REVIEWS

APPLICATION OF PLATELET-RICH PLASMA FOR ALVEOLAR RIDGE PRESERVATION. A REVIEW ARTICLE

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ABSTRACT

INTRODUCTION: Bone quality and quantity are key prerequisites for dental implant surgery. The methods of reducing tissue resorption after tooth extraction are called alveolar ridge preservation and have recently gained increasing popularity. One of them is the application of autologous platelet concentrates. They release an abundance of growth factors with the potential to accelerate the healing process.

AIM: The present review aims to observe the application of platelet-rich plasma in postextraction dental sockets and evaluate its efficacy for hard and soft tissue healing and preservation according to the literature. We carefully analyzed, compared, and summarized the collected data and found numerous research and methodological gaps that can explain the heterogeneity in the studies.

MATERIALS AND METHODS: The review is based on the existing scientific database and includes 222 studies. It provides a comparative analysis and guidelines for further research.

RESULTS: There is high heterogeneity among studies, regarding the effect of platelet concentrates and platelet-rich plasma in particular on alveolar ridge preservation. Most of them validate its beneficial impact on tissue healing and volumetric preservation, which facilitate the subsequent implant placement.

CONCLUSION: The scientific data about the efficacy of platelet concentrates for soft tissue healing and preservation of the alveolar ridge are not univocal. Further research, longitudinal studies, randomized controlled trials, systematic reviews, and meta-analyses are required to evaluate its efficacy and determine whether it is superior to other methods for socket preservation.

Keywords: *alveolar ridge preservation, autologous platelet concentrates, platelet-rich plasma*

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INTRODUCTION

Successful dental implantation requires adequate bone quality and quantity and often necessitates additional procedures, called alveolar ridge preservation (ARP), to be performed before implant placement. The allografts used broadly in the clinical practice showed variable osteoinductive properties, which resulted in clinicians being in search of additional biologically active materials. Examples of such materials are those, acting as growth factor delivery systems, used to facilitate tissue healing and regeneration in periodontal and intrabony defects (1–7). There is an accumulation of platelets during the cellular phase of healing. They contain α-granules with growth factors (GFs), which play an essential role in bone regeneration.

Recently, autologous platelet concentrates (APCs) have gained increasing attention in the fields of oral surgery and dental implantology due to the abundance of growth factors that they release. Growth factors have an osteoinductive capacity and guide the formation of periodontal tissues (8). These platelet-released factors are: platelet-derived growth factor (PDGF), transforming growth factor β (TGFβ), epidermal growth factor (EGF), platelet-derived angiogenesis factor (PDAF), insulin-like growth factor (IGF), platelet factor-4, etc. (9).

Along with GFs, APCs also provide delivery systems for cytokines, chemokines, and other proteins in the wound, which play a vital role in tissue repair mechanisms (10–13) and have chemostatic and mitogenic potential, affecting cell proliferation and differentiation, angiogenesis, and tissue regeneration (12–19).

Some authors have suggested that APCs facilitate and accelerate the process of hard and soft tissue healing (20–23), enhance bone formation around implants (24), and preserve the marginal bone (25,26). Despite these statements, there is still not enough evidence of their beneficial effects during immediate implant placement (26,27) and the reports on their efficacy for hard tissue healing (28–31) and osseointegration (32–35) remain controversial.

The concentration of 1 million platelets/μL in 5 mL plasma was stated to improve hard and soft tissue healing. This effect was not observed when smaller concentrations were used, neither did greater concentrations further accelerate healing (36).

Platelet-rich plasma (PRP) is an increased concentration of autologous platelets in a small volume of plasma after centrifugation. It is an efficient source of GFs (37). Their amount in PRP is stated to be 6–8 times more than in whole blood (38). Platelet-rich plasma is applied as a barrier membrane for RP; in conjunction with bone graft materials for GBR; and treatment of osseous defects (39).

Platelet-rich plasma facilitates graft handling and placement, improves its stability, enhances revascularization, soft tissue healing, and bone formation (36). Platelet-rich plasma also contains inflammatory cells, proteins, growth factors, and adhesion molecules, which facilitate cell recruitment, proliferation, and angiogenesis (40–42).

