Int. J. Oral Maxillofac. Surg. 2019; 48: 250–262
https://doi.org/10.1016/j.ijom.2018.06.003, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Systematic Review
Pre-Implant Surgery

Effects of leukocyte–platelet-rich fibrin (L-PRF) in different intraoral bone grafting procedures: a systematic review

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P. Dragonas, T. Katsaros, G. Avila-Ortiz, L. Chambrone, J.H. Schiavo, A. Palaiologou: Effects of leukocyte–platelet-rich fibrin (L-PRF) in different intraoral bone grafting procedures: a systematic review. Int. J. Oral Maxillofac. Surg. 2019; 48: 250–262.

Abstract. This systematic review aimed to assess the effects of leukocyte–platelet-rich fibrin (L-PRF) on bone regeneration, soft tissue healing, and postoperative complications in patients undergoing ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures. A comprehensive literature search was conducted by two independent reviewers. Only randomized and non-randomized controlled clinical trials were selected. Outcome data were extracted and critically analyzed. A total of 17 articles were included in the qualitative synthesis. The use of L-PRF in extraction sockets was associated with a modest beneficial effect by decreasing alveolar ridge remodeling and postoperative pain when compared to natural healing. In contrast, the use of L-PRF in maxillary sinus augmentation procedures was not associated with more favorable outcomes, and its use in ridge augmentation procedures could not be assessed adequately as it was reported in only one study. No meta-analysis could be conducted due to the heterogeneity of the selected studies. The limited evidence on the effects of L-PRF in intraoral bone grafting procedures highlights the need for further research to fully assess its clinical indications, with an emphasis on the application of standardized protocols for the preparation of this autologous product.

Key words: leukocytes; platelet-rich fibrin; maxillary sinus; alveolar ridge augmentation; sinus floor augmentation; tooth extraction; growth factors.

Accepted for publication 7 June 2018
Available online 7 July 2018

Leukocyte–platelet-rich fibrin (L-PRF) was initially introduced by Dr Joseph Choukroun in the early 2000s as a therapeutic adjuvant to enhance wound healing and tissue regeneration following intraoral surgical procedures[1]. L-PRF is considered a second-generation platelet concentrate, characterized by a simplified preparation method without any biochemical manipulation or exogenous additives to the blood sample[2]. For its preparation, venous blood is harvested and centrifuged in a tube

without anticoagulants, resulting in three distinct layers: red blood corpuscles at the bottom, an intermediate layer that represents the L-PRF, and platelet-poor plasma on top[2].

L-PRF is mainly composed of a dense fibrin scaffold that allows for the enmeshment of platelets and leukocytes, which are known to release cytokines and growth factors, playing a crucial role in the healing process[3,4]. Neutrophils and macrophages eliminate bacteria and necrotic tissue via phagocytosis, thus debriding the wound and preventing secondary infections. Platelets and macrophages also secrete growth factors, including transforming growth factor beta 1 (TGF-β1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), which contribute to wound healing through the stimulation of re-epithelialization, angiogenesis, and extracellular matrix formation[5]. When compared to other platelet concentrates, L-PRF has been reported to release higher levels of growth factors over a 10-day period[6]. In vitro and animal studies have shown that L-PRF improves soft tissue wound healing by promoting angiogenesis and cell proliferation[7]. Additionally, clinical studies from different medical fields have reported a positive effect of L-PRF in soft tissue regeneration and angiogenesis[7]. Aside from its beneficial action on soft tissues, the application of L-PRF has also been associated with positive results in bone tissue repair and regeneration. When compared to a widely used porcine collagen membrane, L-PRF appeared to render superior results in terms of the proliferation of human osteoblasts and periosteal cells in vitro[8,9].

Given the reported benefits in soft tissue and bone remodeling in preclinical and in vitro studies, L-PRF has been applied in a plethora of periodontal and oral surgery indications. L-PRF has been employed to reduce postoperative inflammation[10,11], patient-reported pain[12], and the frequency of alveolar osteitis[13,14] after the extraction of third molars. The healing capacity of L-PRF has also been studied in periodontal regenerative and plastic surgery. A recent meta-analysis showed a difference of 1.1 mm probing depth reduction, 1.2 mm clinical attachment gain, and 1.7 mm bone fill in intrabony defects in favor of L-PRF + open flap debridement when compared to open flap debridement alone[15]. When compared with a coronally advanced flap alone, a coronally advanced flap in combination with L-PRF was associated with superior root coverage outcomes in the treatment of Miller class I and II gingival recession[15].

L-PRF has also been utilized widely in oral implantology procedures in an effort to enhance and accelerate tissue healing – as a clot, mixed with a bone graft, or as a membrane. In fact, one of the earliest applications of L-PRF in dentistry was in this field[16]. However, variable results have been reported so far in the dental implant literature regarding its benefits. While some studies have shown that the addition of L-PRF in maxillary sinus augmentation and ridge preservation procedures accelerates new bone formation and reduces alveolar bone resorption[16,17], others have failed to report any gains in similar applications[18,19].

The aim of this systematic review was to critically evaluate the benefits, if any, of L-PRF in different intraoral bone grafting procedures, more specifically in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures.

Methods

This systematic review was structured and conducted according to the preferred reporting items of the PRISMA statement[20].

Focused PICO question

To formulate the question, the following PICO was established: the population (P) comprised systemically healthy patients in need of ridge preservation, ridge augmentation, or maxillary sinus augmentation; the intervention (I) was the addition of L-PRF as biomaterial; the comparison (C) was no addition of L-PRF in the aforementioned procedures; the outcomes (O) assessed were bone regeneration, soft tissue healing, and postoperative complications.

The research question was: ''Does the addition of leukocyte–platelet-rich fibrin enhance bone regeneration and soft tissue healing, and reduce postoperative complications, in systemically healthy patients undergoing ridge preservation (a), ridge augmentation (b), and/or maxillary sinus augmentation (c) procedures, when compared to surgical approaches that do not involve the application of this blood-derived product?''

With the purpose of comprehensively addressing all facets of the main focused question, five specific surrogate questions were formulated: (1) Can L-PRF be used as a substitute for (i) bone grafting materials and (ii) barrier membranes in procedures (a), (b), and (c)? (2) Does the addition of L-PRF to bone grafting materials lead to enhanced bone quantity and bone quality outcomes in procedures (a), (b), and (c)? (3) Does the addition of L-PRF to bone grafting materials accelerate bone maturation in procedures (a), (b), and (c)? (4) Does the adjuvant use of L-PRF improve soft tissue healing in procedures (a), (b), and (c)? (5) Does the use of L-PRF result in less postoperative swelling and patient-reported postoperative pain?

Outcome variables

Outcomes included (1) bone regeneration reported as the percentage of newly formed bone (bone quality), alveolar ridge dimensional changes in millimeters, and socket bone fill (bone quantity) assessed through histology/histomorphometry, clinical measurements, and radiographic analysis; (2) soft tissue healing, reported as healing index scores (tissue color, response to palpation, presence/absence of granulation tissue, incision margin opening) and socket orifice dimensions/closure in millimeters at a given time point; (3) postoperative complications, reported as postoperative swelling and patient-reported pain assessed through questionnaires and clinical presentation.

Eligibility criteria

Inclusion criteria were randomized controlled trials (RCT) and non-randomized controlled clinical trials (CCT) that assessed the treatment of systemically healthy patients undergoing (a) ridge preservation, (b) ridge augmentation, or (c) maxillary sinus augmentation procedures involving the use of L-PRF alone or in combination with bone grafting materials.

Exclusion criteria were studies on other biological healing enhancers, such as fibrin glue, platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), recombinant human PDGF (rh-PDGF), enamel matrix derivative (EMD), and bone morphogenetic proteins (BMPs); studies on the regeneration of periodontal intrabony and furcation defects or periodontal plastic surgery; studies on third molar extraction sockets, as these are not normally related to site preparation for future dental implants; prospective and retrospective cohort studies and case-series; studies including fewer than five patients; in vitro studies; preclinical (animal) studies.

