Fifteen Years of Platelet Rich Fibrin in Dentistry and Oromaxillofacial Surgery: How High is the Level of Scientific Evidence?

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Platelet-rich fibrin is a blood concentrate system used for soft tissue and bone tissue regeneration. In the last decade, platelet rich fibrin (PRF) has been widely used in different indication fields, particularly in oral and maxillofacial surgery. This review investigates the level of scientific evidence of published articles related to the use of PRF for bone and soft tissue regeneration in dentistry and maxillofacial surgery. An electronic literature research using the biomedical search engine "National Library of Medicine" (PubMed-MEDLINE) was performed in May 2017. A total of 392 articles were found, 72 of which were classified for each indication field. When comparing PRF with biomaterials vs biomaterial alone in sinus lift (5 studies; IIa), no statistically significant differences were detected. Socket preservation and ridge augmentation using PRF significantly enhanced new bone formation compared to healing without PRF (7 studies Ib, IIa, IIb). Reepithelialization and bone regeneration was achieved in 96 of 101 patients diagnosed with medication-related osteonecrosis of the jaw (5 studies, III). In periodontology, PRF alone (6 studies; Ib, IIa, IIb) or its combination with biomaterials (6 studies; Ib, IIa, IIb) significantly improved the pocket depth and attachment loss compared to a treatment without PRF. Over 70% of the patients were part of studies with a high level of scientific evidence (randomized and controlled prospective studies). This published evidence (38 articles), with a high scientific level, showed that PRF is a beneficial tool that significantly improves bone and soft tissue regeneration. However, the clinical community requires a standardization of PRF protocols to further examine the benefit of PRF in bone and soft tissue regeneration in reproducible studies, with a higher scientific level of evidence.

Key Words: platelet rich fibrin, scientific evidence, dentistry, maxillofacial surgery, LSCC, I-PRF

INTRODUCTION

The development and application of biomaterials has increased over the past years. In dentistry and maxillofacial surgery, biomaterials of autologous, allogenic, and xenogeneic sources are widely used,[1–4] and there are advantages and disadvantages associated with each.[5] Surgical techniques performed to obtained autografts can be difficult and are associated with higher morbidity. Despite the difficulties, they are considered the gold-standard method in bone and soft tissue regeneration, particularly because of their autologous regenerative capacity.[6] However, alternative autologous techniques introduced platelet concentrates (PC), autologous blood derivatives that are characterized by the ease of the technique used to obtain them.[7] The history of PC can be traced back to 1940, when Young and Medawar[7] described that they successfully reunited peripheral nerves in animals, sealing them in blood plasma. Based on these findings, Helena Matras[7] developed the fibrin sealant technique during experiments on rat skin and later through clinical applications in maxillofacial surgery in 1982. This fibrin sealant product consisted of a mixture of fibrinogen and thrombin, which formed a clot that was used for wound covering.[8] The natural evolution turned fibrin sealants into PC when platelets were

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added to the formula.[9] The first PC protocols were described by the so-called autologous platelet-derived wound healing factors (PDWHF) and were published in 1986 by Knighton et al and in 1998, by Marx, with the name "platelet-rich plasma" (PRP), emphasizing platelets and growth factor content.[10–12] This PC system requires the addition of anticoagulants during its processing procedure and concentrates platelets but eliminates blood-derived leukocytes. In 2001, as an alternative to PRP with numerous advantages, Choukroun developed platelet-rich fibrin (PRF), a second generation of PCs that does not require the addition of anticoagulants.[13]

PRF is a one-step standardized method of obtaining PCs. Through centrifugation of peripheral blood, physiologic clot formation and fractioning are induced without the requirement of additives such as anticoagulants; thus, PRF is the only PC system that is fully autologous.[14] Using specific tubes with a glass surface initiates the coagulation cascade and activates platelets during centrifugation. The resulting PRF consists of a fibrin scaffold that contains platelets, leukocytes, and plasma proteins. After centrifugation, the resulted 3D matrix of the PRF clot serves as a reservoir of growth factors.[15] Bioactive molecules—growth factor, cytokines, fibrinogen, fibronectin, thrombospondin, adhesive proteins, and coagulation factor—are primarily released from the alpha and dense platelet's granules.[16] Additionally, cell interaction between activated platelets and the included leukocytes and their subfamilies, such as neutrophils, seems to substantially increase the degranulation of inflammatory cytokines (IL-1β, IL-8) and chemokine (MCP-1).[17]

The initial protocol to obtain PRF described the need of the application of high relative centrifugal forces (RCF).[18,19] As a first attempt to understand PRF, our group reduced RCF through a further histological analysis of the PRF clot and found that reducing the RCF increases the number of platelets and leukocytes, with a balanced distribution of cells within the matrix.[20] In that manner, a systematic analysis (gradual reduction approach) of the influence of RCF on the PRF-based matrices was conducted: By further reducing the RCF, an even higher increase of cell concentration was obtained, as well as the release of growth factors.[21]

Basic science and translational research investigated the influence of PRF in soft and bone regeneration in vitro. The behavior of osteoblasts treated with PRF in vitro found a significantly improved activity compared to the nontreated osteoblasts.[22] In addition, a significantly higher migration rate, collagen formation and growth factor release activity was observed in gingival fibroblasts treated with PRF compared to fibroblasts treated with PRP or without PRF treatment in vitro.[23]

Based on the previous results, the low-speed centrifugation concept (LSCC) was introduced as a possible tool to create solid and liquid matrices of PRF, thereby generating more bioactive PRF matrices. These matrices contain high leukocyte and platelet concentrations, as well as advanced growth factor release, according to the clinical requirements.[21]

Since PRF was first introduced in 2001 as a second-generation PC, it has found its way into different fields of dentistry and oral maxillofacial surgery. In the last decade, there has been a constant increase in the number of published papers related to PRF's clinical applications with a great diversity of experimental methods and results. This diversity has caused uncertainty about the level of scientific evidence of published articles and whether the results are reproducible. This review is focused on individual evaluation of these published articles with a certain level of scientific evidence and reports their contributions to dentistry and maxillofacial surgery.

Materials and Methods

Literature research

An electronic literature research was conducted using the biomedical search engine "National Library of Medicine" (PubMed-MEDLINE) in May 2017. To obtain results that involved the whole scope of dentistry and PRF, the keywords used for the search were "PRF," "PRF and bone," and "PRF and soft tissue." The search resulted in a total of 392 articles. The articles were selected by reviewing the titles and abstracts of the articles; 72 were selected, according to the following inclusion criteria:

- Articles with the word platelet rich fibrin (PRF) in the title
- Articles related only to clinical applications in general dentistry and its different application fields
- Human studies
- Articles published in English

Systematic reviews obtained through the electronic literature research were not included in the study but were used to identify potentially relevant information. If needed, the references of the selected articles were examined to search for the description of the used methodology. The full texts of the selected articles were examined by three authors (S.G., C.H., and S.A.), and data was extracted using a standardized Excel data sheet as a collection tool. The following information was recorded: name of the first author, publication year, field of dentistry (endodontics, implantology, maxillofacial surgery, orthodontics, periodontology), follow-up, number of patients involved, use of biomaterials, country, and level of scientific evidence. All collected data was arranged in tables, bars, or maps using Microsoft Excel Power View 2013 (Redmond, Wash) and analyzed. The results were grouped and presented in each field (Figure 1, Table 1).

Classification of the level of evidence

All articles were independently examined by three authors (S.G., C.H., and S.A.), and after a consensus, a level of scientific evidence was assigned to each article, according to the US Agency for Healthcare and Quality (Table 2). The result of the search was 21 randomized clinical trials (Ib), 21 nonrandomized controlled prospective studies (IIa), 13 quasi-experimental studies (IIb), and 17 case control studies (III). The method of assigning a level of scientific evidence was initiated in 1979 by the Canadian Task Force on the Periodic Health Examination, with the intention of supporting its literature recommendations on evidence-based medicine. Since the first description, randomized clinical trials have been placed at the highest level

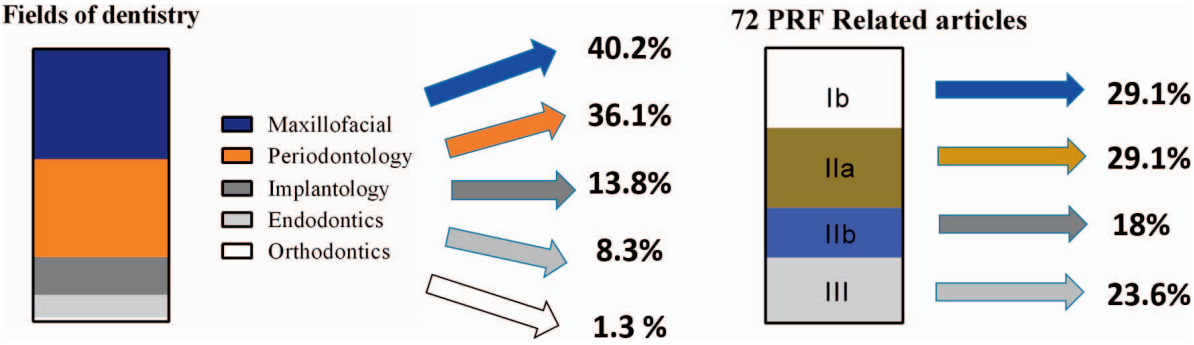


Figure 1. Distribution of all included articles by field of application and the level of scientific evidence. PRF indicates platelet rich fibrin.

of the scientific hierarchy because they are designed to be unbiased and create less risk of systematic errors. Evaluation of the published clinical articles of PRF by their level of scientific evidence could help clinicians select the best treatment options for their patients.[24–28]

Paper evaluation

In the second step, the most used evaluation parameters in the field of periodontology (ie, pocket depth [PD] and clinical attachment level [CAL]) were selected, and the results between the control and test groups (level of scientific evidence Ib, IIa, and IIb) were extracted as the mean values of PD and CAL and calculated as the difference between the baseline and the reevaluation after 6, 9, or 12 months for each study separately. The data was presented graphically using Graph-Pad Prism version 6.0 (GraphPad Software, La Jolla, Calif). The results from each paper were reported individually without comparison or statistical analysis among the studies. Statistical differences were reported in this manuscript only when the article being examined demonstrated a significant difference in their results. The results from the studies with a level III of scientific evidence (case reports) were extracted and reported in the corresponding field. In addition, the biomaterials being evaluated in the studies and the ratio (when included) in which they were mixed with PRF were arranged and cross-referenced, as shown in Table 3.