AIM

This review aims to summarize the current knowledge of the use of PRP for ridge preservation (RP) and evaluate its efficacy. The high study heterogeneity required an in-depth and comprehensive analysis of the methodology, patient recruitment, treatment and examination protocols, and all additional factors, that could have possibly led to misleading results. We identified the research gaps and uncertainties in the existing literature and gave recommendations for further research.

MATERIALS AND METHODS

The present review is based on the scientific electronic database and includes 222 studies on the application of PRP for ARP. The results were compared and summarized to define the success rate and reliability of this technique. The study heterogeneity was carefully analyzed to determine the cause and give guidelines for future assessment.

RESULTS

According to the majority of articles, the history of this technique dates back to 1998 and the work of Marx et al. However, much earlier (in 1970) Matras et al. (43) used fibrin glues for soft tissue healing in rats (44). Rosenthal (45) described the use of platelet-fibrinogen-thrombin mixture for sealing corneal wounds. In the last decades, several authors—Dohan Ehrenfest et al. (46-49), Everts et al. (50, 51), Cieslik-Bielecka et al. (52, 53), have shed light on the features and terminology of platelet concentrates (44).

The term PRP was introduced by Kingsley in 1954 (54) and its regenerative properties were then described by Ross et al. (55). Dohan Ehrenfest et al. had a major contribution to the research of PRP (46, 56–58). The material gained popularity due to its capacity to participate in hemostasis and facilitate tissue healing (12, 59–67).

It turned out that growth factors in platelets enhanced bone formation and therefore PRP was found beneficial for jaw reconstructions (43). Whitman et al. (68) were the first to use autologous platelet gel in maxillofacial surgery with the placement of titanium implants. The authors found it beneficial for the consolidation of the osseous fragments and the adherence of the soft-tissue flap.

In the 1990s the application of PRP was regarded as a promising treatment protocol (12,69,70). It was introduced in dentistry in 1998 when Marx et al. used it in combination with autologous bone for mandibular reconstruction following resection. The authors observed promising results regarding new bone formation (13). Since then numerous studies validated its application in dentoalveolar and reconstructive surgeries, implantology, and periodontal treatment (14,21,22,46,71–90). The combination of PRP with bone grafts has been introduced in implant dentistry as a method that accelerates soft tissue healing and regeneration (63,65,66).

In 1999 Anitua introduced the first 100% autologous PRP replacing the previously used xenogenic thrombin with calcium ions. The outcomes demonstrated that this combination led to improved epithelialization after 4 days and increased bone maturation after 10–16 weeks compared to the cases with only autogenous bone (70).

It has been suggested that PRP improves soft tissue healing, facilitates reepithelialization and revascularization (39), and has positive effects on bone preservation and augmentation. It enriches bone graft materials with GFs that accelerate bone regeneration; the volume and quality of newly formed tissues are improved (8,91–94).

There is high heterogeneity in the electronic database regarding hard and soft tissue healing, bone density, bone regeneration, and patient morbidity following the application of leukocyte PRP (L-PRP) (21,95–99). On the other hand, there is more consistent evidence regarding the use of pure PRP (P-PRP). Five randomized controlled trials (RCTs) reported better healing and less discomfort when P-PRP had been used (20,22,23,100,101). A recent split-mouth RCT showed higher bone density in the P-PRP sites (102). It was proven by histomorphometric analysis that P-PRP had led to higher bone regeneration compared to spontaneous healing in the third molar region (23). On the contrary, another non-randomized CT found no statistically significant difference regarding bone volume in 1-month and 2-month follow-up (30).

In 2020 Anitua et al. published a review article on the application of PRP in oral and maxillofacial surgery based on the existing literature by that time. They noticed that P-PRP was more beneficial in RP, GBR, and management of postoperative complications. The authors also suggested that the key point for the efficacy of PRP was the method of its preparation (103).

Del Fabbro et al. (104) performed a systematic review and a meta-analysis with CCT and RCT to assess the effect of APCs on RP. They reported that APCs promoted soft-tissue healing, improve bone density and reduce postoperative symptoms.

Annunziata et al. (105) also published a systematic review on the utilization of APCs for RP. Their article included controlled CT with a total of 320 extractions. Autologous platelet concentrates were reported to have improved soft tissue healing and patient morbidity following the extractions. Their potential for bone regeneration, however, was not convincing enough. The authors suggested further methodologically standardized research to clarify the efficacy of APCs.