Search strategy

A literature search was conducted employing seven databases: Ovid MEDLINE, Scopus, Embase, Central (Cochrane Library), Web of Science, ProQuest (Dis-

sertations and Theses and Nursing and Allied Health Database), and Google Scholar in an attempt to capture the grey literature, up to December 20, 2017. No date limitations were used in the search and only studies published in the English language were included. Medical subject heading (MeSH) and key terms included platelet-rich fibrin, PRF, alveolar ridge preservation, tooth socket preservation, dental implants, dental implantation, maxillary sinus, sinus floor augmentation, and alveolar ridge augmentation. A decision was made to include platelet-rich fibrin and PRF as MeSH and key terms in this search instead of leukocyte–platelet-rich fibrin and L-PRF, in order to be more inclusive and avoid eliminating studies that may have employed a less precise terminology. The MEDLINE search was adapted for use in searching the other databases. The search was supplemented by hand searches, citation screening, and scanning of all reference lists of selected papers and related reviews. The full search strategies are included in the **Supplementary Material**.

Screening and selection of studies

Titles and abstracts obtained were independently screened by two authors (P.D. and T.K.). If sufficient information was not provided, the full-text article was obtained. Full-text versions of all the eligible articles upon initial screening were obtained and examined independently by both reviewers. The selection of publications was made based on the pre-established eligibility criteria. Disagreements, if any, were resolved by open discussion. In the case that a disagreement was not resolved, an arbiter (G.A.) was consulted. Authors were contacted in the case of incomplete or unpublished results, or for clarification of the data. All of the selected studies were processed for data extraction.

Data collection and analyses

All selected publications were subdivided according to the procedure performed in three separate tables: (a) ridge preservation, (b) ridge augmentation, (c) maxillary sinus augmentation. Two reviewers (P.D. and T.K.) independently extracted relevant data using a pre-designed data extraction table. Data extraction included the first author, year of publication, and study design; population characteristics; parameters recorded and methodology; L-PRF preparation protocol; details of the surgical intervention; comparison/control; treatment outcomes, complications, and patient-reported outcomes.

Risk of bias and quality assessment of included studies

For interventional studies, the methodological quality of the trials was evaluated using the Cochrane Collaboration tool for assessing risk of bias[21], as adapted by Chambrone et al.[22,23], to permit qualification of non-randomized trials. In brief, the following criteria were classified as adequate (+), inadequate (−), unclear (?), or not applicable (NA): the method of randomization; allocation concealment; the blinding of participants, personnel, and outcome assessors; the completeness of follow-up; selective reporting; other sources of bias. Based on this tool, the risk of bias was classified as 'low' if all criteria were met, as 'unclear' if one or more criteria were partly met, or as 'high' if one or more of the criteria were not met.

Results

Study selection

The article selection process is depicted in Fig. 1. A total of 1282 potentially eligible articles were identified following the removal of duplicates. After the application of the eligibility criteria, 1262 articles were excluded based on title and abstract assessment. After a review of the remaining 20 full-text articles, a total of 17 publications were considered for the qualitative analysis[16–19,24–36]; three articles were excluded for multiple reasons (Table 1)[37–39]. The characteristics of all included studies on L-PRF and alveolar ridge preservation, ridge augmentation, and maxillary sinus augmentation are presented in Tables 2, 3, and 4, respectively. A total of eight studies on L-PRF and ridge preservation, one study on L-PRF and ridge augmentation, and eight studies on L-PRF and maxillary sinus augmentation were included.

Risk of bias and quality assessment of included studies

The quality assessment of all included RCTs and CCTs is presented in Table 5. No study with a low risk of bias was identified. Five (30%) out of the 17 studies were identified as having an unclear risk of bias and 12 (70%) as having a high risk of bias, based on the previously established criteria.

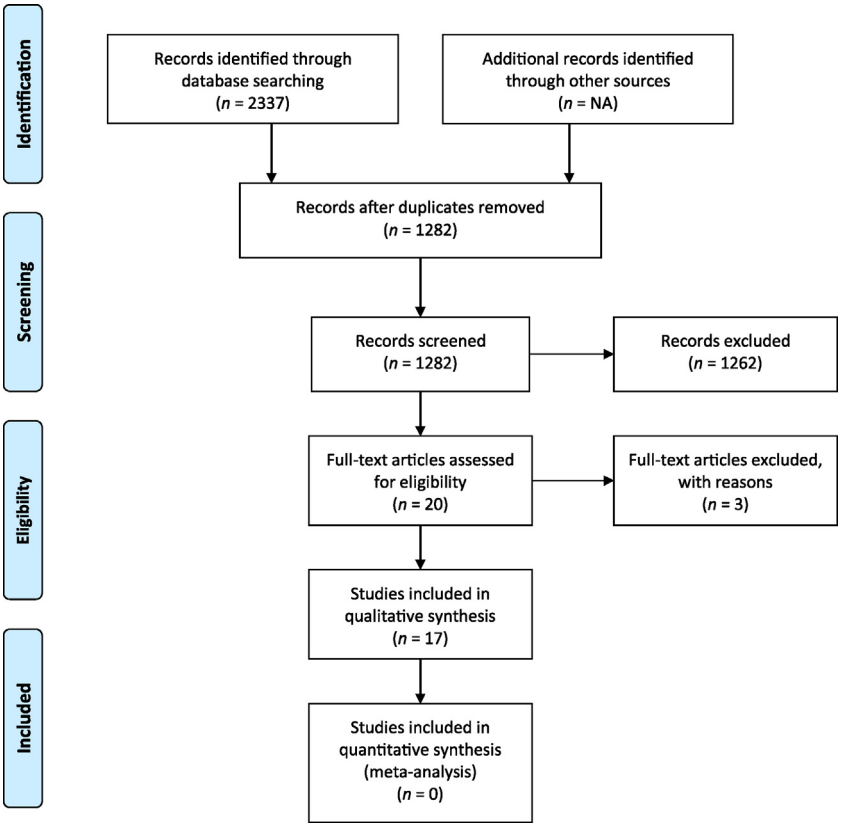

Fig. 1. Flow diagram of the article selection process.

Table 1. Studies excluded after full text reading and reasons for exclusion.

Study	Reasons for exclusion
Oncu and Kaymaz[37]	Histomorphometry bone outcomes were not presented in perforated vs. non-perforated maxillary sinuses
Barbu et al.[38]	Absence of statistical analyses
Angelo et al.[39]	Protocol used for the preparation of L-PRF not specified

L-PRF, leukocyte–platelet-rich fibrin.

Can L-PRF be used as a substitute for (i) bone grafting materials and (ii) barrier membranes in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Bone grafting materials

With regard to ridge preservation, four studies compared horizontal bone loss (HBL) and vertical bone loss (VBL) in post-extraction sockets either treated with L-PRF or allowed to heal naturally[17,19,24,25]. Temmerman et al. reported HBL of 0.8 ± 2.5 mm on the buccal (B) aspect and −0.6 ± 2.2 mm on the lingual (L) aspect at 1 mm below the crest for the L-PRF sites, which accounted for a total width reduction (TWR) of 22.84 ± 24.28%[17]. The observed outcomes were significantly superior when compared with natural healing (HBL/B: −2.9 ± 2.7 mm; HBL/L: −2.1 ± 2.5 mm; TWR: 51.92 ± 40.31%). Hauser et al. reported a mean alveolar ridge width reduction of 0.06 mm for the L-PRF treated sockets, which was significantly less than the 0.43 mm reduction observed for the naturally healed sites at 8 weeks post extraction[24]. Alzahrani et al. also reported less alveolar width reduction and greater radiographic bone fill at 4 and 8 weeks post extraction for the L-PRF treated sockets compared to natural healing[25]. In contrast, Suttapreyasri and Leepong found no difference in alveolar ridge contour changes and VBL between L-PRF and natural healing at 8 weeks[19]. Only one study compared L-PRF with a bone grafting material (beta-tricalcium phosphate with type I collagen (β-TCP-Cl); Septodont, Saint-Maur-des-Fosses, France)[26]. Mean HBL as assessed through cone beam computed tomography (CBCT) on the coronal third was −1.52 mm for the L-PRF vs. −0.86 mm for the β-TCP-Cl sites. However, no analysis on statistical significance was reported for the findings of that study.