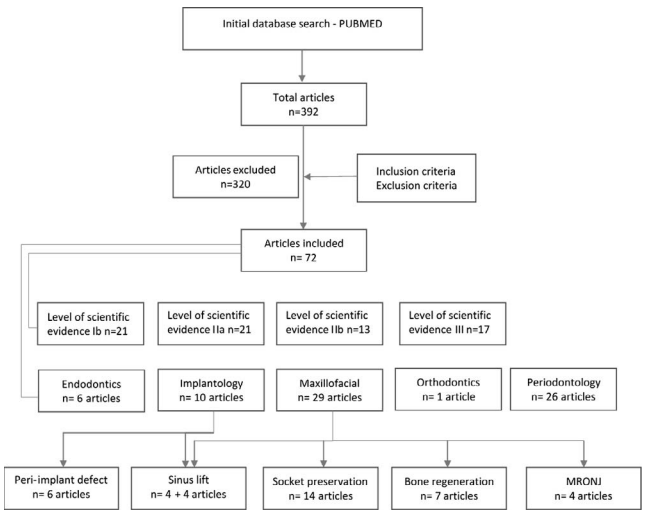


Figure 2. Flowchart of the study design and results. MRONJ indicates medication-related osteonecrosis of the jaw.

Results

The flowchart demonstrates the number of examined articles grouped by their level of scientific evidence and fields of dentistry (Figure 2). The rated 72 articles selected for the review showed that in the last decade, most papers were published in 2015 and 2016. By adding all patients found in the rated 72 articles, we obtained a result of 1822 patients involved in PRF studies; 708 (38.8%) participated in randomized level Ib studies, 566 (31.0%) participated in well-designed controlled prospect level IIa studies, 293 (22.1%) participated in quasi-experimental level IIb studies, and 144 (7.9%) participated in level III case control studies (Figure 1). The field of dentistry that showed a higher development in PRF was oral and maxillofacial surgery (40.2%), followed by periodontology (36.1%; Figure 1).[19,29–99] In recent years, the use of PRF in different fields has expanded, according to the selection of published papers in the last two years (Figure 3). There were no complications reported in 28 dental pathologies treated with PRF (Table 1). Furthermore, as seen in the extracted information, India is the country with the highest number of published PRF articles, particularly in the field of periodontology. The world map proportionally shows the number of papers published in each country, represented by different circle sizes (Figure 4).

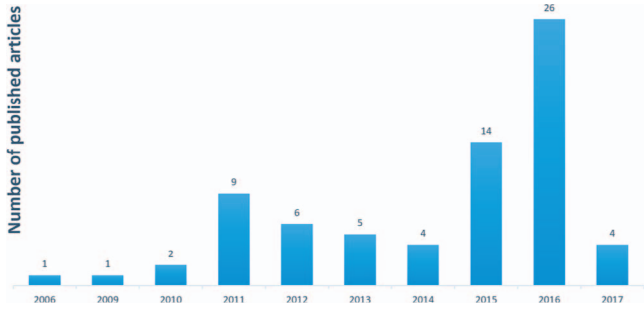


Figure 3. The number of published platelet rich fibrin articles in clinical dentistry over the last decade. The literature review was conducted in May 2017.

TABLE 1

All collected data were organized by field of dentistry*

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Geeta et al[29]	Endodontics (R/A) of non-vital tooth	Chronic periapical abscess	PRF was placed into the canals. 1. Revascularization of non-vital immature teeth 2. Regenerative pulpotomy 3. Apical barrier for apexification of non-vital immature tooth 4. Periapical surgery	1. Induce faster periapical healing 2. Ideal scaffold in revascularization of immature permanent teeth with necrotic pulps	4	18	III
Dhiman et al[30]	Endodontics (R/A) of non-vital tooth	Suppurative chronic apical periodontitis and apicomarginal communication	Peri-radicular curettage enucleation Test group: PRF gel was carefully placed into the cavity. Control group: without PRF	PRF group showed a statistically significant ($P = .046$) better improvement in PD than the control group. Within the limits of this study, it can be concluded that a high success rate may be attained in apicomarginal defects with endodontic microsurgery. PRF may not necessarily improve the outcome.	30	12	Ib
Singh et al[31]	Endodontics (BR/A)	Periradicular lesions of endodontic origin	Peri-radicular curettage enucleation PRF gel was carefully placed into the cavity.	Radiographically, all patients showed complete bone regeneration at the end of 6 mo. It requires around 1 y for complete healing to occur after the periapical surgery while with the use of PRF, healing is fastened and requires approx. 6 mo for complete regeneration of bone.	15	6	III
Subash et at[32]	Endodontics (R/A) of non-vital tooth	Necrotic pulp and symptomatic apical periodontitis	Fragmented PRF membrane was placed in the pulp chamber and pushed apically with the help of endodontic pluggers.	Radiographic examination revealed resolution of periapical lesion, thickening of the dentinal walls, root lengthening with apical closure showing a continuous lamina dura.	1	12	III
Bakhtiar et al[33]	Endodontics (R/A) of non-vital tooth	Immature teeth with necrotic pulps Acute apical abscess	The liquid that was obtained by compression of the PRF clot was used to irrigate the root canal. The PRF membrane was inserted inside the root canal.	The tooth was asymptomatic at the 6-mo follow-ups. Parallel radiographic examination revealed no periapical lesion at the 1-mo follow-up. The initiation of apical closure was obvious by the 3-mo follow-up. Signs of apical closure were observed after 6 mo. Thickening of dentinal walls and complete apical closure were noted over 18 mo.	4	18	III
Shivashankar et al[93]	Endodontics (R/A)	Necrotic pulp and open apex	The PRF was condensed into the canal using a finger plugger until the level of cementoenamel junction. Gray MTA was placed directly over the PRF to a thickness of 3 mm. The patient was recalled after 3 d and the setting of MTA was confirmed. The access cavity was then double sealed with GIC and composite restoration	Tooth #8 showed negative response to percussion and palpation tests and responded positive to CO_2 ice or an EPT. Radiograph revealed continued thickening of the dentinal walls, root lengthening, regression of the periapical lesion, and apical closure.	1	12	III
Simonpieri et al[34]	Implantology (SL)	Severe maxillary resorption	Sinus-lift PRF clots and membranes as sole filling material during lateral sinus-lift with immediate implantation	A total of 52 implants were placed. The main results in this case series were that no implant was lost during this 6-y experience and that the vertical bone gain was always substantial and stable. The final bone gain was always very significant, between 8.5 and 12 mm bone gain (10.4 ± 1.2).	20	72	IIa
Shang et al[35]	Implantology (SL)	Maxillary bone atrophy with a residual crest height of less than 5 mm	Sinus lift: Test group: A mixture of deproteinized bovine bone mineral and PRF preparation was inserted in sinuses. Control group: The sinuses were grafted with deproteinized bovine bone alone.	The percentage of newly formed bone in the PRF group was about 1.4 times that of the control group (18.35%, 5.62% vs 12.95%, 5.33%). No statistically significant difference between groups.	10	6	IIa

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Hamzacebi et al[36]	Implantology (BR/A)	Peri-implant bone defect	Flap surgery group (control) and flap surgery + PRF group (PRF). Full thickness mucoperiosteal flap, debridement, implant surface decontamination and filling with PRF membranes	100% survival of all implants. After 6 mo, the PRF group showed a statistically significantly higher reduction in PD and gain in CAL than the control group. Clinically more effective that open flap alone regardless of the defect configuration.	19	6	IIa
Öncü et al[37]	Implantology (BR/A)	Partially or fully edentulous	Test: implants, PRF+ group; Control: implants without PRF. PRF membranes were applied to one of the implant osteotomies. The related implant was thoroughly rinsed with PRF liquid and inserted.	At the end of the first mo, the mean ISQ in the PRF+ group in type 2 bone was significantly higher. Secondary stability increases over time. PRF enhanced the stability of implants	20	1	IIb
Bolukbasi et al[38]	Implantology (SL)	Atrophic posterior maxilla	Sinus lift: Test group: Bovine bone graft and PRF. Control group: Resorbable collagen membrane and bovine bone graft.	Overall implant survival rate was 100% in both test and control groups. Bone height gain and resorption were calculated radiologically in the test and control groups, the differences were not statistically significant ($P = .093$).	25	24	IIa
Boora et al[39]	Implantology (BR/A)	Partially edentulous in anterior maxilla	Group I: PRF group (the immediately prepared PRF was placed over the surgical site); Group II: Non-PRF group. One stage nonfunctional immediate prosthetic protocol.	In PRF group, statistically significant crestal bone level changes were noted within 3 mo. The amount of crestal bone level changes as exhibited in the study group had statistically significant lesser mean value than the control group. Intergroup comparison for probing depth and bleeding and probing at 1 mo and 3 mo was statistically insignificant.	20	8	Ib
Angelo et al[41]	Implantology (BR/A)	Maxillary atrophy	Group 1: Particles of 40% beta-TCP and 60% HA; Group 2: Microporous particles of pure beta-TCP; Group 3: beta-TCP and PRF placed subperiosteal	All subperiosteal tunnel augmentation sites presented sufficient, even buccal bone gain in radiographic follow-up. The results of the current study back the experimental findings concerning the advantages for more reliable bone regeneration when A-PRF is used and suggest A-PRF to enhance biomechanical bone quality to a constant higher level in the clinical routine in conjunction with piezotome surgery and BiSHB grafts. No statistical significant differences were found ITVs.	82	7	IIa
Hehn et al[42]	Implantology (BR/A)	Patients aged 18+, who required an implant in the posterior mandible, were eligible for this study	Bone augmentation and tissue thickening: titanium implants were inserted at bone level with primary stability. In the test group, the tissue was augmented with a PRF membrane using a double-layered technique. In the control group, the implant treatment was realized without mucosa thickening.	Though surgical flaps were all sutured completely free of tension, a postoperative dehiscence above the implant could be observed in all test patients within the first wk. This process resulted in a complete loss of mucosal and augmented tissues above the implant. The open areas were healed by secondary intention. All implants were clinically osseointegrated and stable and showed no sign of infection. The comparison of the differences in bone loss showed no significance between the control and test groups.	31	6	Ib
Kanayama et al[40]	Implantology (SL)	Atrophic posterior maxilla	Sinus lift: floor elevation procedures by the crestal approach; PRF as sole filling material	This 1-y prospective study showed that the use of PRF as the sole grafting material during simultaneous sinus lift and implantation is a safe and reliable method.	27	12	III