Several reviews have suggested that the use of PRP was beneficial for bone density and soft tissue regeneration, but the outcomes regarding bone preservation remained unclear (106,107).

Alissa et al. conducted an RCT to evaluate the effect of PRP for hard and soft tissue preservation following tooth removal. They reported that PRP led to improved soft tissue healing, better volumetric preservation, and formation of denser, longer and wider trabeculae. However, the sample size was not big enough to detect a statistically significant enhancement of bone healing (21).

Edrev et al. evaluated the effect of the application of PRP after the removal of impacted teeth and odontogenic cysts. After the surgical intervention, the wounds were filled with either PRP alone or in conjunction with collagen or autologous bone graft. The efficacy of PRP was assessed by the following criteria: pain and swelling (a subjective assessment) and bone density, evaluated by CBCT (an objective assessment). The authors reported that the best results, regarding bone density, were achieved when PRP was used in conjunction with autogenous bone, followed by the application of PRP, combined with collagen, and then PRP alone. They concluded that the utilization of PRP could improve bone healing successfully (108).

Celio-Mariano (109) demonstrated an improved bone regeneration in postextraction sockets following third mandibular molar removal and PRP application.

In contrast, after radiographic and histomorphometric assessments Aghaloo et al. (110) reported that the use of PRP for cranial defects in rabbits did not improve bone formation.

Yamamoto et al. (111) conducted a study in rats to evaluate the efficacy of PRP for RP. After histological and histomorphometric analyses, the authors reported that PRP led to more collagen deposition than bone formation during the first month. On the 30th day, there was no statistically significant difference between the experimental group and the control one. Platelet-rich plasms did not enhance wound healing and even showed less bone formation during the intermediate periods of healing. Similar results were reported when PRP was used for the treatment of bone defects in dog, goat, and rabbit models (Gerard et al. (112), Mooren et al. (113), Oliveira Filho et al. (114)). Likewise, DeNicolo et al. (115) demonstrated that the utilization of PRP alone or in conjunction with xenografts (bovine bone) did not improve bone regeneration. Plachkova et al. (116) even suggested that many of the positive reports on PRP efficacy did not meet the standards for study quality.

Several studies have suggested that PRP has positive antibacterial properties against Gr(+) oral bacteria, and thus has a beneficial role in soft tissue healing (Menzes et al. (117), Drago et al. (118)).

Garcia-Martinez et al. (119) carried out an in vitro study, which demonstrated that PRP treatment enhanced cell proliferation for 15 days. However, they did not have a long-term effect (for 1 month), which the authors explained by cell exhaustion.

YS Kim et al. evaluated clinically and radiologically whether absorbable gelatin sponge and sponge soaked with PRP could prevent bone resorption and facilitate its regeneration after tooth removal. Eighty patients participated in the study and were divided into three groups—extraction sites, filled with a gelatin sponge (group A), with a sponge and PRP (gr. B), and a control group. In a 12-week follow-up, the authors observed accelerated wound healing and better gingival height preservation in both experimental groups, compared to the control one. There was no statistically significant difference in terms of horizontal width preservation. The radiographic assessment confirmed the clinical results and showed less bone height resorption and higher bone density in the experimental groups. The difference between group A and group B was insignificant (120).

According to Dutta et al., the application of PRP and platelet-rich fibrin (PRF) in postextraction alveoli led to reduced pain and swelling and accelerated wound healing compared to the use of hydroxyapatite at 3rd, 7th, and 14th day (121).

Taschieri et al. (122) compared the clinical and radiographic results of immediate implant placement with and without the application of PRP. They analyzed retrospectively the soft tissue healing, the level of the marginal bone, the survival rates of implants and prosthetic constructions, and the postsurgical complications. The study presented 126 implants with a 5-6-year follow-up after their loading. No significant difference in terms of survival was registered between both groups (97.4% in the test group versus 97.8% in the control group). The difference in the marginal bone was insignificant, too. The soft tissue healing score, however, showed better results in the test group on the 3rd and 7th days postoperatively. The clinical and radiographic assessment did not prove the superiority of PRP utilization during immediate implant placement. The long-term follow-up (4–5 years) showed similar results regarding implant and prosthesis survival, bone preservation, and functional success. The only sufficient difference was that the PRP group demonstrated improved soft tissue healing one week after the surgery.