With regard to maxillary sinus augmentation/ridge augmentation, no controlled studies addressing this question could be identified.

Barrier membranes

No controlled studies addressing this question could be identified for ridge preservation/ridge augmentation.

With regard to maxillary sinus augmentation, Bosshardt et al.[27] and Gassling et al.[28] evaluated the histomorphometric outcomes following the use of L-PRF membranes as compared to an absorbable collagen membrane (Bio-Gide; Geistlich, Wolhusen, Switzerland) to cover the lateral window after direct sinus augmentation. Both studies reported no difference in the proportion of vital bone formation and residual grafting material after 5 to 11 months.

Does the addition of L-PRF to bone grafting materials lead to enhanced bone quantity and bone quality outcomes in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Ridge preservation

One RCT evaluated the effects of adding L-PRF to bone grafting materials (demineralized freeze-dried bone allograft, DFDBA) with regard to ridge preservation[29]. The authors reported a HBL of 0.75 ± 0.49 mm for the DFDBA + L-PRF sites versus 1.36 ± 0.7 mm for the control (DFDBA) sites after 6 months, whereas no difference was noted in terms of VBL.

Ridge augmentation

Moussa et al. studied the effects of covering palatal autogenous blocks with L-PRF membranes on bone augmentation outcomes and reported significantly greater bone graft resorption in the absence of L-PRF membranes at 4 months (0.8 ± 0.6 mm vs. 1.6 ± 0.9 mm)[30].

Maxillary sinus augmentation

Five controlled studies reported histomorphometric outcomes after the use of bone grafting materials mixed with L-PRF in direct sinus augmentation[16,18,31–33]. Three studies used xenograft (Bio-Oss; Geistlich, Wolhusen, Switzerland)[18,31,32], one study used freeze-dried bone allograft (FDBA) (Phoenix; TBF, Lyon, France)[16], and one used β-TCP (Suprabone; BMT Calsis, Ankara, Turkey)[33]. In all studies, the addition of L-PRF to bone grafting materials did not produce more favorable histomorphometric outcomes in terms of the proportion of vital bone formation and residual grafting material.

Does the addition of L-PRF to bone grafting materials accelerate bone maturation in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Ridge preservation and ridge augmentation

No pertinent studies on these specific treatment modalities were identified in regard to ridge preservation and ridge augmentation.

Maxillary sinus augmentation

Tatullo et al. compared bone maturation in xenograft + L-PRF (test) vs. xenograft alone (control) in direct sinus augmentation, after 106, 120, and 150 days[31]. A gradual increase in trabecular bone (%) was noted from 106 to 150 days; however, no statistically significant difference was found between the test group and the control group at any time point regarding the percentages of trabecular bone, osteoid borders, and medullary spaces. Furthermore, no statistically significant difference in implant stability quotient (ISQ) was reported between the test and control groups at any of the time points. The authors claimed that the use of L-PRF reduced the healing time and that good primary stability could be achieved as early as 106 days post direct sinus augmentation with no implant failures at subsequent follow-ups.

Choukroun et al. reported equivalent histomorphometric bone outcomes between FDBA + L-PRF vs. FDBA alone in direct sinus augmentation at 4 and 8 months, respectively (average vital bone 20.95% vs. 20.3%), concluding that L-PRF reduces the healing time and that implants could be placed as early as 4 months post direct sinus augmentation[16].

Does the adjuvant use of L-PRF improve soft tissue healing in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Ridge preservation

Suttapreyasri and Leepong reported no difference in soft tissue healing between L-PRF vs. natural healing up to 8 weeks post-extraction[19]. The dimensions of the socket orifices were measured clinically using a periodontal probe at 0, 1, 2, 4, 6, and 8 weeks. Although the orifices in the L-PRF groups were slightly narrower at the 8-week inter-

Table 2. Studies on L-PRF and alveolar ridge preservation.

First author Year of publication Study design	Population characteristics	Parameters recorded (P) Methodology (M)	L-PRF preparation protocol	Surgical intervention details	Comparison/ control	Treatment outcomes, complications, and patient-reported outcomes
Hauser et al.[24] 2013 RCT	22 patients 9 M/14 F Premolar extractions (20 Max; 2 Mand) Group 1 = 8 Group 2 = 6 Control = 8	P: HBL (4 mm below the gingiva), VBL, intrinsic bone quality, bone microarchitecture at week 8, food intake changes M: Caliper, standardized PA radiographs, bone biopsy, micro-CT analysis (nanoindentation test), food questionnaire	2700 rpm, 12 min Four 8-ml tubes per patient	Group 1: L-PRF membranes Group 2: L-PRF membranes and flap + L-PRF membranes on top of the socket (Number of L-PRF membranes used per socket not specified)	Blood clot	HBL: L-PRF 0.06 mm (SSD vs. control); L-PRF–flap 0.42 mm; control 0.43 mm VBL: L-PRF -1.21 ± 0.40 (M) vs. 0.76 ± 0.25 (D); L-PRF–flap -0.86 ± 0.34 (M) vs. -2.15 ± 1.05 (D); control -0.77 ± 0.17 (M) vs. -2.15 ± 1.05 (D) Intrinsic bone quality: L-PRF > L-PRF–flap; NSSD for L-PRF vs. control; no difference in tissue hardness Bone microarchitecture: NSSD in BV/TV between groups; Tb.N: L-PRF > L-PRF–flap and L-PRF > control; Tb.Th: NSSD between groups; Tb.Sp: L-PRF < L-PRF–flap and L-PRF < control; NSSD in bone density between groups No changes in food intake between groups
Temmerman et al.[17] 2016 Split-mouth RCT	22 patients 15 M/7 F Single bilateral extractions Test: 22 Control: 22	P: HBL (-1, -3, and -5 mm below crest), VBL, socket bone fill at 3 months, postop. pain M: CBCT, VAS, questionnaire	2700 rpm, 12 min	2–5 L-PRF clots in the socket, covered with 2–3 L-PRF membranes to seal the socket	Blood clot	Results presented for dehiscences including: VBL (B): -1.5 ± 1.3 (control) vs. 0.1 ± 1.6 (test) (SSD); VBL (L): -0.7 ± 0.8 (control) vs. -0.4 ± 1.1 (test) (NSSD) HBL (L): at -1 mm, -2.1 ± 2.5 (control) vs. -0.6 ± 2.2 (SSD); at -3 mm, -0.3 ± 0.3 (control) vs. -0.1 ± 0.3 (NSSD); at -5 mm, -0.1 ± 0.0 (control) vs. -0.1 ± 0.0 (NSSD). HBL (B): at -1 mm, -2.9 ± 2.7 (control) vs. -0.8 ± 2.5 (SSD); at -3 mm, -1.0 ± 1.1 (control) vs. -0.8 ± 2.5 (SSD); at -5 mm, -0.5 ± 0.6 (control) vs. -0.4 ± 1.7 (NSSD) Total width reduction (%): at -1 mm, -51.92 ± 40.31 (control) vs. -22.84 ± 24.28 (SSD); at -3 mm, -14.51 ± 19.6 (control) vs. 5.42 ± 6.16 (SSD); at -5 mm, 4.47 ± 4.89 (control) vs. -2.91 ± 4.54 (SSD) Socket bone fill: 94.7 ± 26.9 (test) vs. 63.3 ± 31.9 (control) (SSD) Less postop. pain for test group on days 3, 4, and 5
Suttapreyasri and Leepong[19] 2013 Split-mouth RCT	8 patients 5 F/3 M 20 symmetrical premolars Test: 10 Control: 10	P: Soft tissue healing at the socket orifice, alveolar ridge contour changes, VBL at 1, 2, 4, 6, and 8 weeks M: Socket orifice measurements, study models/ acrylic jigs, standardized PA radiographs	3000 rpm, 10 min	1 L-PRF clot in the socket No L-PRF membranes to seal the socket	Blood clot	NSSD in dimensions of socket orifice at weeks 0, 1, 2, 4, 6, and 8 Alveolar ridge contour changes at week 8: (B): 1.96 ± 1.10 (test) vs. 2.59 ± 0.70 (control) (NSSD); (L): 1.59 ± 0.64 (test) vs. 1.78 ± 0.47 (control) (NSSD) VBL at week 8: (M): 0.7 mm (test) vs. 1.33 mm (control) (NSSD); (D): 1.23 mm (test) vs. 1.14 mm (control) (NSSD)
Thakkar et al. [29] 2016 RCT	36 single-rooted teeth Test: NR Control: NR	P: HBL, VBL at 90 and 180 days M: Vernier caliper, standardized PA radiographs	3000 rpm, 10 min	Graft: DFDBA + L-PRF Collagen membrane	Graft: DFDBA Collagen membrane	HBL (at 180 days): test: -0.75 mm ± 0.49 vs. control: -1.36 mm ± 0.7 (SSD) VBL (at 180 days): test: -1.08 mm ± 0.42 vs. control: -1.38 mm ± 0.5 (NSSD)