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Peck et al[94]	Implantology (BR/A)	Partially edentulous	Alveolar ridge preservation: tooth roots were extracted atraumatically. A total of 3 L-PRF membranes were formed and inserted into the extraction socket site.	The extraction site showed signs of healing with no evidence of residual inflammation. The site was free of infection and the L-PRF membrane was still clearly visible. Even though it remained exposed to the oral environment, there were no signs of membrane disintegration or infection. The patient also reported minimal pain during the postoperative period. At implant insertion, the quality of the newly formed bone was such that it allowed for the implant to be inserted at an insertion torque of more than 35 Ncm.	1	3	III
Choukroun et al[19]	Maxillofacial surgery (SL)	Maxillary atrophy	Sinus lift: Control group (FDBA without PRF); Test group (FDBA with PRF) filling with freeze-dried bone allograft (FDBA) + PRF	The histomorphometric results of control group (FDBA without PRF) after 8 mo appear equivalent to those of the test group (FDBA with PRF) after 4 mo. It is possible to consider sinus floor augmentation surgery with a shorter healing period before implant placement (4 mo instead of 8 mo). PRF membranes appear to be able to treat sinus membrane perforation and permit the surgery to be completed.	9	8	IIa
Ruga et al[45]	Maxillofacial surgery (SP) (PC)	Impacted third molar	Socket preservation: Control: No PRF test; PRF was placed into the extraction socket	In the study group, less pain was referred, and hygienic maintenance was facilitated by a more rapid alveolar socket fulfillment; consequently, distal periodontal condition was also improved. The healing processes seemed to be accelerated, and the patient's postoperative comfort seemed to be positively influenced.	14	6	IIb
Sammartino et al[48]	Maxillofacial surgery (SP)	Records of mechanical heart valve substitution Tooth extraction	Socket preservation: PRF was placed into the extraction socket	There were only 2 hemorrhagic complications (4%); these occurred in 2 patients with an INR of 3.7: a 61-year-old man and a 54-year-old woman.	50	7 d	IIa
Singh et al[43]	Maxillofacial surgery (SP)	Impacted third molar	Socket preservation: Test group: PRF was placed into the extraction socket; Control: Without PRF	Healing Index of Soft Tissue: There was significant difference between study and control site in all 20 patients. Assessment of bone density after 12 wk showed that average gray scale value for PRF (study) site was comparatively higher than non-PRF (control) site. There was no significant difference between study and control site.	20	3	IIa
Tatullo et al[50]	Maxillofacial surgery (SL)	Maxillary atrophy	Sinus lift: Control: Deproteinized bovine bone and test: amorphous and membranous PRF together with deproteinized bovine bone	PRF leads to the production of new bone, already 106 d after reconstructive surgery. No statistically significant differences ($P > .05$) regarding ISQ mean values were found between test groups and control groups in each protocol we performed.	60	36	IIa
Soydan et al[53]	Maxillofacial surgery (WH) (SP)	MRONJ	Socket preservation: PRF was placed into the extraction socket	Total bone closure was achieved and new mucosa was visible. No gingival loss, inflammation, or infection was detected at the postoperative 6-mo follow-up, and the patient was able to use his dentures 1 mo after the procedure.	1	6	III

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Suttapreyasri et al[54]	Maxillofacial surgery (SP)	postextraction socket	Socket preservation: tooth extraction. Test group: The PRF was filled in the socket. Control group: The alveoli were filled with natural blood clot.	Soft-tissue healing: No statistically significant differences were detected among the groups. Alveolar ridge contour: Statistical significance at the first week (T1) between the PRF and the control group. Radiographic evaluation: No statistically significant differences were detected among the groups.	8	2	IIa
Marenzi et al[46]	Maxillofacial surgery (SP)	Root fracture, residual root, periapical granuloma, and orthodontic reason	Socket preservation: Control: natural healing; Study: the sockets were filled with L-PRF	All patients completed the study. No cases of bleeding, infection, alveolar osteitis, or other surgical complications were reported. Comparisons between values relative to the study and control sides showed better healing and faster socket closure for the side treated with L-PRF, with differences statistically significant at d 3 and 7.	26	1	IIa
Kumar et al[51]	Maxillofacial surgery (SP) (PC)	Impacted third molar	Socket preservation: Test: PRF was placed into the extraction socket, followed by flap approximation; Control: only primary closure	Difference between the 2 groups was statistically significant ($P = .017$) indicating that the application of PRF in the extraction socket aided in reducing the patient's postoperative pain, swelling, and interincisal distance.	31	3	Ib
Yelamali et al[55]	Maxillofacial surgery (SP)	Impacted third molar	Socket preservation: split-mouth experiment. PRF was placed on the right side and PRP on the left side.	Healing capability for PRF group was significantly higher as compared to PRP group. The mean values of bone density for PRF groups were significantly higher as compared to PRP groups.	20	4	IIb
Doiphode et al[44]	Maxillofacial surgery (SP)	Impacted third molar	Socket preservation; Group I: control; Group IIa: filled with PRP gel; Group IIb: filled with PRF	Group I showed dehiscence in 5 (33.3%) out of 15 cases. Group IIa showed dehiscence in 3 (20%) cases, whereas Group IIb (PRF) did not show any sign of wound dehiscence. The difference in the decrease in ABH at 2, 4, and 6 mo postoperatively in Group IIb was statistically significant.	30	6	IIa
Kotsakis et al[47]	Maxillofacial surgery (SP) (PC)	Maxillary upper-right first premolar Class I mobility	Socket preservation: tooth extraction, placement of a PRF plug and membrane in the socket. Eight wk later implants were places for "early accelerated implant placement".	The implant remained successfully in function at the 48-mo follow-up, with no signs of mobility or inflammation and no subjective symptoms, such as pain, or altered sensation.	1	48	III
Shawky et al[49]	Maxillofacial surgery (BR/A)	Alveolar cleft	Bone regeneration: Group A: maxillary alveolar cleft reconstruction with anterior iliac crest bone graft combined with PRF; Group B: autogenous anterior iliac crest bone graft	No recurrence of the oronasal fistulae and no signs of infection or evidence of bone graft loss. Group A: The mean amount of newly formed bone volume was 0.78 cm^3 and the percentage of newly formed bone was 82.6%. Group B: The mean amount of newly formed bone volume was 0.62 cm^3, and the mean percentage of newly formed bone was 68.38%. There was a statistically significant increase in the percentage of newly formed bone in Group A.	24	6	Ib
Nørholt et al[52]	Maxillofacial surgery (WH)	MRONJ	Elevation of a mucoperiosteal flap. Necrotic bone was removed and bone surface was smoothened; bone covered with PRF.	Successful outcome was defined as complete mucosal healing and no symptoms from the jaw. The outcome of the surgical treatment was successful in 14/15 patients (93%). In conclusion, 14/15 patients in this study had a successful outcome following the surgical treatment of ONJ with the use of PRF membranes to ensure a multilayered closure.	15	6	IIb

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Kumar et al[56]	Maxillofacial surgery (SP)	Impacted third molar	Socket preservation: Test: PRF was placed into the extraction socket; Control: Without PRF	These numbers show that PRF gradually increases the osseous healing at every follow-up, and the mean value remains consistently higher in the experimental group. The values for fractal analysis were 0.03 (95% CI −0.02 to 0.08) higher in the experimental group across the time points compared with the control, but the difference was not significant.	34	6	III
Kapustecki et al[57]	Maxillofacial surgery (BR/A)	Oroantral communication and fistula	Bone regeneration: collection of monocortical bone blocks from mental protuberance or mandible oblique line. The graft was stabilized using a bicortical screw. The graft and surrounding bone were covered with a PRF membrane.	Complete healing of the operated area in 18 patients. In the study group, in all cases closure of the oroantral communication was observed. Mean measurement alveolar width values in a group of 20 patients = postextraction: alveolus (mm): 13.5; control: 13. Mean measurement alveolar height values in a group of 20 patients = postextraction alveolus (mm): 13; control: 12.5.	20	6	III
Anwandter et al[58]	Maxillofacial surgery (SP)	Unrestorable caries lesions and advanced periodontal disease	Socket preservation: the teeth were extracted. The socket was completely filled with several L-PRF clots. Finally, L-PRF membranes were positioned over the clots, inside the socket.	The mean horizontal bone loss was 1.56 mm. A total horizontal resorption of 1.53 mm was reported at the alveolar crest. During the first 4 mo after tooth extraction the sockets reduced 4.5 mm in depth. The center of the socket had a significant filling of 5.72 ± 3.6 mm ($P = .0001$) and the oral cortical plate had a mean vertical gain of 0.09 mm 1.57 mm ($P = .9$). This would bring L-PRF effectiveness to the same level as these osseous substitutes.	18	4	IIb
Gönen et al[61]	Maxillofacial surgery (WH)	MRONJ	Bone regeneration: one layer of PRF was laid into the alveolar bone cavity. The second layer was placed superficially and sutured to the surrounding gingiva. Acellular plasma was injected submucosally around the wound after the procedure.	Epithelization occurred in the second wk postoperatively, and there was no infection or inflammation of the gingival tissues. New gingival tissue formation was observed after 4 wk, and healing was uneventful without any paresthesia. Three mo after the surgical procedure, whole closure of the exposed bone with new gingival tissue was achieved.	1	12	III
Gurler et al[62]	Maxillofacial surgery (SL) (PC)	Posterior maxillary bone height of less than <5 mm.	Sinus lift: study group: allogeneic freeze dried corticocancellous bone chips mixed with L-PRF and Bony sinus windows were covered with 2 layers of PRF membranes; control: Allogeneic bone graft and bony sinus windows were covered with a resorbable collagen membrane	There were gradual improvements in postoperative pain, swelling, sleeping, eating, phonetics, activities of daily living, and missed work days in the L-PRF group, but the differences between the groups were not significant. HI scores of the L-PRF group (4.2 ± 0.9) were higher than that of the control group (3.6 ± 0.7) on the 7th (4.7 ± 0.4) and 14th postoperative d (4.4 ± 0.5); differences were not statistically significant.	24	14	IIa
Cortese et al[63]	Maxillofacial surgery (BR/A)	Reabsorbed edentulous ridge secondary to previous extraction	Bone augmentation: split crest flapless new technique for implant insertion. Test group: autologous PRF has been used to fill the osteotomy gap or simply as regenerative material; control group: traditional technique.	All patients underwent an uneventful implant surgery. At T1 mean height loss was of 0 mm and of 1.2 mm at T3 for group 1 (new flapless technique) while for group 2 patients (traditional implant insertion technique) mean height bone loss was 2.4 mm at T1 and of 3.4 at T3. Mean difference for height bone loss between the two groups of patients was 2.4 mm at T1 and 2.2 mm at T3.	10	6	IIb