Schlegel et al. (123) used PRP in animals and reported that it had a beneficial effect on osseointegration of dental implants after 2 and 4 weeks. However, it did not have such effect after 8 weeks.

Zechner et al. (124) performed a histomorphometric evaluation of the osseointegration process with and without PRP application. The authors observed better results in the PRP group after 3 and 6 weeks, but not after 12 weeks.

Mancuso et al. (125) conducted a study to evaluate the effect of plasma rich in growth factors (PRGF) following tooth removal. The authors reported a decrease in the incidence of alveolar osteitis when PRGF was used. In addition, better hemostasis and faster soft tissue healing were observed in the experimental group. Furthermore, the application of PRGF in postextraction osseous defects was reported to have led to an increased bone width, greater bone density, and improved tissue closure (70).

Mozzati et al. reported satisfactory results after PRGF application in postextraction alveoli in diabetic insulin-dependent patients with reduced pain and improved wound healing in the first 2 weeks (20). Anitua et al. reported that PRGF had beneficial effects regarding bone regeneration (volume and density), soft tissue healing, patient morbidity, the thickness of keratinized tissues, and the amount of newly formed bone (23).

On the contrary, Farina et al. found no difference regarding bone density and mineralization (30).

The combination autogenous bone-PRP has been reported to accelerate osteogenesis and improve the quality of the newly formed bone (13). It has been suggested that PRP led to early consolidation and accelerated mineralization of the bone grafting material for twice the time needed with an autograft alone (15). Furthermore, PRP has been stated to increase the trabecular bone density by about 15–30% (13).

Some studies suggest that PRP promotes bone formation not only when autogenous bone is used, but also with bone grafting materials. It reduces the healing time and the donor site morbidity; accelerates tissue healing and improves the quality of the newly formed bone (126–131).

Orabee et al. conducted a study to evaluate the osteoinductive properties of the combination of calcium sulfate and PRP (CS-PRP). They investigated 52 extraction sites. Ridge preservation with CS-PRP was performed in half of the sockets. The other half served as a control group and were left on spontaneous healing. After 9 months the authors measured the bone density and height in the grafted sites and the control group and concluded that the CS-PRP combination could be used as a successful, cost-effective method for RP (36).

After histological and radiographic observations, Cheah et al. reported that PRP combined with calcium sulfate hemihydrate (PRP-CSH) showed positive results on preservation and augmentation in horizontal and vertical aspects of the ridge, and enhanced new bone formation, as well (132).

In 2012 Kutkut et al. compared the results of PRP with a collagen material (control group) with those with calcium sulfate and PRP. The histomorphometric evaluation demonstrated a significant difference in the amount of newly formed bone (66% versus 38% in the control group) (133).

Yerke et al. reported that the combinations PRP-CSH and PRF-CSH did not show significant improvement regarding soft tissue healing. The authors recommend further research with histologic assessment, longer follow-up periods, and the inclusion of more cases (134).

In split-mouth research, Sammartino et al. performed a histological evaluation of PRP incorporation onto collagen barriers after third molar removal (99). They reported accelerated bone maturation but without an increase in regeneration.

Nisar et al. (135) conducted a comparative study in a split-mouth manner to assess the dimensional changes after RP with a collagen plug and PRP (test side) and spontaneous healing (control). The follow-up examination on the 3rd and 6th months after the surgery showed a statistically significant difference regarding bone height preservation, which was better on the grafted side. In terms of bone width—a statistically significant difference was not observed between the groups. The authors were the first to describe the application of PRP and a collagen plug for RP to combine their regenerative properties. This combination serves as a scaffold for periodontal cells and can be used for tissue engineering (136, 137).

In 2004 Suba et al. published the results of socket grafting in dogs with β-tricalcium phosphate alone and in combination with PRP (test side). They observed high-density new bone in the test side (after 6 weeks). After 12 weeks the difference between the groups was moderate. After 24 weeks the bone density at the test and control sides was equal (138).

Torres et al. reported that PRP could prevent titanium mesh exposure. The test group showed no exposure, while the control one—27%. In addition, there was an increase in bone formation when PRP was used (139).