Das et al.[26] 2016 RCT	26 patients 13 F/13 M 30 teeth: 15 L-PRF ($n = 14$), 15 β-TCP-Cl ($n = 12$)	P: HBL (2 mm apical to most coronal point of socket), VBL, bone quality, bone density (HU) at 6 months M: Extraction with flaps, acrylic stents, dental casts, caliper, CBCT, bone biopsy/ histology	2500 rpm, 10 min	Graft: L-PRF (Whether L-PRF clots or membranes were placed in the socket and their number were not reported)	Graft: β-TCP-Cl	Clinical: HBL (no analysis of statistical significance): −3.85 mm (L-PRF) vs. −3.15 mm (β-TCP-Cl) CBCT: HBL (no analysis of statistical significance): coronal third: −1.52 (L-PRF) vs. −0.86 (β-TCP-Cl); middle third: −1.02 (L-PRF) vs. −0.18 (β-TCP-Cl); apical third: −1.43 (L-PRF) vs. +0.36 (β-TCP-Cl) VBL (no analysis of statistical significance): −1.17 (L-PRF) vs. −0.35 (β-TCP-Cl) Density in HU at 6 months was greater for coronal and middle third for L-PRF vs. β-TCP-Cl
Marenzi et al.[35] 2015 Single-blind RCT with a split-mouth design	26 patients 17 F/9 M 108 extractions	P: Postop. pain at 24, 48, and 72 h; soft tissue healing at 3, 7, 14, and 21 days postop. M: VAS questionnaire, healing index modified (bleeding, suppuration, tissue color, and consistency of healing tissue)	2700 rpm, 12 min 18–54 ml per patient	L-PRF membranes placed in the socket (Number not specified)	Blood clot	Less pain in L-PRF sites (SSD) Soft tissue healing faster for L-PRF sites at 7, 14, and 21 days Healing index L-PRF vs. control: 3 days: 4.8 ± 0.6 vs. 5.1 ± 0.9; 7 days: 4.5 ± 0.5 vs. 4.9 ± 0.3 (SSD); 14 days: 4.2 ± 0.2 vs. 4.3 ± 0.3 (SSD); 21 days: 4.1 ± 0.1 vs. 4.2 ± 0.2 (SSD)
Alzahrani et al.[25] 2017 RCT	24 patients 15 F/9 M 24 extractions Test: 12 Control: 12	P: Horizontal ridge width reduction (at 5 mm apical to the crest), radiographic bone fill at 1, 4, and 8 weeks M: Acrylic stents, dental casts, caliper, PA radiographs	3000 rpm, 10 min 20 ml per patient	L-PRF membranes placed in the socket (Number not specified)	Blood clot	Horizontal ridge width reduction (as a %): week 1: 3.26 ± 2.21 (control) vs. 2.09 ± 0.84 (test) (NSSD); week 4: 9.79 ± 6.02 (control) vs. 5.22 ± 0.80 (test) (SSD); week 8: 13.54 ± 6.57 (control) vs. 8.58 ± 1.73 (test) (SSD) Radiographic bone fill (as a %): week 1: 68.82 ± 1.07 (control) vs. 74.05 ± 1.66 (test) (SSD); week 4: 74.03 ± 1.22 (control) vs. 81.54 ± 3.33 (test) (SSD); week 8: 80.35 ± 2.61 (control) vs. 88.81 ± 1.53 (test) (SSD)
Yerke et al.[34] 2017 RCT	23 patients 12 F/11 M Group A ($n = 5$) Group B ($n = 8$) Group C ($n = 5$) Group D ($n = 5$)	P: Soft tissue closure at extraction sites at 10 and 21 days M: Measurement of buccolingual and mesiodistal dimensions at socket midpoints with a periodontal probe	400 *g*, 10–12 min	Group A: Resorbable collagen dressing Group B: Calcium sulfate + PRP in the socket covered by collagen membrane Group C: Calcium sulfate + one L-PRF membrane in pieces in the socket covered by one L-PRF membrane	Group D: Blood clot	NSSD between groups for soft tissue closure at 21 days

(B), buccal; β-TCP-Cl, beta-tricalcium phosphate with type I collagen; BV/TV, bone volume fraction; CBCT, cone beam computed tomography; (P), parameters recorded; DFDBA, demineralized freeze-dried bone allograft; F, female; HBL, horizontal bone loss (buccolingual direction); HU, Hounsfield units; (L), lingual; L-PRF, leukocyte–platelet-rich fibrin; M, male; (M), Methodology; Mand, mandible; Max, maxilla; micro-CT, micro-computed tomography; NR, not reported; NSSD, no statistically significant difference; PA, peri-apical; PRP, platelet-rich plasma; RCT, randomized controlled trial; SSD, statistically significant difference; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; VAS, visual analog scale; VBL, vertical bone loss (apico-coronal direction).

Table 3. Studies on L-PRF and ridge augmentation.

First author Year of publication Study design	Population characteristics	Parameters recorded (P) Methodology (M)	L-PRF preparation protocol	Surgical intervention details	Comparison/ control	Treatment outcomes, complications, and patient-reported outcomes
Moussa et al.[30] 2016 CCT	12 patients 7 F/5 M 14 RA: 7 test, 7 control	P: Bone gain, bone graft resorption at 4 months M: Bone caliper, CBCT	3500 rpm, 12–15 min	Graft: Palatal bone block One L-PRF membrane over bone block	Graft: Same Control: No membrane	Agreement between CBCT vs. bone caliper NSSD in bone gain between test and control Less bone graft resorption at 4 months in the test group (0.8 ± 0.6 vs. 1.6 ± 0.9) (SSD)

CBCT, cone beam computed tomography; CCT, controlled clinical trial; F, female; L-PRF, leukocyte–platelet-rich fibrin; M, male; NSSD, no statistically significant difference; RA, ridge augmentation; SSD, statistically significant difference.

val, the differences were not statistically significant. Yerke et al. also reported no difference in soft tissue closure at 21 days in sockets that were covered by a collagen membrane, a PRF membrane, a resorbable collagen dressing, or allowed to heal naturally[34]. In contrast, Marenzi et al. reported improved soft tissue healing for the extraction sockets treated with L-PRF at 7, 14, and 21 days[35]. A modified healing index ranging from 4 (excellent healing) to 12 (severely impaired healing) was utilized in that study. The values were assigned by one examiner after taking into consideration bleeding, suppuration, tissue color, and consistency of the soft tissues. The corresponding values for the L-PRF group were 4.5 ± 0.5, 4.2 ± 0.2, and 4.1 ± 0.1 vs. 4.9 ± 0.3, 4.3 ± 0.3, and 4.2 ± 0.2 for the control group (statistically significant difference).

Ridge augmentation

No studies addressing this question could be identified with regard to ridge augmentation.

Maxillary sinus augmentation

Gurler and Delilbasi reported superior outcomes using a soft tissue healing index (tissue color, response to palpation, presence/absence of granulation tissue, and incision margin opening) for sites where L-PRF was placed over the lateral window and below the flap prior to closure as compared to a collagen membrane alone[36]. However, the difference was not statistically significant at 7 and 14 days postoperative.