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Asaka et al[64]	Maxillofacial surgery (WH)	MRONJ	Socket preservation: PRF group (prospective) and a control group (retrospective). PRF was laid directly over the bone to fill the socket, which was then sutured using 4.0 nylon sutures.	Postoperative infections and the onset of MRONJ, characterized by exposed necrotic bone or fistulae, were also absent at the time of follow-up in all patients. All sockets were filled with granulation tissue within 2 wk and completely epithelized by 4 wk. Radiographic bone regeneration as a radiopaque rise was observed after 3 mo in all PRF cases. Early epithelization was confirmed in all PRF patients including patients receiving steroids and immunosuppressants. The prevalence of delayed recovery was significantly higher in the control group ($P < .05$) than in the PRF group.	102	3	IIb
Temmerman et al[66]	Maxillofacial surgery (SP)	Symmetrical bilateral tooth extractions in the maxilla or mandible	Socket preservation: At the test site 2–5 PRF clots, depending on the size of the socket, were inserted and compressed with a large plunger. The site was covered with 2–3 L-PRF membranes. At the control site, a cross-suture was performed to stabilize the coagulum.	Statically significant differences ($P = .004$) were found in the percentage of socket fill between test [94.7% (26.9)] and control sites [63.3% (31.9)].	22	3	Ib
Dar et al[68]	Maxillofacial surgery (BR/A)	Cystic lesions	Bone regeneration: all cystic lesions were enucleated and PRF was placed in the bony defects	Radiographically, all patients showed that PRF promotes faster osseous regeneration within the 3rd postoperative mo, and within 6th postoperative mo, complete bone regeneration was seen.	20	6	III
Moussa et al[80]	Maxillofacial surgery (BR/A)	Horizontally deficient edentulous maxillary anterior ridges ($\leq$ 4.5 mm)	Bone augmentation: Test group: palatal bone block covered with PRF; Control group: only bone block graft	PRF showed superior results when used to cover the palatal bone block, decreasing the block's surface resorption when compared with only using bone block graft. The test group showed statistically significantly lower mean graft resorption than the control group (test, 0.8 $\pm$ 0.6 mm; control, 1.6 $\pm$ 0.9 mm; $P = .006$)	12	4	IIa
Öncü et al[60]	Maxillofacial surgery (BR/A)	Indications for dental extraction	Bone regeneration: after the extraction, using split-mouth design, test sockets were coated with L-PRF and control sockets without L-PRF	Results showed a statistically significant difference between the stability of L-PRF+ and L-PRF− implants at 1 wk and at 1 mo. Mean marginal bone resorption was higher in the control group at 1 y.	26	12	IIb
Park et al[59]	Maxillofacial surgery (WH)	MRONJ	Bone regeneration and healing of tissue – Group 1: L-PRF. Group 2: L-PRF+rhBMP2 L-PRF was placed at the bone surface and primary closure of the mucoperiosteal flap was performed.	L-PRF (n = 25): complete resolution, n = 9 (36.0%), delayed resolution: 13 (52.0%), no resolution n 3 (12.0%); L-PRF Plus+BMP-2 (n = 30) complete resolution: 18 (60.0%), delayed resolution: 11 (36.7%), no resolution: 1 (3.3%); statistically significant compared with that of the therapy using L-PRF alone ($P = .028$)	55	6	IIa
Varghese et al[65]	Maxillofacial surgery (SP)	Impacted mandibular third molars	Socket preservation: randomization was performed after extraction. On one side the socket was sutured primarily (control site); on the other side, autologous PRF gel was placed and the socket was sutured (test site).	The average percentage of bone fill in the PRF group was 57.90 (SD, 26.789) and that of the non-PRF group was 46.74 (SD, 17.713; $P < .05$). Soft tissue healing as evaluated by the healing index of Landry et al also was found to be better at the PRF test site and it was statistically significant ($P < .05$).	30	3	IIa

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Bilginaylar et al[67]	Maxillofacial surgery (BR/A)	Odontogenic orocutaneous fistula	Bone regeneration: the treatment started with root canal treatment. Two d after the filling of the root canal, apical resection was performed and PRF was administered into the bone cavity; a PRF membrane was used to close the site as well.	At the 3rd mo follow-up, radiographically, intraoral, and extra oral examinations revealed complete healing of bone at periapical lesion area and spontaneous healing of orocutaneous fistula.	1	3	III
Inchingolo et al[95]	Maxillofacial surgery (SL) (BR/A)	Severe maxillar bone atrophy	Surgical procedure of "one-stage sinus lift" (implant insertion occurred concurrently with sinus lift, and the healing and integration time was 6–9 mo); before inserting the implant, a small quantity of filling material was placed in the cavity (Bio-Oss and PRF).	In all the cases included in this protocol, the authors observed a successful implant-prosthetic rehabilitation. All patients reported no pain to percussion, no sign of tissue suffering to the soft peri-implant tissues, and the presence of an optimal primary stability of the inserted implants. An average increase in the peri-implant bone density of 31%.	23	6	IIb
Muñoz et al[69]	Orthodontics (BR/A)	Moderate to severe crowding, Class II or III malocclusions	PAOO + (PRF+ Puros/Bio-Oss graft + Metronidazole)	Our results support the wound healing and osteogenic properties of L-PRF, yet also suggest that the healing capacity of L-PRF may exceed the limits reported. This combinatorial approach seems to reduce the risk of tear/dehiscence of the flap with subsequent graft exposure and contamination, providing an optimal environment for wound healing.	11	24	III
Sharma et al[73]	Periodontology (PAR)	Intra-bony defects Grade II furcation defect	Randomly allocated and treated either with (test group) autologous PRF and OFD or (control group) OFD.	Test sites presented with a significantly greater reduction in PD than control sites, with a difference of 2.17 mm. The gain in attachment level (CAL) was significantly greater in the test sites. Test sites presented with a significantly greater vertical defect fill (50.8–6.24) than the control sites (16.7–6.42) at 9 mo.	18	9	Ib
Sharma et al[74]	Periodontology (PAR)	Chronic periodontitis	Autologous PRF (test group) with OFD or OFD alone (control group) in the treatment of 3-wall IBDs	Test sites presented with a significantly greater PD reduction (4.55 ± 1.87 mm) than control site. The PAL gain was also greater in test sites (3.31 ± 1.76) compared to the control group (2.77 ± 1.44 mm). Test sites (48.2%–5.72%) presented with a significantly greater IBD fill than did control sites.	32	9	Ib
Thorat et al[85]	Periodontology (PAR)	Intrabony defects	Conventional flap surgery with autologous PRF (test group); OFD alone (control group); PRF in the treatment of intra bony defects in chronic periodontitis patients	The mean PD and CAL at baseline and after 9 mo in control and test group was 6.75 ± 1.69, 6.50 ± 1.75 and 3.19 ± 1.52, 4.38 ± 2.16 mm, respectively, and was found to be significant ($P < .01$). IBD at baseline (4.40 ± 1.04) and test group (4.52 ± 1.11) was compared, it was found to be non-significant at baseline ($P < .05$) and was significant at 9-mo comparison ($P < .05$).	32	9	Ib
Chang et al[86]	Periodontology (PAR)	Chronic periodontitis Infrabony defects	Minced PRF with bioactive glass was applied to the defect walls and root surfaces. The PRF membrane was adapted over the grafted defect and above the CEJ.	These results indicated that PRF may contribute to the differentiation of human PDLFs into osteoblasts. In this study, PRF enhanced p-ERK, OPG and ALP expression. The application of PRF for periodontal osseous defects achieves probing depth reduction, clinical attachment gain, and radiographic defect fills.	6	12	IIa

