.73±0.53*, B:1.7±0.45* &amp; C: 1.1±0.38 CAG in A (mm): 1.56±0.62*, B:1.7±0.52* &amp; C:0.86±0.58</td>
</tr>
<tr>
<td>Gupta et al. (87) RCT</td>
<td>44, PID with CP</td>
<td>L-PRF EMD</td>
<td>Clinical &amp; CBCT</td>
<td>After 6 months**:</td>
</tr>
<tr>
<td>Bansal et al. (89) SMD</td>
<td>20, PID</td>
<td>DFDBA+</td>
<td>Clinical &amp;</td>
<td>After 6 months**:</td>
</tr>
</tbody>
</table>

Bajaj et al. (89)  
**RCCT**  72, degree II MFI  
L-PRF+OFD PRP+OFD OFD  
Clinical & radiographic  
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±11.39* & PRP: 56.85±14.01* 

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* 

Pradeep et al. (76)  
**CT**  90, PID with CP  
L-PRF+OFD PRP+OFD OFD  
Clinical & radiographic  
After 9 months: 
PDR (nm): L-PRF (3.77±1.19) & PRP (3.77±1.07)  
CAG (nm): 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: 4.0±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 PRF vs. OFD (mm): 3.69±0.44 vs. 2.13±0.43*  
RBF in 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. 18.0±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): 4.05±0.416* vs. 2.89±0.676  
RVCAG in test vs. control (mm): 2.333±0.483* 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 


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

<table>
<thead>
<tr>
<th>Number of cases &amp; Problem</th>
<th>Used materials</th>
<th>Evaluation methods</th>
<th>Bone gain</th>
</tr>
</thead>
</table>
| 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 |
Table 7. Included clinical trials using L-PRF in endodontic surgery

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Number of cases, problem</th>
<th>Used materials</th>
<th>Evaluation methods</th>
<th>Bone gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhiman et al (99)</td>
<td>RCT</td>
<td>30, Apico-marginal lesions</td>
<td>L-PRF</td>
<td>Clinical and radiographic</td>
</tr>
<tr>
<td>Singh et al (15)</td>
<td>CT</td>
<td>15, peri-apical lesions</td>
<td>L-PRF</td>
<td>Radiographic</td>
</tr>
</tbody>
</table>

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 peri-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

<table>
<thead>
<tr>
<th>No of cases</th>
<th>problem</th>
<th>Used materials</th>
<th>Evaluation methods</th>
<th>Bone gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vidhale et al(2015)(112)</td>
<td>3</td>
<td>RC</td>
<td>L-PRF+ Iliac bone graft</td>
<td>Radiographic</td>
</tr>
<tr>
<td>Nagaveni et al (2015)(102)</td>
<td>1</td>
<td>PID with EI (immature tooth)</td>
<td>L-PRF</td>
<td>Clinical &amp; radiographic</td>
</tr>
<tr>
<td>Varughese et al (2015)(103)</td>
<td>1</td>
<td>PID with EI</td>
<td>L-PRF+ bone graft+ membrane</td>
<td>Clinical &amp; radiographic</td>
</tr>
<tr>
<td>Karunakar et al (2014)(104)</td>
<td>2</td>
<td>PID with EI</td>
<td>L-PRF</td>
<td>Clinical &amp; radiographic</td>
</tr>
<tr>
<td>Panda et al (2014)(100)</td>
<td>1</td>
<td>PID with EI</td>
<td>PRF+ bone graft</td>
<td>Clinical &amp; radiographic</td>
</tr>
<tr>
<td>Goyal et al (2014)(22)</td>
<td>1</td>
<td>EPL</td>
<td>L-PRF+BG</td>
<td>Clinical &amp; radiographic</td>
</tr>
<tr>
<td>Sam and Shivashankar (2014)(105)</td>
<td>1</td>
<td>PID+EI</td>
<td>L-PRF</td>
<td>Clinical &amp; radiographic</td>
</tr>
</tbody>
</table>
**Table 9. Included studies on peri-implant bone defects treated by L-PRF**

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Aim</th>
<th>Number of cases</th>
<th>Used materials</th>
<th>Evaluation method</th>
<th>Results</th>
</tr>
</thead>
</table>
| 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                           | 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. |

Table 10. Included studies using L-PRF in treatment of bisphosphonate-related osteonecrosis of the jaw

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

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

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

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, Knappen 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 Hounsfield 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-β1), 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 sheep (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 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 relative 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 hydroxypatite (54) or ABG with using vertical alveolar distraction (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 millimeter) by crestal approach (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 millimeter 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 effectiveness 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 height 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 procedure 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 baseline, 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 baseline (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 complete 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), tricalcium 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.

Conflict of Interest: ‘None declared’.

**References**