Tonito T. et al. (140) conducted a clinical trial to evaluate the effect of PRP in conjunction with anorganic bovine bone on alveolar ridge preservation. They filled the postextraction sockets with a mixture of xenograft particles and PRP gel and covered them with a PRP clot membrane. Biopsies were obtained 4 months after the extraction and histomorphometric evaluation was performed. The results showed 26.5% new bone, 45.6% bone marrow spaces, and 24.5% residual graft material. There was no statistically significant difference regarding these ratios compared to previous reports (by Vance) (141). However, the bone regeneration index (2.12 ± 0.1) and structural density index (2.7 ± 0.11) showed a significant difference (1.89 ± 0.10 and 2.3 ± 0.12 reported by Vance, respectively) (140).

Yilmaz et al. (142) utilized PRP and bovine xenograft in deep intrabony defects and observed a significant improvement one year following the procedure.

Mahdi et al. observed the effects of PRP and platelet-poor plasma (PPP) on postextraction alveoli with buccal dehiscence. The authors performed clinical and histomorphometric analyses and found that PRP enhanced bone formation in the first month but did not have a prolonged effect after 2 months. They reported significant horizontal bone resorption in a 1- and 2-month period (143). These results correspond to the findings of Araujo and Lindhe, (144) who reported a significant volumetric alternation in the first two months after the removal of mandibular premolars in dogs, and to the findings of Fickl et al. (145) who found that horizontal bone loss occurred after RP procedures in dogs. Mahdi et al. also observed that all sockets were filled with newly formed bone one month following the extractions. These results corresponded to the findings of Cardaropoli et al. (146) in dog models, who reported that most of the alveoli were filled with new bone after 1 month.

Hatakeyama et al. (147) conducted a study in dogs to determine the efficacy of PPP, PRP, and PRF for ridge augmentation of postextraction alveoli with artificially created buccal dehiscence. The extraction sites were grafted with one of the materials (PPP, PRP, PRF) or were left on spontaneous healing (a control group). The specimens were evaluated histologically and by microcomputed tomography. The PPP group showed the highest results regarding the median area of newly formed bone and the bone width. However, PRP- and PRF-treated sites showed better maturation. By scanning electron microscope, they found that the fibrin network was more condensed in the PRF group. The authors reported that under severe circumstances the GFs from platelets could interfere with bone formation and recommended the application of PPP in cases with buccal dehiscence. After a careful assessment, they concluded that bone regeneration depended on the selected material, the size of the postextraction socket, and the condition of its walls.

Similar to Mahdi et al., Gawai and Sobhana (148) demonstrated an improved osteogenic response in the first month after PRP use but with no long-term effects. Thorwarth et al. (149) also observed only short-term results after PRP use.

Several studies demonstrated that the combination of PRP with allografts for the treatment of intrabony defects demonstrated promising results (150–155).

Shanaman et al. (93) published a case series aiming to evaluate the efficacy of the combination PRP-allograft material for bone regeneration in osseous defects with vertical and horizontal deficiencies. The authors observed 3 cases in which the combination decalcified freeze-dried bone allograft (DFDBA)-PRP was used for regeneration of osseous defects before implant insertion. The graft mixture was easy to handle and facilitated its placement and initial stability. They reported gains in width and height, observed clinically and radiographically, which promoted the following implant placement. The histologic assessment showed newly formed bone and residual graft, surrounded by connective tissue. However, the addition of PRP did not show better results compared to those reported in similar studies where only bone grafts were used. It is difficult to determine the efficacy of PRP when combined with different bone grafts and substitutes. There are numerous clinical variables, which can ultimately change the treatment results, independent of the application of PRP. The fact that all of the cases required additional grafting subsequently suggested that PRP did not show good osteoinductive capacity. Moreover, the histologic evaluation suggested that its addition did not improve the quality of the new bone. On the contrary, some other studies suggested that PRP accelerated the consolidation and mineralization, thus improving the quality and quantity of the newly formed bone (13,15,70). These reports, however, observed the application of PRP only in conjunction with autologous bone.

The opinions in the literature regarding the regenerative potential of platelets remain controversial (156–159). Even though an increased platelet count (1 to 3 times) shows good regenerative potential (156,160,161), some authors have demonstrated that too high concentrations (3–8 times) do not have the same impact (162–165). It has even been suggested that such concentrations inhibit osteoblasts (157) and the excessive amount of GFs has a cytotoxic effect (158).