Does the use of L-PRF result in less postoperative swelling and patient-reported postoperative pain?

Ridge preservation

Two RCTs investigated patient-reported postoperative pain using visual analog scales (VAS)[17,35]. Both of them reported less pain in post-extraction sockets treated with L-PRF versus natural healing during the early stages of healing (5 days and 3 days postoperative, respectively).

Ridge augmentation

No studies addressing this question could be identified with regard to ridge augmentation.

Maxillary sinus augmentation

One RCT investigated postoperative outcomes including pain, swelling, and the performance of various daily activities when L-PRF membranes were placed below the flap versus not in direct sinus augmentation[36]. Both groups reported an improvement in these parameters over the first 7 days postoperative; however no statistically significant difference was noted between the two groups.

Discussion

The possibility of conducting a meta-analysis was explored for the two following questions: (1) What is the effect of L-PRF on ridge dimension alterations compared to natural healing/blood clot following tooth extraction? (2) What is the effect of L-PRF membrane compared to collagen membrane for the coverage of the lateral window during maxillary sinus augmentation?

For the first question, in the four RCTs comparing the use of L-PRF vs. blood clot, the radiographic methods used to evaluate the outcomes varied significantly, from micro-computed tomography[24], to peri-apical radiographs[19,24,25] and CBCT[17], resulting in heterogeneity between the studies that did not allow for a meta-analysis. Similarly, for the second question, several determining factors can affect the clinical and histological outcomes of maxillary sinus augmentation, including the size of the lateral window and the inherent anatomy of the antral cavity, among others[40,41]. None of these factors were reported in detail in the three RCTs that utilized L-PRF membrane to cover the lateral window as compared to a collagen membrane[28,31,36], thus a meta-analysis addressing that question could not be conducted either.

Method of L-PRF preparation

The two most commonly used protocols for L-PRF preparation were centrifugation at 2700 rpm for 12 min[17,24,35,36] and centrifugation at 3000 rpm for 10 min[19,25,27,29,31,33]. Different protocols were applied in the other studies: 3500 rpm for 12–15 min[30], 2500 rpm for 10 min[16,26], 400 *g* for 10–12 min[28,32,34], and 300 *g* for 10 min[18]. Some of the authors described the preparation protocol using revolutions per minute (rpm) as the measuring unit, while others used the relative centrifugal force (*g*), which is dependent, among other parameters, on the radius of the device used. This lack of standardization and the effect it has on the final product was pointed out in a recent study, which concluded that centrifuge characteristics significantly impact cell viability, growth factor expression, and the fibrin architecture of L-PRF constructs[42]. Heterogeneity was also noted regarding the membrane preparation protocol, which may have an impact on the plasma content, three-dimensional fibrin meshwork, and platelet content of L-PRF membranes[6]. The methods used varied, and included compression of PRF using sterile gauzes[16,31], sterile glass and/or metal surgical Plates[17,35], and PRF boxes[25], among others. However, as the available evidence on the effects of different preparation protocols on the effectiveness of L-PRF is still limited, it was decided to include studies with protocol variability to avoid excluding articles that may provide evidence on the clinical effects of L-PRF.

Table 4. Studies on L-PRF and maxillary sinus augmentation.

First author Year of publication Study design	Population characteristics	Parameters recorded (P) Methodology (M)	L-PRF preparation protocol	Surgical intervention details	Comparison/ control	Treatment outcomes, complications, and patient-reported outcomes
Tatullo et al.[31] 2012 RCT	60 patients 48 F, 12 M 72 DSA: 42 test, 30 control 240 DIs: Group A ($n = 20$): DIs at 106 days Group B ($n = 20$): DIs at 120 days Group C ($n = 20$): DIs at 150 days	P: Implant survival at 36 $\pm$ 10 months, implant stability, bone quality M: Bone biopsy from lateral window site, HIS/HMP	3000 rpm, 10 min	Graft: Xenograft + L-PRF Two L-PRF membranes over lateral window (Number of L-PRF clots mixed with xenograft not specified)	Graft: Xenograft CM over lateral window	100% implant survival NSSD in ISQ values between groups A, B, C Group A: NB: 22.79 (test) vs. 26.44; osteoid: 7.01 (test) vs. 5.12; MED-SP: 70.2 (test) vs. 68.44 Group B: NB: 26.15 (test) vs. 28.7; osteoid: 3.84 (test) vs. 3.12; MED-SP: 70.01 (test) vs. 68.18 Group C: NB: 37.06 (test) vs. 38.97; osteoid: 3.53 (test) vs. 2.88; MED-SP: 61.41 (test) vs. 58.15 NSSD between test and control groups for all protocols and all parameters measured
Bosshardt et al.[27] 2014 CCT	8 patients 7 F/1 M 12 DSA: 8 L-PRF, 4 CM	P: Bone quality at 7–11 months M: Bone biopsy from osteotomy site, HIS/HMP	3000 rpm, 10 min	Graft: Alloplast One L-PRF membrane over lateral window (test)	Graft: Alloplast CM over lateral window	NB: 28.74 $\pm$ 4.44 (control) vs. 28.59 $\pm$ 6.90 (test) (NSSD) Soft tissue: 45.76 $\pm$ 3.18 (control) vs. 45.74 $\pm$ 9.30 (test) (NSSD) REMN: 25.50 $\pm$ 7.64 (control) vs. 25.67 $\pm$ 8.75 (test) (NSSD)
Choukroun et al.[16] 2006 CCT	9 DSA: 6 test, 3 control	P: Bone quality at 4 months for test group and 8 months for control group M: Bone biopsy at osteotomy site after elimination of native bone, HIS/HMP	2500 rpm, 10 min	Graft: FDBA + L-PRF L-PRF membrane over lateral window (Number of L-PRF clots mixed with FDBA and number of membranes over window not specified)	Graft: FDBA Membrane (?)	NB: 20.306 (18.02–23.694) (control) vs. 20.95 (18.65–30.3) (test) REMN: 10.934 (9.28–12.206) (control) vs. 9.41 (9.03–12.7) (test) Osteoid: 1.94 (control) vs. 2.26 (test) MED-SP: 67.7 (control) vs. 66.5 (test) Equivalent results, no statistics run
Gassling et al.[28] 2013 RCT	6 patients 12 DSA: 6 L-PRF, 6 CM	P: Bone quality at 5 months M: Bone biopsy from lateral window site, HIS/HMP	400 *g*, 12 min	Graft: Xenograft + autogenous (1:1) One L-PRF membrane over lateral window	Graft: Xenograft + autogenous (1:1) CM over lateral window	NB: 17.0 (7.8–27.8) (test) vs. 17.2 (8.5–24.2) (control) REMN: 15.9 (0.9–33.4) (control) vs. 17.3 (0.7–33.5) (test) Equivalent results, no statistics run
Zhang et al.[18] 2012 RCT	10 patients 2 F/8 M 11 DSA: 6 test, 5 control	P: Bone quality at 6 months M: Bone biopsy from osteotomy site, HIS/HMP	300 *g*, 10 min	Graft: Xenograft + L-PRF One L-PRF membrane over lateral window (Number of L-PRF clots mixed with xenograft not specified)	Graft: Xenograft No membrane over lateral window	NB: 12.95 $\pm$ 5.33 (control) vs. 18.35 $\pm$ 5.62 (test) (NSSD) REMN: 28.54 $\pm$ 12.01(control) vs. 19.16 $\pm$ 6.89 (test) (NSSD) Bone-to-bone substitute contact (%): 18.57 $\pm$ 5.39 (control) vs. 21.45 $\pm$ 4.57 (test) (NSSD)
Gurler and Delilbasi[36] 2016 RCT	24 patients 14 F/10 M 24 DSA: 12 test, 12 control	P: Soft tissue healing (tissue color, response to palpation, presence/absence of granulation tissue, incision margin opening) on days 7 and 14 postop., pain, swelling, sleeping, eating, phonetics, activities of daily living, and missed work days M: Healing index (HI) questionnaires	2700 rpm, 12 min	Graft: Two L-PRF clots in pieces + allograft Two L-PRF membranes over lateral window	Graft: Allograft CM over lateral window	HI was higher for test vs. control on days 7 and 14 postop. (NSSD) NSSD in any of the self-assessed parameters between the test group and the control group