Table 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Jankovic et al[83]	Periodontology (PAR) (PC)	Gingival recession Miller Class I or II	On one side, the gingival recession was treated with a CAF and PRF membrane (PRF group). The other side was treated with a CTG in combination with a CAF (control).	No side effects were reported. VRD, CAL, and PD differences among the groups were not statistically significant at baseline or 6 mo. Healing index: Results obtained in the PRF group were statistically superior in reference with data recorded in the CTG group ($P < .05$). The pain intensity was statistically different among groups for the first 7 d, favoring the PRF group.	15	6	Ib
Bansal et al[77]	Periodontology (PAR)	Chronic periodontitis Interproximal intrabony defects	Mucoperiosteal flap elevation followed by the placement of Group I: DFDBA alone. In Group II, mixture of PRF with DFDBA was done.	A combination of PRF with DFDBA demonstrated better results in probing pocket depth reduction and clinical attachment level gain as compared to DFDBA alone in the treatment of periodontal intrabony defects. On comparison, the difference between the 2 groups was not statistically significant at all time intervals.	10	6	IIb
Bajaj et al[81]	Periodontology (PAR)	Chronic periodontitis Mandibular degree II furcation defects	PRF with OFD or autologous PRP with OFD, or OFD alone. Treatment of degree II furcation defects	Both PRF and PRP sites presented with a significantly greater PD reduction (4.29 ± 1.04 mm, 3.92 ± 0.93 mm, respectively) than control site (1.58 ± 1.02 mm) at 9 mo postoperatively ($P < .05$). RVCAL gain was also greater in the PRF (2.87 ± 0.85 mm) and PRP (2.71 ± 1.04 mm) sites as compared to control site (1.37 ± 0.58 mm). There was no significant difference between PRP and PRF groups.	42	9	Ib
Joseph et al[82]	Periodontology (PAR)	Chronic periodontitis	PRF gel (experimental group I); PRF gel and PRF membrane (experimental group II); OFD alone (control group)	The magnitude of changes was higher for both the experimental groups compared to control ($P < .05$) and there was no significance difference between the experimental groups ($P > .05$). Radiographic bone levels RCH (−1 ± 2.8 mm in control, 1 ± 4.7 mm in group I, 0.33 ± 2.28 mm in group II) at baseline and 9 mo postsurgery showed no significant differences in all groups ($P > .05$). The negative value for RCH in control group implies resorption of alveolar bone postoperatively compared to baseline.	15	9	IIa
Pradeep et al[70]	Periodontology (PAR)	Chronic periodontitis Interproximal intrabony defects	Four treatment groups: OFD alone, OFD with PRF, OFD with 1% MF, and OFD + PRF +1% MF. Treatment of 2/3 wall IBDs with OFD + PRF +1% MF gel	All treated cases showed uneventful wound healing and the drug was well tolerated by all the patients. Greater PD reduction and RAL gain seen in PRF+1% MF group. IBD depth reduction in MF group and PRF group was not statistically significant when compared to each other.	126	9	IIb
Pradeep et al[71]	Periodontology (PAR)	Chronic periodontitis	OFD+placebo gel (Group 1), PRF+HA with OFD (Group 2), RSV 1.2 mg gel+PRF+HA with OFD (Group 3)	Results of our study suggest that furcation defects, when treated simultaneously with RSV 1.2 mg+HA+PRF (Group 3) showed significantly positive correlation with PD reduction (4.62 ± 1.03 mm) and RVAL, RHAL gain (4.17 ± 0.70 and 4.05 ± 0.76 mm, respectively) with greater defect depth reduction (3.68 ± 0.32 mm) and % bone defect fill (61.94 ± 3.54 %).	120	9	Ib

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Agarwal et al[75]	Periodontology (PAR)	Chronic periodontitis Interproximal intrabony defects	Test group: PRF/DFDBA and control group: the DFDBA/saline. DFDBA was mixed with PRF at a proportion of 1:1 (v/v) and filled into the defect. A membrane of compressed PRF was trimmed and adapted over the grafted defects.	PRF/DFDBA group exhibited statistically significantly greater changes compared with the DFDBA/saline group in PD (4.15 ± 0.84 vs 3.60 ± 0.51 mm), CAL (3.73 ± 0.74 vs 2.61 ± 0.68 mm), REC (0.47 ± 0.56 vs 1.00 ± 0.61 mm), bone fill (3.50 ± 0.67 vs 2.49 ± 0.64 mm), and defect resolution (3.73 ± 0.63 vs 2.75 ± 0.57 mm).	30	12	Ib
Mathur et al[76]	Periodontology (PAR)	Generalized chronic periodontitis	Treated with OFD and filled with PRF (OFD with PRF) or OFD with ABG	There was significant mean PPD reduction and CAL gain, in both the treated groups; PRF (2.67 ± 1.29 mm, 2.53 ± 1.06 mm) and the ABG treated group (2.4 ± 1.06 mm, 2.67 ± 1.63 mm). No significant difference in mean change after intervention between the two groups was observed for clinical parameters (PI, GI, PPD, CAL, AC, and BD level).	25	6	IIa
Sandhu et al[78]	Periodontology (PAR)	Chronic periodontitis Interproximal intrabony defects Grade II furcation defects	The debrided defect was slightly overfilled with Gengigel. PRF was filled into the furcation defect. A GTR membrane was used to cover the furcation. The reflected flap was repositioned over the PRF membrane.	These studies support the fact that the combined use of Gengigel in conjunction with PRF seems to have an added benefit in the regeneration of Class II furcation, as described in this case report.	1	6	III
Ajwani et al[79]	Periodontology (PAR)	Chronic periodontitis Two and three-wall intrabony defects ≥3 mm	The control group consisted of sites treated with OFD alone, whereas test-group sites were treated with OFD with autologous PRF.	Intragroup and intergroup comparisons showed statistically significant reduction with PD and RAL and no difference was observed with GML levels. Statistically significant improvements were seen with the mean defect fill (cement enamel junction to base of the defect [CEJ-BOD] and AC-BOD) ($P = .003$*) when intragroup and intergroup comparisons were made. PRF + OFD stimulated a significant improvement in the clinical and radiographic parameters and increase in bone fill compared to OFD alone at 9 mo.	20	9	Ib
Gamal et al[72]	Periodontology (PAR)	Severe chronic periodontitis	Group 1: bone substitute grafting DBM control group; Group 2: PRGF combined with DBM; Group 3: PRF combined with DBM; papillary preservation flap, filling with PRF and xenograft in intrabony periodontal defects	PRF and control group GF levels were found also not significantly different. All groups showed statistically significant improvement in PD reduction, CAL gain and IBD fill compared to baseline data. No statistically significant differences were found between groups.	30	9	Ib
Agarwal et al[84]	Periodontology (PAR)	Gingival recession Miller Class I or II	CAF procedures under the microsurgical approach in the management of Miller's Class I and II gingival recession defects with the use of either PRF or AM in comparison to CAF alone	Root coverage was obtained in 52.3% patients, our results reported superior root coverage in PRF treated site as compared to control group. At 6-mo follow-up, significant increase in GT measurements in Group I (CAF with PRF), whereas nonsignificant increase for Group II (CAF with AM) and no change or decrease for Group III (CAF alone) as compared to baseline was observed.	23	6	IIa

Table 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Bansal et al[87]	Periodontology (SD) (WH) (PC)	Gingiva hyperpigmentation	Split mouth design: 1 quadrant was covered with PRF membrane and 2 quadrant was covered with a periodontal dressing (CoePack)	HI after both 3 and 5 days postoperatively; CoePack sites had greater erythematous area as compared to PRF. At 7 days postoperatively, both sites exhibited normal tissue architecture. After 5 d, 2 patients complained of slight pain at CoePack site whereas on PRF site, none of the patients reported pain.	5	7 days	IIb
Biswas et al[88]	Periodontology (PAR)	Mandibular molar class II furcation defects	Group I: 10 furcation defects were treated using bioactive glass (NovaBone) bone graft putty material. Group II: 10 furcation defects were treated using PRF.	Both treatments showed improvement in GI and PI. There was an overall reduction in both vertical and horizontal probing depth in both groups; however, vertical probing depth reduction in Group II showed better statistically significant results than did Group I at the end of 3 months (P −.0004), 6 months (P −.00001), and 9 months (P −.0004).	15	9	IIb
Sezgin et al[89]	Periodontology (PAR)	Generalized, severe, chronic periodontal disease	Split-mouth design: The selected sites were randomly divided into Xontrol (ABBM alone) and Rest (ABBM-PRF) groups. The defect was filled to the existing alveolar crest. PRF was used to cover the defect as a barrier.	Significantly greater CAL gain was detected in the test group than in the control group ($P < .05$). In addition, increase in GR was not statistically significant at 6 mo after treatment compared to baseline ($P > .05$) in the Rest group, whereas this increase was statistically significant in the control group ($P < .05$); moreover, PD decreased significantly compared to baseline at 6 mo after treatment in both groups ($P < .05$), but the inter-group differences were not statistically significant at any evaluation time point ($P > 0.05$).	21	6	Ib
Chandradas et al[90]	Periodontology (PAR)	Chronic periodontitis–intrabony defect	Group A (PRF with DBM), Group B (PRF alone), and Group C (OFD) The mixture was delivered into the defect.	Mean PD reduction and RAL gain were greater in Group A (4.25 ± 1.48, 3.92 ± 0.90) and Group B (3.82 ± 0.75, 3.27 ± 0.65) than control (3.00 ± 1.21, 2.25 ± 0.62). Furthermore, statistically significant improvement in LBG and %BF was found in Group A (3.47 ± 0.53, 61.53 ± 4.54) compared to Group B (2.55 ± 0.61, 49.60 ± 14.08) and Group C (1.21 ± 0.80, 24.69 ± 15.59).	38	9	Ib
Kanoriya et al[91]	Periodontology (PAR)	Mandibular degree II furcation defects	Group 1 treated with open-flap debridement; group 2 treated with access therapy with autologous PRF; and group 3 treated with access therapy and autologous PRF + 1% ALN gel	Reduction in PD was greater in Group 3 (4.4 ± 0.57 mm) when compared with Group 2 (3.69–0.76 mm) and Group 1 (2.41–0.77 mm). RVAL and RHAL gain was greater in Group 3 (4.12–0.6 mm and 3.64–0.90 mm) when compared with Group 2 (3.39–0.49 mm and 2.86–0.062 mm) and Group 1 (2.33–0.48 mm and 2.04–0.35 mm). Group 3 showed greater significant radiographic bone fill (56.01%–2.64%) as opposed to Group 2 (49.43%–3.70%) and Group 1 (10.25%–3.66%).	72	9	Ib