Some studies have suggested that PRP accelerates bone formation when applied in conjunction with autogenous bone (13,166,167), xenografts (168), and allografts (169). In contrast, there are reports, suggesting that the combination PRP-autogenous bone (110,113,170) or PRP-xenograft (166) did not show statistically significant improvement in terms of bone regeneration.

Moraschini and Barboza (107) published a review on the effect of APCs on RP. They found high heterogeneity concerning the study design and methodology, surgical approaches, the length of follow-up periods, and the protocol of APC preparation. Most of the studies confirmed that APCs accelerated soft-tissue healing and epithelization (21,70,98,171–174). Regarding hard tissue regeneration and preservation, some studies reported better results in the alveoli treated with APCs, compared to the control groups (21,175), while other studies found no statistically significant difference (30,171).

The reported efficacy of APCs for bone preservation is heterogeneous, which might be due to various reasons. One of them is the different techniques for the measurement of bone changes. For qualitative assessment, the authors use periapical radiographs, histomorphometry, micro-computed tomography, nanoindentation test, cone-beam computer tomography (CBCT) (105). Several authors reported no qualitative difference between sockets treated with APCs and those left on natural healing (21,23,30,175). Two studies (23,176) evaluated by CBCT the horizontal alveolar resorption and the bone filling rate and demonstrated significantly greater bone filling and less bone resorption in the test group.

In line with some previous reviews (29,104,107,177), Annunziata et al. concluded that a quantitative analysis of the efficacy of APCs could not be performed due to the heterogeneity of the existing data (105). These previous studies suggested that APCs might be beneficial in reducing postoperative morbidity (pain, swelling, trismus, inflammation) (104,107,177) and enhancing soft-tissue healing (29,107). They reported only limited evidence for the efficacy of APCs for bone regeneration (29,107,177).

The lack of specific standards for the preparation of APCs sufficiently limits the consistency of the existing data. The authors suggested better standardization of the experimental designs, further research on the correlation between platelet count and concentration of GFs, and their biological behavior and effects (105).

DISCUSSION

Platelets play a key role in repair mechanisms. Their alpha granules contain vital GFs that participate in cell migration, differentiation, and proliferation (178–181). Most of the studies demonstrate that platelet products facilitate cell proliferation (specifically those, sensitive to their GFs—osteoblasts (182–187), chondrocytes (188), fibroblasts (189,190), endothelial and periodontal cells (191–193), while others suggest that PRP does not influence the proliferation of fibroblasts and osteoblasts (194,195) and even has a negative effect on macrophage-like cells (196). Platelet viability and activity depend on the centrifugation method (speed and time), the volume of the collected blood, the types of cell separators, anticoagulants, platelet activators, etc. (197,198).

Several systematic reviews and meta-analyses (104,199–203) were performed aiming to summarize the current knowledge. However, the data on the effects of PRP in tissue preservation, healing, and regeneration remains controversial (204). Some authors

(205–211) have reported that PRP is a suitable material for bone regeneration, while others (175,209,212–217) have disclaimed its efficacy.

It remains controversial whether PRP accelerates and improves bone formation (218). However, its adhesive properties are undisputed (219,220). Recently, PRP utilization in oral surgery has been researched thoroughly and several types of the product have been used in clinical practice (103).

After careful analysis of the above-mentioned studies, we found some possible reasons for the heterogeneity. First of all, there is a lack of standards for the preparation of APCs. We detected some methodological mistakes, such as testing of inactivated suspensions and testing APCs from one species to another without considering an immune response (221,222). Second, we suggest further evaluation when PRP should be used alone and when in conjunction with other grafting materials. Third, there are gaps in the study designs and methods, which could lead to invalid results and a lack of statistical significance. For instance, there are different lengths of follow-up periods, small sample sizes, lack of randomization, etc. Moreover, patient comorbidity should also be considered as there are various health conditions, causing problems with bleeding, wound healing, and tissue regeneration. We also suggest further research to investigate the effects of PRP in medically compromised patients. RCTs carried in a split-mouth manner are also a valuable source of information.

CONCLUSION

Autologous platelet concentrate application aims to accelerate tissue healing and facilitate implant placement.