Table 4 (*Continued*)

First author Year of publication Study design	Population characteristics	Parameters recorded (P) Methodology (M)	L-PRF preparation protocol	Surgical intervention details	Comparison/ control	Treatment outcomes, complications, and patient-reported outcomes
Nizam et al.[32] 2017 Split-mouth RCT	13 patients 9 M/4 F 26 DSA: 13 control, 13 test	P: Bone quality at 6 months M: Bone biopsy from osteotomy site, HIS/HMP	400 *g*, 12 min	Graft: Xenograft + L-PRF CM over lateral window (Number of L-PRF clots mixed with xenograft not specified)	Graft: Xenograft CM over lateral window	NB: 21.25 ± 5.59 (control) vs. 21.38 ± 8.78 (test) (NSSD) Soft tissue: 45.96 ± 8.36 (control) vs. 52.67 ± 12.53 (test) (NSSD) REMN: 32.79 ± 5.89 (control) vs. 25.95 ± 9.54 (test) (NSSD) Bone-to-graft contact:54.04 ± 8.36 (control) vs. 47.33 ± 12.33 (test) (NSSD)
Comert Kilic et al.[33,a] 2017 RCT	17 patients 5 F/12 M 17 DSA: 9 control, 8 test	P: Bone quality at 6 months M: Bone biopsy from osteotomy site, HIS/HMP	3000 rpm, 10 min	Graft: β-TCP + L-PRF CM over lateral window (2 L-PRF clots mixed with β-TCP)	Graft: β-TCP CM over lateral window	NB: 33.40 ± 10.43 (control) vs. 32.03 ± 6.34 (test) (NSSD) Soft tissue: 36.21 ± 10.59 (control) vs. 35.31 ± 10.81 (test) (NSSD) REMN: 30.39 ± 10.29 (control) vs. 32.66 ± 7.46 (test) (NSSD) NSSD in mean density of osteoblasts, osteoclasts, osteocytes, and capillary vessels Inflammatory cells higher and osteoprogenitor cells lower in test vs. control (SSD)

CCT, controlled clinical trial; CM, collagen membrane; DI, dental implant; DSA, direct sinus augmentation; F, female; FDBA, freeze-dried bone allograft; HIS, histology; HMP, histomorphometry; ISQ, implant stability quotient; L-PRF, leukocyte–platelet-rich fibrin; M, male; MED-SP, medullary spaces; NB, new bone; NSSD, no statistically significant difference; RCT, randomized controlled trial; REMN, remnants/residual graft material; SSD, statistically significant difference.

[a]Data for pure platelet-rich plasma (P-PRP) are not presented.

Can L-PRF be used as a substitute for (i) bone grafting materials and (ii) barrier membranes in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Ridge preservation

With the exception of one study[19], more favorable outcomes were reported when L-PRF was compared to a natural blood clot, in terms of a reduction in post-extraction dimensional changes[17,24,25]. Great variability in the number of L-PRF clots and membranes used in the sockets was noted, ranging from one L-PRF clot[19] to 2–5 L-PRF clots per socket[17]. To what extent the number of L-PRF clots and membranes in the sockets affect the outcomes and whether the greater number of cells and fibrin applied to the surgical site through multiple L-PRF clots versus one leads to better results cannot be assessed on the basis of the available evidence. However, as there was only one controlled study with a high risk of bias[26], comparing L-PRF with a bone substitute material (β-TCP-Cl), it seems that even if L-PRF may produce better outcomes than natural socket healing, there is very limited evidence on whether it is as effective as a bone graft substitute in ridge preservation procedures.

Maxillary sinus augmentation

For maxillary sinus augmentation, cohort studies and case-series have reported favorable outcomes in terms of survival rates for implants placed in conjunction with L-PRF alone during crestal and direst sinus augmentation[43–45]. In this systematic review, no CCTs could be identified reporting on outcomes of L-PRF used as a sole grafting material in the sinus as compared to other therapies, thus firm conclusions on whether L-PRF could be used as a bone graft substitute cannot be made. However, based on the promising outcomes reported in long-term controlled studies for implant placement with no grafting in sinus augmentation procedures[46], L-PRF alone might be another alternative, also providing the potential advantage of assisting in repairing membrane perforations[37].

The placement of a barrier membrane over the lateral window in direct sinus augmentation has been associated with higher implant survival rates[47], with some studies reporting a greater percentage of vital bone formation for the covered vs. uncovered group[48]. Two CCTs were identified reporting on bone histomorphometric outcomes when L-PRF membranes were

Table 5. Qualitative analysis of the controlled clinical trials included.

	Method of randomization	Allocation concealment	Blinding of participants, personnel, and outcome assessors	Completeness of follow-up	Selective reporting	Other bias
Tatullo et al.[31]	+	+	?	+	+	–
Bosshardt et al.[27]	NA	NA	?	+	+	+
Choukroun et al.[16]	NA	NA	?	+	+	–
Gassling et al.[28]	+	+	?	+	+	+
Zhang et al.[18]	+	?	?	+	+	+
Gurler and Delilbasi[36]	+	+	?	+	+	+
Hauser et al.[24]	+	?	?	+	+	+
Temmerman et al.[17]	+	+	?	+	+	+
Suttapreyasri and Leepong[19]	+	?	?	+	+	+
Thakkar et al.[29]	+	+	?	+	+	+
Das et al.[26]	–	–	?	+	+	+
Marenzi et al.[35]	+	+	?	+	+	+
Moussa et al.[30]	NA	NA	–	+	+	+
Nizam et al.[32]	+	+	?	+	+	+
Comert Kilic et al.[33]	?	?	?	+	+	+
Alzahrani et al.[25]	?	?	?	+	+	+
Yerke et al.[34]	+	+	?	+	–	+

NA, not applicable.

compared to collagen membrane placed over the lateral window[27,28]. As similar outcomes were reported in terms of the percentage of vital bone formation and residual graft material, L-PRF might be a good alternative to collagen membrane for that purpose.

Does the addition of L-PRF to bone grafting materials lead to enhanced bone quantity and bone quality outcomes in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Ridge preservation

The addition of L-PRF to DFDBA was associated with more favorable results in terms of horizontal bone loss when compared to DFDBA alone following tooth extraction[29]. However, only this one study was identified, and it presented multiple limitations in the design and methodology, including the use of peri-apical radiographs and a manual Vernier caliper for the measurements of HBL and VBL[29]. Hence, it is not feasible to draw conclusions on whether the addition of L-PRF in bone grafting materials improves bone quantity outcomes following alveolar ridge preservation.

Ridge augmentation

With regard to ridge augmentation, no bone histomorphometric evidence exists on the effects of L-PRF when mixed with bone grafts in this type of procedure. Similarly, weak evidence exists on the effects of L-PRF in enhancing ridge augmentation dimensional outcomes. One study reported a reduction in autogenous bone block resorption when the blocks were covered with one L-PRF membrane[30]. The authors attributed this result to the high concentration of growth factors in L-PRF assisting rapid vascularization of the graft and accelerated healing. Whether this is a plausible concept and whether one L-PRF membrane is adequate for these purposes should be investigated further.

Maxillary sinus augmentation

A common clinical approach in grafting procedures is the mixing of bone grafts with biologicals to enhance bone regeneration, particularly in the early stages of the process. Commonly, in contemporary clinical practice, L-PRF is cut into pieces and mixed with bone grafts to enhance handling properties and to accelerate bone regeneration. In this systematic review, although most of the studies reported greater percentages of vital bone formation and lower percentages of residual bone graft when L-PRF was added to the graft, the difference when compared to the controls was not statistically significant in any of them. Furthermore, comparison of the histomorphometric outcomes between studies was difficult due to the heterogeneity in methodology, which may explain the wide range in the reported percentage of vital bone at sites that received L-PRF. More specifically, there was great variability in the timing of bone biopsy harvesting, from 3.5 months[31] up to 6 months[18], and in the location of the biopsy sites between studies. Three studies retrieved the core biopsies from the crestal bone[16,18,32], whereas one retrieved them from the previous lateral window site[31]. That methodological difference could partially explain the outcome variability, as when the distance from the maxillary host bone increases, the amount of detectable bone formation is reduced[41,49]. Currently, there is no consistent evidence regarding improvement in bone quality when L-PRF is added to the bone graft in maxillary sinus augmentation procedures.