TABLE 1

Continued

Study	Dental Field *(indication)	Diagnosis	Treatment	Results	Patients	Follow-up, mo	Level of Scientific Evidence
Ustaoğlu et al[92]	Periodontology (WH)	Inadequate attached gingival and gingival recession defects	FGG donor sites were treated with T-PRF and compared with an untreated control group. An FGG was obtained and then sutured at the prepared recipient bed. The T-PRF membrane was then prepared to be compatible with the FGG donor site.	The T-PRF group showed a significantly higher CWE than did the control group on day 14 (68.7% for the test group; 16.7% for the control group; $P < .001$). CWE was observed in all patients in both groups on day 21. PSTT in the T-PRF group was significantly thicker than that in the control group after 6 mo of healing (4.51 ± 0.58 mm in the T-PRF group and 3.93 ± 0.69 mm in the control group; $P < .05$).	40	21 days	Ib
Aroca et al[96]	Periodontology (PAR)	Miller Class I and II recession defects	CAFs were performed on both sides of the mouth, either in conjunction with a PRF membrane (test side) or without (contralateral control side).	At 6 mo, the difference in root coverage between the 2 groups was statistically significant: 80.7%–14.7% and 91.5%–11.4% for test and control sites, respectively. A significant increase in GTH between baseline and 6 mo was observed only in the test group (from 1.1–0.4 mm to 1.4–0.5 mm).	20	6	Ib
Jankovic et al[97]	Periodontology (PAR)	Bilateral Miller Class I or II maxillary gingival recession	Two treatment groups: CAF combine with EMD or CAF combined with PRF. The flap was advanced to cover the PRF membrane and sutured.	The mean decrease of GR was not statistically significant. The WKT increase at 12 mo was statistically significant favoring the EMD group. PD measurements were not significant. The pain intensity was statistically significantly between groups for the first 5 d, favoring the PRF group. No clinical advantages in between PRF and EMD.	20	12	Ib
Lekovic et al[98]	Periodontology (PAR)	Intrabony defects	PRF-BPBM group and PRF alone group; a membrane of compressed PRF was trimmed and adapted over the grafted defect.	Mean pocket reduction in the PRF group was 3.35 ± 0.68 mm on buccal and 3.24 ± 0.73 mm on lingual sites and in the PRF-BPBM group 4.47 ± 0.78 mm on buccal and 4.29 ± 0.82 mm on lingual sites. The differences observed between the 2 groups were statistically significant in favor of the PRF-BPBM group. The PRF group presented with a clinical attachment gain of 2.24 ± 0.73 mm on buccal sites and 2.12 ± 0.78 mm on lingual sites, while the gain for the PRF-BPBM group was of 3.82 ± 0.78 mm on buccal and 3.71 ± 0.75 mm on lingual sites. The differences in attachment gain observed between the 2 groups were significantly better in the PRF-BPBM group.	17	6	IIa
Bains et al[99]	Periodontology (PAR)	Retrograde periodontitis along with Grade II furcation	The furcation was filled with PRF gel mixed with hydroxyapatite graft and a PRF membrane was placed over it.	The patient was asymptomatic when he last reported 1½ y after the treatment with significant disappearance of radiolucency on radiographs and probing depth reduction from 10 mm to 3 mm.	1	18	III

*ABH indicates alveolar bone height; ABBM, inorganic bovine bone mineral; ABG, autogenous bone graft; AC, alveolar crest; ALP, alkaline phosphatase; AM, amnion membrane; BD, bony defects; beta-TCP, beta tricalcium phosphate; BF, bone fill; BiSHB: biphasic self-hardening biomaterial; BMP, bone morphogenetic protein; BPBM, bovine porous bone mineral; BR/A, bone regeneration and augmentation; CAF, coronally advanced flap; CAL, clinical attachment level; CEJ, cementoenamel junction; CTG, connective tissue graft; CWE, complete wound epithelization; DBM, demineralized bone matrix; DFDBA, demineralized freeze-dried bone allografts; EMD, enamel matrix derivative; EPT, electric pulp tester; FDBA, freeze-dried bone allografts; FGG, free gingival graft; GI, gingival index; GT, gingival thickness; GTH, gingival thickness; GTR, guided tissue regeneration; HA, hydroxyapatite; HI, healing index; IBD, intrabony defects; INR, international normalized ratio; ISQ, implant stability quotients; ITVs, insertion-torque-value; LBG, linear bone growth; L-PRF, leukocytes platelet rich fibrin; MF, metformin; MRONJ, medication-related osteonecrosis of the jaw; OFD, open flap debridement; ONJ, osteonecrosis of the jaw; OPG, osteoprotegerin; PAOO, periodontally accelerated osteogenic orthodontics; PAL, periodontal attachment level; PD, pocket depth; PDLF, periodontal ligament fibroblasts; p-ERK, phosphorylated extracellular signal-regulated protein kinase; PI, plaque index; PPD, probing pocket depth; PC, pain control; PRF, platelet-rich fibrin; PRGF, preparation rich in growth factors; PRP, platelet rich plasma; PSTT, palatal soft-tissue thickness; PSTT, pbone crest height; R/A, revascularization/apexification of non-vital tooth; REC, mucosal recession; RHAL, relative horizontal attachment level; RVCAL, relative vertical clinical attachment level; RSV, Rosuvastatin; SD, surgical depigmentation; SL, sinus lift; SP, socket preservation; VRD, vertical gingival recession depth; WH, wound healing; WKT, width of the keratinized tissue.

Table 2

Classification of the level of scientific evidence, according to the US Agency for Healthcare Research and Quality

Level	Type of scientific evidence
Ia	Scientific evidence obtained from meta-analyses of randomized clinical trials
Ib	Scientific evidence obtained from at least one randomized clinical trial
IIa	Scientific evidence obtained from at least one well-designed, non-randomized controlled prospect study
IIb	Scientific evidence obtained from at least one well-designed, quasi-experimental study
III	Scientific evidence obtained from well-designed observational studies, such as comparative studies, correlation studies or case control studies.
IV	Scientific evidence obtained from documents or opinions of experts committees or clinical experiences of renowned opinion leaders.

Figure 4. The world map shows the tendency towards research on PRF. The circle sizes correspond to the sum of articles collected in this literature review, related to each country.

PRF in endodontics

Six studies were associated with the endodontic field. Five articles were case control studies (level III),[29,31–33,93] while one was a randomized study (level Ib).[30] In this field, a total of 55 patients were treated with PRF by placing it into the dental canals or in the periradicular lesions. One study reported 5 patients with incomplete healing. Two patients did not respond to treatment at all[30]; in the remaining 48 patients, complete resolution and bone regeneration of the apical lesions were achieved. The treated pathologies were immature teeth with necrotic pulps, acute chronic apical abscess, and suppurative chronic apical periodontitis. Apical closure and root lengthening were observed in all cases diagnosed with immature necrotic pulps of the teeth.[29,31–33,93]

PRF in implantology

A total of 255 patients participated in 10 studies related to the use of PRF in implantology, with the level of scientific evidence Ib,[39–42] IIa,[34–36,38,41] IIb,[37] and III.[40,94] The treated pathologies were severe maxillary or mandibular resorption and peri-implant bone defects.[36.37.39] Several treatment options were also described, in which PRF was used as a sole biomaterial or in combination with other biomaterials.[34,40] Follow-up care ranged from 6 months to 6 years without implant loss.[36] The articles reported successful osseointegra-

Table 3

The mixing ratio of platelet rich fibrin and the autologous grafts and/or biomaterials cross-referenced

Autologous Graft/Biomaterial	Comparison/Ratio of Mixture	Reference
Freeze-dried bone allograft	Not reported	19
Deproteinized bovine bone mineral	Not reported	35
Bovine bone graft mixture	1:2	38
40% beta-tricalcium phosphate (beta-TCP) and 60% hydroxyapatite (HA) beta-tricalcium phosphate (beta-TCP)	Not reported	41
Deproteinized bovine bone	Not reported	50
Allogenous freeze dried cortico-cancellous bone chips	Not reported	62
Cortico-cancellous particulate allograft and deproteinized bovine bone (3:2)	Not reported	69
1% Metformin	1:1	70
Porous hydroxyapatite + Rosuvastatin 1.2 mg	1:1	71
Freeze-dried bone allograft	Not reported	72
Decalcified freeze-dried bone allograft (DFDBA)	1:1	75
Autogenous bone graft	Compared	76
Demineralized freeze-dried bone allograft	No reported	77
Gengigel - hyaluronic acid	Not reported	78
Amnion allograft membrane	Not reported	84
Bioactive glass	Not reported	86
Bioactive glass	Not mixed	88
Anorganic bovine bone mineral	Not reported	89
Demineralized bone matrix	Not reported	90
1% Alendronate Gel	1:1	91
Deproteinized bovine bone	Not reported	95
Enamel matrix derivative	Compared	97
Bovine porous bone mineral	1:1	98
Hydroxyapatite graft	Not reported	99

tion,[42] enhancement of biomechanical quality,[41,94] safe and reliable sinus floor elevation,[40] significant crestal bone gain compared to a control group without the use of PRF,[39] and an increase of the secondary stability of implants.[37] An additional study reported dehiscence in 31 patients after performing implant placement and tissue augmentation with PRF using a double-layer technique. After 6 months, all implants were osseointegrated, without any signs of infections.[42] Furthermore, rinsing dental implants prior to treatment significantly increased secondary stability over time[37] and significantly reduced bone resorption when PRF was used to cover the implant site.[39] A total a total of 19 patients presenting with peri-implantitis defect classes Ib+II, Ic+II, Id+II (38 implants) were treated with PRF and demonstrated a survival rate of 100% after 6 months of follow-up.[36,100]

PRF in maxillofacial surgery

In the field of oral and maxillofacial surgery, 4 groups were identified: sinus lift, socket preservation, bone regeneration/augmentation, and medication related osteonecrosis of the jaw (MRONJ).