However, the scientific data about APC efficacy for soft tissue healing and volumetric preservation of the alveolar ridge are not univocal.

The heterogeneity among studies might be due to the different treatment protocols. Some authors used APCs in conjunction with bone substitutes, while others applied APCs alone (21,30). Moreover, the methods of preparation were not the same.

Due to the high heterogeneity in the existing literature and the controversial results among studies, it is difficult to give a strong opinion and specific recommendations on the application of PRP. For more reliable and comparable results, standardization of study methods and treatment protocols is needed.

Longitudinal studies, RCTs, and meta-analyses are required to evaluate its efficacy and validate its positive impact on newly formed tissues. We carefully studied, compared, and analyzed the electronic database and not only summarized the current knowledge but also gave guidelines for further research.

REFERENCES

1. Sigurdsson TJ, Nygaard L, Tatakis DN, Fu E, Turek TJ, Jin L, Wozney JM, Wikesjö UM. Periodontal repair in dogs: evaluation of rhBMP-2 carriers. Int J Periodontics Restorative Dent. 1996;16(6):524-37.

2. Schwartz Z, Somers A, Mellonig JT, Carnes DL Jr, Wozney JM, Dean DD, et al. Addition of human recombinant bone morphogenetic protein-2 to inactive commercial human demineralized freeze-dried bone allograft makes an effective composite bone inductive implant material. J Periodontol. 1998;69(12):1337-45. doi: 10.1902/jop.1998.69.12.1337.

3. Becker W, Lynch SE, Lekholm U, Becker BE, Caffesse R, Donath K, et al. A comparison of ePTFE membranes alone or in combination with platelet-derived growth factors and insulin-like growth factor-I or demineralized freeze-dried bone in promoting bone formation around immediate extraction socket implants. J Periodontol. 1992;63(11):929-40. doi: 10.1902/jop.1992.63.11.929.

4. Cochran DL, Nummikoski PV, Jones AA, Makins SR, Turek TJ, Buser D. Radiographic analysis of regeneration bone around endosseous implants in the canine using recombinant human bone morphogenetic protein-2. Int J Oral Maxillofac Implants. 1997;12(6):739–48.

5. Cochran DL, Schenk R, Buser D, Wozney JM, Jones AA. Recombinant human bone morphogenic protein-2 stimulation of bone formation around endosseous dental implants. J Periodontol. 1999;70(2):139-50. doi: 10.1902/jop.1999.70.2.139.

6. Howell TH, Fiorellini J, Jones A, Alder M, Nummikoski P, Lazaro M, Lilly L, Cochran D. A feasibility study evaluating rhBMP-2/absorbable collagen sponge device for local alveolar ridge preservation or augmentation. Int J Periodontics Restorative Dent. 1997 Apr;17(2):124-39. PMID: 9497707.

7. Nevins M, Kirker-Head C, Nevins M, Wozney JA, Palmer R, Graham D. Bone formation in the goat maxillary sinus induced by absorbable collagen sponge implants impregnated with recombinant human bone morphogenetic protein-2. Int J Periodontics Restorative Dent. 1996;16(1):8–19.

8. Anitua E. The use of plasma-rich growth factors (PRGF) in oral surgery. Pract Proced Aesthet Pent. 2001;13(6):487-93.

9. Gholami AG, Mohammadi M, Abrishami MR. Platelet rich plasma: review of literature. J Dent Sch Shahid Beheshti Univ Med Sci. 2014;32(3):176-86.

10. Borzini P, Mazzucco L. Platelet gels and releasates. Curr Opin Hematol. 2005;12(6):473-9. doi: 10.1097/01.moh.0000177831.70657.e8.

11. Everts PA, Knape JT, Weibrich G, Schönberger JP, Hoffmann J, Overdevest EP, Box HA, van Zundert A. Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol. 2006;38(2):174-87.

12. Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004;91(1):4-15. doi: 10.1160/TH03-07-0440.

13. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: Growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(6):638-46. doi: 10.1016/s1079-2104(98)90029-4.

14. Anitua E, Sánchez M, Orive G, Andía I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials. 2007;28(31):4551-60. doi: 10.1016/j.biomaterials.2007.06.037.

15. Marx RE. Bone graft physiology with the use of platelet-rich plasma and hyperbaric oxygen. In: Jensen O, editor. The sinus bone graft. Chicago: Quintessence Int; 1999. pp 183–9.