Does the addition of L-PRF to bone grafting materials accelerate bone maturation in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

Maxillary sinus augmentation

In vitro and animal studies have shown beneficial effects of L-PRF in soft tissue healing and bone remodeling[7,9]. Due to these properties, attributed to the high concentration of growth factors, L-PRF has been studied as an adjuvant to reduce the time needed between augmentation procedures and implant placement. Two controlled studies were identified in this systematic review addressing this issue. Tatullo et al. performed histological and histomorphometric analyses of bone core samples obtained 106 days post augmentation from maxillary sinuses grafted either with xenograft + L-PRF (test group) or xenograft alone[31]. More favorable his-

tological outcomes (i.e., graft vascularization, increased number of osteocytes and osteoblasts) at the test sites were reported. The authors argued that L-PRF could reduce the healing time from the standard 6 months, favoring optimal bone regeneration. However, as histomorphometry outcomes, ISQ values, and implant survival rates were similar in the groups, the use of L-PRF as a complementary therapy to reduce the healing period is not strongly substantiated by this study. Additionally, no definite conclusions can be drawn from Choukroun et al.[16], as histomorphometric analyses were performed at different time points, preventing an adequate comparison. A more accurate assessment of the wound healing effects of L-PRF would have been possible had a comparison been made between the FDBA-only group at 4 months and the FDBA + L-PRF group. Therefore, there is limited evidence on whether L-PRF, when used in combination with bone grafts in sinus augmentation, could accelerate wound healing and reduce the duration of treatment.

Does the adjuvant use of L-PRF improve soft tissue healing in ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures?

The use of L-PRF is commonly indicated in clinical practice to improve soft tissue healing in augmentation procedures. Platelet concentrates and more specifically PRP in the form of membranes have been reported to reduce the incidence of titanium mesh exposures[50]. However, in this systematic review, no studies could be identified reporting the effects of L-PRF in ridge augmentation procedures on soft tissue healing and the incidence of wound dehiscence. Better soft tissue healing in direct sinus augmentation and ridge preservation sites was reported when L-PRF was used, however the difference was not statistically significant[19,35,36]. As the evaluation of soft tissue healing is subjective, the use of examiners, blinded to the intervention, is highly valuable. Only one out of the three studies included in this review reported the participation of a blinded examiner[36], which raises questions about possible risk of bias in the available literature. Thus, although L-PRF may enhance soft tissue healing, the available evidence on the extent and significance of these potential improvements is limited. Controlled studies comparing soft tissue maturation and healing with and without L-PRF application in augmentation procedures are warranted.

Does the use of L-PRF result in less postoperative swelling and patient-reported postoperative pain?

The use of L-PRF in post-extraction sockets of third molars has been associated with favorable outcomes in terms of decreased postoperative inflammation and pain[10,11,51,52]. A reduction in postoperative pain associated with L-PRF use in ridge preservation procedures was also noted by Temmerman et al.[17] and Marenzi et al.[35], who attributed it to a possible supportive effect of L-PRF on the immune system. However, Gurler and Delilbasi did not find any difference regarding postoperative swelling and pain in direct sinus augmentation procedures when L-PRF was used[36]. Additionally, no controlled studies could be identified reporting on postoperative outcomes after L-PRF use in ridge augmentation procedures. Thus, apart from favorable outcomes in managing the symptoms that follow tooth extraction, there is no evidence to support similar outcomes of L-PRF in other augmentation procedures.

The findings of this systematic review suggest that there is limited evidence on the potential benefits of L-PRF in bone regeneration, soft tissue healing, and postoperative complications in systemically healthy patients undergoing ridge preservation, ridge augmentation, and maxillary sinus augmentation procedures. The use of L-PRF in post-extraction sockets was associated with a modest beneficial effect by decreasing alveolar ridge remodeling and postoperative pain as compared to natural healing. In contrast, the use of L-PRF in maxillary sinus augmentation procedures does not seem to render more favorable outcomes. Likewise, its use in ridge augmentation procedures is not adequately reported in the literature. It is important to highlight that, given its autologous nature, biological properties, ease of preparation, and low cost, relevant outcomes of L-PRF should be investigated further in future, well-conducted RCTs with larger subject populations and standardization of PRF preparation protocols and long term follow-ups, in order to expand our knowledge on the clinical effectiveness of and indications for this autologous product.

Funding

No financial support was received to conduct this study.

Competing interests

The authors report no conflicts of interest.

Ethical approval

Not required.

Patient consent

Not required.

References

1. Choukroun J. Une opportunite en paroimplantologie: le PRF. *Implantodontie* 2001:55–62.
2. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, Gogly B. 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**:e37–44.
3. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, Gogly B. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part III: leucocyte activation: a new feature for platelet concentrates? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**101**:e51–5.
4. Dohan Ehrenfest DM, Del Corso M, Diss A, Mouhyi J, Charrier JB. Three-dimensional architecture and cell composition of a Choukroun's platelet-rich fibrin clot and membrane. *J Periodontol* 2010;**81**:546–55.
5. Tsirogianni AK, Moutsopoulos NM, Moutsopoulos HM. Wound healing: immunological aspects. *Injury* 2006;**37**(Suppl 1):S5–12.
6. Kobayashi E, Fluckiger L, Fujioka-Kobayashi M, Sawada K, Sculean A, Schaller B, Miron RJ. Comparative release of growth factors from PRP, PRF, and advanced-PRF. *Clin Oral Investig* 2016;**20**:2353–60.
7. Miron RJ, Fujioka-Kobayashi M, Bishara M, Zhang Y, Hernandez M, Choukroun J. Platelet-rich fibrin and soft tissue wound healing: a systematic review. *Tissue Eng Part B Rev* 2017;**23**(February (1)):83–99. http://dx.doi.org/10.1089/ten.TEB.2016.0233. Epub 2016 Oct 10.
8. Gassling V, Douglas T, Warnke PH, Acil Y, Wiltfang J, Becker ST. Platelet-rich fibrin membranes as scaffolds for periosteal tissue engineering. *Clin Oral Implants Res* 2010;**21**:543–9.
9. Gassling V, Hedderich J, Acil Y, Purcz N, Wiltfang J, Douglas T. Comparison of platelet rich fibrin and collagen as osteoblast-seeded scaffolds for bone tissue engineering applications. *Clin Oral Implants Res* 2013;**24**:320–8.
10. Ozgul O, Senses F, Er N, Tekin U, Tuz HH, Alkan A, Kocyigit ID, Atil F. Efficacy of platelet rich fibrin in the reduction of the pain and swelling after impacted third molar surgery: randomized multicenter split-mouth clinical trial. *Head Face Med* 2015;**11**:37.
11. Uyanik LO, Bilginaylar K, Etikan I. Effects of platelet-rich fibrin and Piezosurgery on