Sinus Lift Treatment (Maxillofacial Surgery/Implantology)

Eight articles and 198 patients were identified in this group, with IIa,[19,34,35,38,50,62] IIb,[95] and III levels of evidence.[40] Two studies evaluated PRF as a sole filling biomaterial using the lateral or crestal approach,[34,40] and the results demonstrated that the regenerated bone was sufficient for implant insertion and without bone resorption for up to 6 years; the final bone gain was significant, between 8.5 and 12 mm (10.4 ± 1.2).[34,40] After a 1-year prospective study, PRF as a sole graft material was also said to be reliable and stable.[40] In a case control study, PRF was mixed with deproteinized bovine bone, and the study reported a 31% increase in the peri-implant bone density.[95] Five studies evaluated PRF in combination with biomaterial versus biomaterial alone. In the PRF group, accelerated regeneration was observed; however, no statistically significant between-group differences was observed in new bone formation.[19,35,38,50,62]

Socket Preservation

A total of 14 articles investigated the effect of PRF in the treatment of socket preservation with the level of scientific evidence Ib,[51,66] IIa,[43,44,46,48,54,65] IIb,[45,55,58] and III.[47,53,56] The evaluation parameters focused on bone regeneration and pain assessment. Nine studies, with a total of 343 patients, evaluated the influence of PRF on bone regeneration (PRF vs blood clot).[43–45,54–56,58,65,66] Six studies showed significant improvement of socket bone fill,[56,65,66] vertical gain of oral cortical plate,[58] alveolar ridge contour,[53] and bone density[55] in the groups using PRF compared to the control group without PRF. Three studies showed improved bone regeneration in the PRF group but were not statistically significant.[43,45,56]

Pain was evaluated using the visual analog scale score (PRF vs natural healing); the group treated with PRF showed significantly reduced pain compared to natural alveolus healing.[45] However, Abhishek Singh et al[43] reported that although pain could be reduced in the study group, it was not statistically significant.

A further study with a IIa level of scientific evidence evaluated the use of PRF as a tool to manage hemorrhagic complications. Fifty patients with records of heart surgery and anticoagulant therapy were treated by placing PRF in 168 post-extraction sockets; only 2 complications were reported in patients, with an international normalized ratio (INR) of 3.7. The study showed that PRF could serve as a sealing material to avoid hemorrhagic complications.[48] Furthermore, a case study evaluated the stability of implants inserted in PRF-preserved sockets vs no socket preservation. Significantly higher implant stability and significantly lower bone resorption were achieved compared to implants inserted in nonpreserved sockets.[47]

Bone regeneration and ridge augmentation

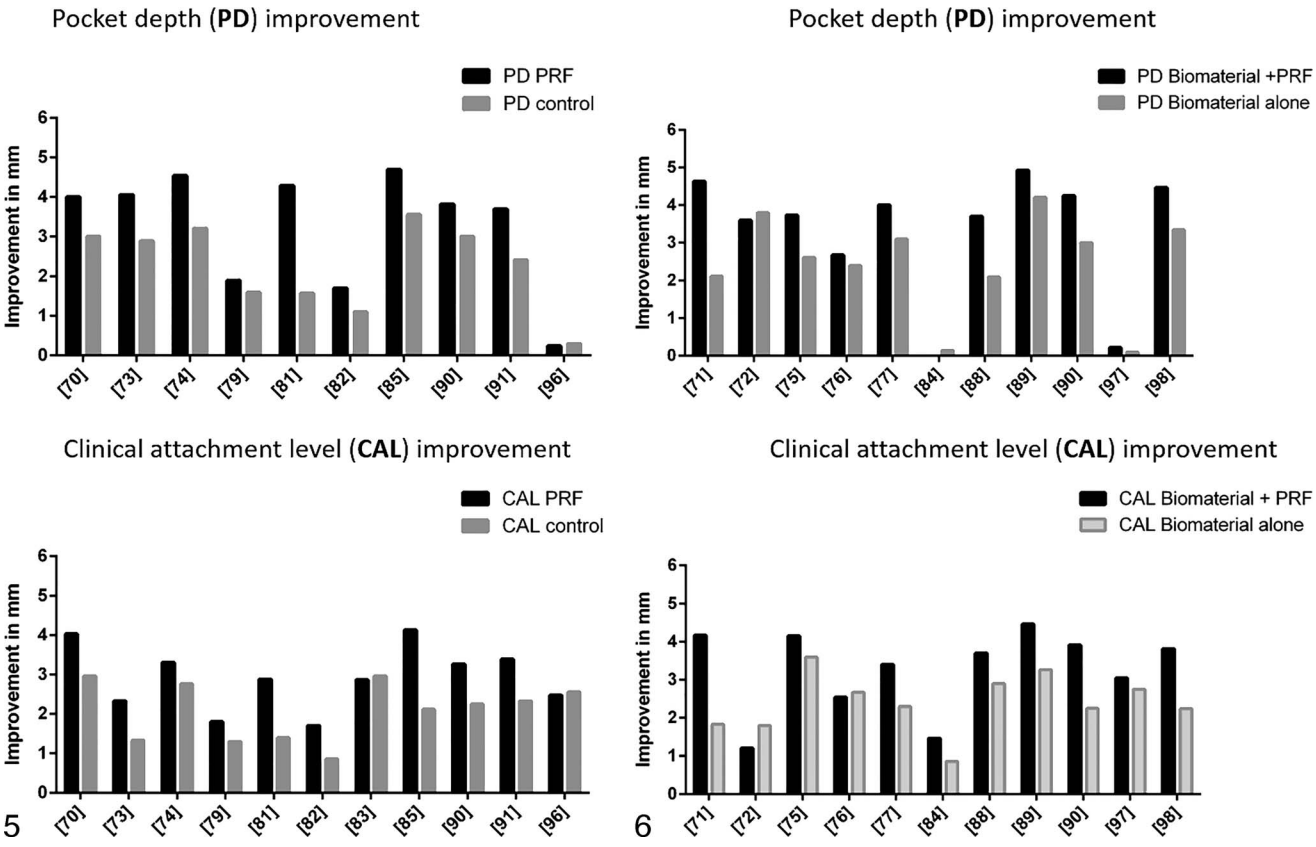
One study with a Ib level of scientific evidence involved 24 patients diagnosed with cleft alveolar ridge reported statistically significant new bone formation after the treatment with iliac crest graft combined with PRF (test group) compared to iliac crest grafts without PRF (control group).[49] In an additional study, 20 patients with cyst lesions were treated with PRF; the bone defects were filled with PRF after cyst enucleation (evidence level III, without controls). The bone defects partially regenerated after 3 months, with complete bone healing after 6 months.[68]

Medication Related Osteonecrosis of the Jaw (MRONJ)

In total, 5 articles investigated the effect of PRF in the treatment of MRONJ (level of scientific evidence IIa, IIb, III). Two studies with a IIa and IIb level of evidence reported statistically significant improvement of wound healing compared to the control group. Epithelization was observed in the PRF group within 2–4 weeks and in the control group within 2–8 weeks.[59,64] The remaining 3 case control studies with a level of evidence IIb and III reported positive clinical results.[52,53,61] A total of 101 patients with MRONJ were treated using PRF as a multilayer coverage of the bone; 3 studies reported a complete healing of all the cases[53,61,64]; the remaining two articles reported no resolution in 1/15 cases[52] and 4/55 of the cases.[59] The studies showed a fast epithelialization within 4 weeks to 3 months and a total bone closure of the defect in 96 patients (during antiresorptive treatment or with an interrupted treatment prior to surgery). A group of 25 patients were treated with a mixture of PRF plus recombinant human bone morphogenetic proteins 2 (rhBMP2) and compared to a control group of 30 patients treated with PRF only; the results showed statistically significant improvements in healing in the PRF+BMP2 group.[59]

Orthodontics

Only 1 article was found in this field with a level III of scientific evidence. An orthodontic-surgical treatment using Wilcko's modified periodontally accelerated osteogenic orthodontics (PAOO) was performed in 11 patients; PRF was minced or applied as a membrane combined with mineralized human cancellous bone allograft + deproteinized bovine bone material (3:2) and metronidazole (500 mg). All patients healed without



Figures 5–6. Figure 5. The use of platelet rich fibrin (PRF) as sole filling material vs conventional open access flap. **Figure 6.** The use of PRF with biomaterial vs biomaterials alone.

any problems; orthodontic treatment took, on average, 9.3 months, with stable treatment after 2 years.[69]

Periodontology

A total of 26 articles were selected with different levels of scientific evidence Ib,* IIa,[76,82,84,86,98] IIb,[70,77,87,88] and III.[78,99] More randomized studies with control and test groups were found in this field. The pathologies treated were chronic periodontitis with different levels of bone defects, gingival recession, and gingiva hyperpigmentation. A total of 13 of the 26 articles included a PRF study-group as a sole treatment compared to conventional treatments (eg, open flap debridement, connective tissue graft, and autogenous bone graft).† Ten of these studies reported that the use of PRF improved equally (4 articles)[70,83,91,97] or significantly (6 articles)[73,74,79,81,85,90] for PD or CAL compared to the conventional surgical treatments. An additional study showed no significant differences in PD reduction and CAL gain[82] (Figures 5 and 6). As opposed to measuring PD and CAL, the previously mentioned articles and 2 others obtained improvements in pain reduction, healing index[83,87,92,97] and bone-defect fill.[79,70]

A total of 14 studies investigated the combination of PRF with different biomaterials (eg, hydroxyapatite bone graft,[71,99] freeze-dried bone allograft [DFDBA],[72,75,77,90] autogenous bone graft,[76] amnion allograft membrane,[84] bioactive glass calcium phosphosilicate,[86,88] anorganic bovine bone mineral,[89] enamel matrix derivative,[97] bovine porous bone mineral,[98] and bioactive Gengigel hyaluronic acid).[78] The most frequent combination used was PRF+DFDBA; the used ratio of the mixture was reported only in 6 articles (1:1 or 1:2); Table 3. Three studies reported statistically significant improvements in PD and CAL compared to the sole use of biomaterial or PRF.[90] Six studies that combined PRF with biomaterials of allogenic or xenogeneic source showed significantly improved CAL and PD in the PRF group compared to the control group (biomaterial without PRF). Two studies did not show significant results between the evaluated groups,[97] and 1 reported better root coverage in the control group.[96] Furthermore, the use of autogenous bone graft was compared to the use of PRF as a sole filling material for bone regeneration, and no statistical significant improvement was observed between the evaluated groups after the intervention.[76] Two studies observed that the use of bioactive Gengigel or hydroxyapatite graft combined with PRF seemed to have advantages in terms of the bone regeneration of furcation intrabony defects.[78,99]

Discussion

In the present review, a level of scientific evidence was assigned to each article to establish a parameter of comparison and to give guidance to clinicians. To avoid bias in the selection of the

*References 71–75, 79, 81, 83, 85, 89–92, 96, 97.
†References 70, 73, 74, 79, 81–83, 85, 87, 90–92.

articles, the initial inclusion criteria was based on the title of the articles and, second, on the content of the abstract to verify its relationship to dentistry and its different fields. The extracted data was reported based on the articles in Table 1.