impacted mandibular third molar surgery outcomes. *Head Face Med* 2015;**11**:25.
12. Kumar YR, Mohanty S, Verma M, Kaur RR, Bhatia P, Kumar VR, Chaudhary Z. Platelet-rich fibrin: the benefits. *Br J Oral Maxillofac Surg* 2016;**54**:57–61.
13. Eshghpour M, Dastmalchi P, Nekooei AH, Nejat A. Effect of platelet-rich fibrin on frequency of alveolar osteitis following mandibular third molar surgery: a double-blinded randomized clinical trial. *J Oral Maxillofac Surg* 2014;**72**:1463–7.
14. Hoaglin DR, Lines GK. Prevention of localized osteitis in mandibular third-molar sites using platelet-rich fibrin. *Int J Dent* 2013;**2013**:875380.
15. Castro AB, Meschi N, Temmerman A, Pinto N, Lambrechts P, Teughels W, Quirynen M. Regenerative potential of leucocyte- and platelet-rich fibrin. Part A: intra-bony defects, furcation defects and periodontal plastic surgery. A systematic review and meta-analysis. *J Clin Periodontol* 2017;**44** (January (1)):67–82. http://dx.doi.org/10.1111/jcpe.12643. Epub 2016 Nov 24. Review.
16. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL, Mouhyi J, Dohan DM. 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**:299–303.
17. Temmerman A, Vandessel J, Castro A, Jacobs R, Teughels W, Pinto N, Quirynen M. The use of leucocyte and platelet-rich fibrin in socket management and ridge preservation: a split-mouth, randomized, controlled clinical trial. *J Clin Periodontol* 2016;**43**:990–9.
18. 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**:321–8.
19. Suttapreyasri S, Leepong N. Influence of platelet-rich fibrin on alveolar ridge preservation. *J Craniofac Surg* 2013;**24**:1088–94.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;**62**:1006–12.
21. Higgins J, Green S. *Cochrane handbook for systematic reviews of interventions version 5.1.0*. The Cochrane Collaboration; 2011.
22. Chambrone L, Chambrone D, Pustiglioni FE, Chambrone LA, Lima LA. The influence of tobacco smoking on the outcomes achieved by root-coverage procedures: a systematic review. *J Am Dent Assoc* 2009;**140**:294–306.
23. Chambrone L, Chambrone LA, Lima LA. Effects of occlusal overload on peri-implant tissue health: a systematic review of animal-model studies. *J Periodontol* 2010;**81**:1367–78.
24. Hauser F, Gaydarov N, Badoud I, Vazquez L, Bernard JP, Ammann P. Clinical and histological evaluation of postextraction platelet-rich fibrin socket filling: a prospective randomized controlled study. *Implant Dent* 2013;**22**:295–303.
25. Alzahrani AA, Murriky A, Shafik S. Influence of platelet rich fibrin on post-extraction socket healing: a clinical and radiographic study. *Saudi Dent J* 2017;**29**:149–55.
26. Das S, Jhingran R, Bains VK, Madan R, Srivastava R, Rizvi I. Socket preservation by beta-tri-calcium phosphate with collagen compared to platelet-rich fibrin: a clinico-radiographic study. *Eur J Dent* 2016;**10**:264–76.
27. 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**:259–67.
28. Gassling V, Purcz N, Braesen JH, Will M, Gierloff M, Behrens E, Acil Y, Wiltfang J. 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**:76–82.
29. Thakkar DJ, Deshpande NC, Dave DH, Narayankar SD. A comparative evaluation of extraction socket preservation with demineralized freeze-dried bone allograft alone and along with platelet-rich fibrin: a clinical and radiographic study. *Contemp Clin Dent* 2016;**7**:371–6.
30. Moussa M, El-Dahab OA, El Nahass H. Anterior maxilla augmentation using palatal bone block with platelet-rich fibrin: a controlled trial. *Int J Oral Maxillofac Implants* 2016;**31**:708–15.
31. Tatullo M, Marrelli M, Cassetta M, Pacifici A, Stefanelli LV, Scacco S, Dipalma G, Pacifici L, Inchingolo F. Platelet rich fibrin (P.R.F.) in reconstructive surgery of atrophied maxillary bones: clinical and histological evaluations. *Int J Med Sci* 2012;**9**:872–80.
32. Nizam N, Eren G, Akcali A, Donos N. Maxillary sinus augmentation with leukocyte and platelet-rich fibrin and deproteinized bovine bone mineral: a split-mouth histological and histomorphometric study. *Clin Oral Implants Res* 2018;**29**(January (1)):67–75. http://dx.doi.org/10.1111/clr.13044. Epub 2017 Aug 8.
33. Comert Kilic S, Gungormus M, Parlak SN. Histologic and histomorphometric assessment of sinus-floor augmentation with beta-tricalcium phosphate alone or in combination with pure-platelet-rich plasma or platelet-rich fibrin: a randomized clinical trial. *Clin Implant Dent Relat Res* 2017;**19**:959–67.
34. Yerke LM, Jamjoom A, Zahid TM, Cohen RE. The effect of platelet-rich fibrin, calcium sulfate hemihydrate, platelet-rich plasma and resorbable collagen on soft tissue closure of extraction sites. *J Funct Biomater* 2017;**8**. pii: E17.
35. Marenzi G, Riccitiello F, Tia M, di Lauro A, Sammartino G. Influence of leukocyte- and platelet-rich fibrin (L-PRF) in the healing of simple postextraction sockets: a split-mouth study. *Biomed Res Int* 2015;**2015**:369273.
36. Gurler G, Delilbasi C. Effects of leukocyte–platelet rich fibrin on postoperative complications of direct sinus lifting. *Minerva Stomatol* 2016;**65**:207–12.
37. Oncu E, Kaymaz E. Assessment of the effectiveness of platelet rich fibrin in the treatment of Schneiderian membrane perforation. *Clin Implant Dent Relat Res* 2017;**19**:1009–14.
38. Barbu HM, Andreescu CF, Lorean A, Kolerman R, Moraru L, Mortellaro C, Mijiritsky E. Comparison of two techniques for lateral ridge augmentation in mandible with ramus block graft. *J Craniofac Surg* 2016;**27**:662–7.
39. 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**:850340.
40. Avila-Ortiz G, Wang HL, Galindo-Moreno P, Misch CE, Rudek I, Neiva R. Influence of lateral window dimensions on vital bone formation following maxillary sinus augmentation. *Int J Oral Maxillofac Implants* 2012;**27**:1230–8.
41. Avila G, Wang HL, Galindo-Moreno P, Misch CE, Bagramian RA, Rudek I, Benavides E, Moreno-Riestra I, Braun T, Neiva R. The influence of the bucco-palatal distance on sinus augmentation outcomes. *J Periodontol* 2010;**81**:1041–50.
42. Dohan Ehrenfest DM, Pinto NR, Pereda A, Jimenez P, Corso MD, Kang BS, Nally M, Lanata N, Wang HL, Quirynen M. The impact of the centrifuge characteristics and centrifugation protocols on the cells, growth factors, and fibrin architecture of a leukocyte- and platelet-rich fibrin (L-PRF) clot and membrane. *Platelets* 2017:1–14.
43. 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**:77–83.
44. 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**:2056–64.
45. 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**:447–56.
46. Nedir R, Nurdin N, Abi Najm S, El Hage M, Bischof M. Short implants placed with or without grafting into atrophic sinuses: the 5-year results of a prospective randomized controlled study. *Clin Oral Implants Res* 2016;**18**(February (1)):10–8. http://dx.doi.org/10.1111/cid.12279. Epub 2015 Jan 27.
47. Wallace SS, Froum SJ. Effect of maxillary sinus augmentation on the survival of endosseous dental implants. A systematic review. *Ann Periodontol* 2003;**8**:328–43.
48. Tarnow DP, Wallace SS, Froum SJ, Rohrer MD, Cho SC. Histologic and clinical comparison of bilateral sinus floor elevations with and without barrier membrane placement in 12 patients: part 3 of an ongoing prospective study. *Int J Periodontics Restorative Dent* 2000;**20**:117–25.
49. Busenlechner D, Huber CD, Vasak C, Dobsak A, Gruber R, Watzek G. Sinus augmentation analysis revised: the gradient of graft consolidation. *Clin Oral Implants Res* 2009;**20**:1078–83.
50. Torres J, Tamimi F, Alkhraisat MH, Manchon A, Linares R, Prados-Frutos JC, Hernandez G, Torres-Macho J, Lopez-Cabarcos E. Platelet-rich plasma may prevent titanium-mesh exposure in alveolar ridge augmentation with anorganic bovine bone. *J Clin Periodontol* 2010;**37**:943–51.
51. Kumar N, Prasad K, Ramanujam LKR, 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**:1042–9.
52. Bilginaylar K, Uyanik LO. Evaluation of the effects of platelet-rich fibrin and Piezosurgery on outcomes after removal of impacted mandibular third molars. *Br J Oral Maxillofac Surg* 2016;**54**:629–33.

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