As seen in the results of this review, over 70% of the patients were part of a randomized or controlled prospective study. The subsequent data can serve as a compendium for clinical practitioners combining dental pathologies and treatments where PRF is used (Table 1). Note that 1822 patients participated in 72 articles included in this review, resulting in 28 different diagnosis and pathologies. In recent years, the application of PRF in different fields has expanded, as the selection of published papers in the last 2 years indicates (Figure 3). This result may be primarily because of the absence of complications, positive results, autologous source, and the simplified and clinically applicable preparation method.

The PRF map illustrates the presence throughout the world of PRF to give an idea of how research in the clinical environment has developed (Figure 4). All fields of dentistry are involved; however, periodontology and oral-maxillofacial surgery remain the primary areas of application. The properties of PRF to accelerate the healing process of soft and hard tissue, while controlling pain and inflammation opens up a broad area of application to clinicians.

The essence of PRF may rely on the delivery of blood components at an early stage of healing, which diminishes the noxious phases of stress-induced hypermetabolism in response to injury.[101] Additionally, PRF from humans can regulate inflammation, promote vascularization, provide a matrix for cells, and improve the healing of tissue and bone.[20]

Continuous research in the field of PRF has shown that PRF, which is a bioactive autologous system, can be considered as a drug delivery system.[20] Current studies aim to optimize the regenerative capacity of PRF using the low-speed centrifugation concept (LSCC). In this context, PRF matrices that are centrifuged using a low relative centrifugation force (RCF) show higher leukocyte and platelet concentrations compared to PRF matrices that are centrifuged using a high RCF.[21] Consequently, matrices generated in the low RCF range release a higher concentration of growth factors (VEGF, EGF, TGF ß-1) compared to those generated in a high RCF range.[21,102]

The results of the clinical application of PRF in different fields of dentistry and oral-maxillofacial surgery demonstrated that, presently, there is a considerable group of published articles with a high scientific evidence of the effectivity of PRF in bone and soft tissue regeneration.

In the field of periodontology, 23 studies with a scientific evidence of Ib, IIa, or IIb have shown that the application of PRF led to a significantly improved pocket depth (PD) and clinical attachment level (CAL) compared to the groups treated without PRF, and one study with a scientific evidence of Ib reported better root coverage in the control group. Additionally, the results in this review highlight the fact that in the field of periodontology, the use of biomaterials in combination with PRF seems to significantly improve the regeneration potential of the used biomaterials, which may be related to the "biologization" of the acellular biomaterial prior to their application and could facilitate cell-cell communication and biomaterial integration in the application region.[103]

Most studies regarding the surgical-periodontal treatment have focused on periodontitis with different diagnoses. Only 1 study with a scientific evidence of IIa has evaluated the effect of PRF application in peri-implantitis (ie, 100% survival rate of the implants),[36] with significantly improved PD compared to treatment without PRF. A recent Cochrane review focused on the effectiveness of current treatments for peri-implantitis; it associated the use of bovine-derived xenograft with PD and CAL improvement.[104] Interestingly, 6 of the studies included in this review obtained statistically significant improvement of PD and CAL using PRF+biomaterial compared to the sole use of a biomaterial. Furthermore, the most frequent used biomaterial was found to be demineralized freeze-dried bone allograft (DFDBA), showing significant positive results. In particular, it has been described that biomaterials derived from natural bone sources, such as DFDBA, contain BMPs.[75] An additional study included in the review combined PRF+BMPs and obtained significant clinical improvement compared to sole PRF. The observed interaction between PRF and BMPs could help explain how PRF could enhance the regenerative potential in the case of biomaterials derived from natural bone sources. Some points still need to be clarified (eg, if the mixing ratio of PRF and the autologous grafts or biomaterials has any effect over the obtained clinical results). As observed in our review, only 6 of the included articles reported the mixing ratio (1:1 or 1:2; Table 3).[38,70,71,75,91,98] Today, due to the increased application of dental implants in the last decades, peri-implantitis has become a key area in periodontology, as the primary long-term complication after implant placement. The results of the present review could encourage clinicians to use PRF for peri-implantitis treatment, and this process requires further research in this area.

Interestingly, a further application field, such as bone regeneration within the sinus cavity (sinus-lift), showed no statistically significant difference between the new bone regeneration using biomaterials in combination with PRF compared to biomaterials alone in studies with a scientific evidence of Ib, IIa, or IIb. PRF as a sole material was shown to support bone regeneration in the sinus lift. However, the level of scientific evidence of these studies is low due to the lack of a control group. Moreover, there is a general lack of research investigating the bone regeneration in this field.

Bone regeneration after socket preservation with PRF was shown to accelerate/improve bone density and tissue healing compared to physiological defect healing. These results were underlined by 14 of the studies with a level of scientific evidence of Ib, IIa, or IIb. The contribution of PRF to bone healing should be further evaluated in critical bone defects and more complex augmentations, such as the challenge of vertical and horizontal bone augmentation. In this manner, higher evidence can be obtained regarding the benefits in bone and tissue regeneration. A comparison between the combination of PRF with biomaterials and biomaterials alone has not yet been investigated. Therefore, further studies are required to evaluate the role of PRF in combination with biomaterials and their bioactivity.

These studies all utilized clinical and radiological methods to investigate regeneration capacity and bone stability.

However, only a few single studies used histological methods to analyze bone regeneration in humans.

In addition, the application of PRF in socket of extracted third molars led to significantly reduced pain compared to conventional socket healing.[45,47,51] These observations could be explained by the ability of PRF's release of different pro- and anti-inflammatory cytokines, such as IL-4, that modulate the inflammatory response and are involved in the cascade of pain.

In addition, the quality of new bone formation and stability seemed to be improved by the PRF treatment; thus, the mechanical stability and osseointegration of implants inserted in the bone regions treated with PRF or covered by PRF have been shown to exhibit significantly higher secondary stability and experienced significantly less bone resorption compared to implants inserted in non-treated bones.[37,60]

Additionally, five studies have shown that PRF is beneficial in the treatment of medication related to osteonecrosis of the jaw. Reepithelialization and bone regeneration was achieved in 96 of the 101 treated cases. In this context, PRF provided a less invasive treatment option for multimorbid patients. Among others, this disease pattern is related to impaired vascularization and wound healing.[59] Thereby, these results may be achieved due to the bioactivity of PRF and its capability of releasing VEGF and EGF, which primarily contribute to angiogenesis and epithelialization.[102]

In other fields of dentistry, such as endodontics and orthodontics, little research has been performed, with a low level of scientific evidence. There is a general lack of long-term or retrospective studies evaluating the long-term results of implants inserted in bones treated with PRF compared to non-treated bones.

Our results provide published evidence of high scientific level that PRF (38 articles) is a beneficial tool that significantly enhances bone and soft tissue regeneration. Furthermore, 17 articles have reported that with the use of PRF as a sole biomaterial, similar results were obtained compared to the conventional treatment. In contrast, only 1 study reported statistically significant root coverage in the control group (conventional treatment) compared to the test group (PRF). There may be other cases with similar results in this field that have remained unpublished thus far. The remaining 16 articles, with a scientific evidence level III, observed clinical resolution of the treated cases with PRF. In summary, this review serves as an overview of the level of scientific evidence of studies that analyzed the role of PRF in dentistry and oral and maxillofacial surgery. To promote studies with a higher scientific level of evidence, the clinical community requires a standardization of PRF protocols and more well-designed and conducted studies.

Conclusion

The present review provides an overview of the literature regarding the existing clinical research of PRF and its level of scientific evidence. Over 70% of patients participated in studies with a high level of scientific evidence (randomized and controlled prospect studies). In 9 of the studies, the application of PRF in periodontology showed significantly improved pocket depth and clinical attachment level compared to the conventional treatment. Significantly enhanced new bone formation was reported during socket preservation and ridge augmentation procedures (7 articles) comparing the used of PRF to the normal bone healing without PRF. No statistically significant differences were found in the addition of PRF to biomaterial in sinus lift compared to sole biomaterials. When patients were diagnosed with medication-related osteonecrosis of the jaw (MRONJ) treated with PRF, the results obtained are also relevant, resulting in 96 of 101 of the patients healing uneventfully. Thus, the present review highlights the existing studies with a high scientific level of evidence that equally show the contribution of PRF in bone and soft tissue regeneration. From the 72 articles involved in the review, only 1 reported statistically significant results favoring the control group against the PRF group. Although 16 articles with a level III of scientific evidence reported good outcomes, they have the lowest level of scientific evidence. To promote reproducible studies with a higher scientific level of evidence, the clinical community requires a standardization of PRF protocols to show the benefit of PRF in tissue regeneration.

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