16. Marx RE. Platelet concentrate: a strategy for accelerating and improving bone regeneration. In: Davies JE, editor. Bone engineering. Toronto: Em Squared Inc.; 2001. pp 447–453.

17. Alsousou J, Thompson M, Hulley P, Noble A, Willett K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. J Bone Joint Surg Br. 2009;91(8):987-96. doi: 10.1302/0301-620X.91B8.22546.

18. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy. 2012;28(3):429-39. doi: 10.1016/j.arthro.2011.10.018.

19. Pelletier MH, Malhotra A, Brighton T, Walsh WR, Lindeman R. Platelet function and constituents of platelet rich plasma. Int J Sports Med. 2013;34(1):74-80. doi: 10.1055/s-0032-1316319.

20. Mozzati M, Gallesio G, di Romana S, Bergamasco L, Pol R. Efficacy of plasma-rich growth factor in the healing of postextraction sockets in patients affected by insulin-dependent diabetes mellitus. J Oral Maxillofac Surg. 2014;72(3):456-62. doi: 10.1016/j.joms.2013.10.010.

21. Alissa R, Esposito M, Horner K, Oliver R. The influence of platelet-rich plasma on the healing of extraction sockets: an explorative randomised clinical trial. Eur J Oral Implantol. 2010 Summer;3(2):121-34.

22. Ogundipe OK, Ugboko VI, Owotade FJ. Can autologous platelet-rich plasma gel enhance healing after surgical extraction of mandibular third molars? J Oral Maxillofac Surg. 2011;69(9):2305-10. doi: 10.1016/j.joms.2011.02.014.

23. Anitua E, Murias-Freijo A, Alkhraisat MH, Orive G. Clinical, radiographical, and histological outcomes of plasma rich in growth factors in extraction socket: a randomized controlled clinical trial. Clin Oral Investig. 2015;19(3):589-600. doi: 10.1007/s00784-014-1278-2.

24. Georgakopoulos I, Tsantis S, Georgakopoulos P, Korfiatis P, Fanti E, Martelli M, et al. The impact of platelet rich plasma (PRP) in osseointegration of oral implants in dental panoramic radiography: texture based evaluation. Clin Cases Miner Bone Metab. 2014;11(1):59-66.

25. Kutkut A, Andreana S, Monaco E Jr. Clinical and radiographic evaluation of single-tooth dental implants placed in grafted extraction sites: a one-year report. J Int Acad Periodontol. 2013;15(4):113-24.

26. Rosano G, Taschieri S, Del Fabbro M. Immediate postextraction implant placement using plasma rich in growth factors technology in maxillary premolar region: a new strategy for soft tissue management. J Oral Implantol. 2013;39(1):98-102. doi: 10.1563/AAID-JOI-D-11-00043.

27. Del Fabbro M, Boggian C, Taschieri S. Immediate implant placement into fresh extraction sites with chronic periapical pathologic features combined with plasma rich in growth factors:

preliminary results of single-cohort study. J Oral Maxillofac Surg. 2009;67(11):2476-84. doi: 10.1016/j.joms.2009.04.063.

28. Del Fabbro M, Bortolin M, Taschieri S, Weinstein RL. Effect of autologous growth factors in maxillary sinus augmentation: a systematic review. Clin Implant Dent Relat Res. 2013;15(2):205-16. doi: 10.1111/j.1708-8208.2011.00343.x.

29. Del Fabbro M, Corbella S, Taschieri S, Francetti L, Weinstein R. Autologous platelet concentrate for post-extraction socket healing: a systematic review. Eur J Oral Implantol. 2014 Winter;7(4):333-44.

30. Farina R, Bressan E, Taut A, Cucchi A, Trombelli L. Plasma rich in growth factors in human extraction sockets: a radiographic and histomorphometric study on early bone deposition. Clin Oral Implants Res. 2013;24(12):1360-8. doi: 10.1111/clr.12033.

31. Taschieri S, Testori T, Corbella S, Weinstein R, Francetti L, Di Giancamillo A, et al. Platelet-rich plasma and deproteinized bovine bone matrix in maxillary sinus lift surgery: A split-mouth histomorphometric evaluation. Implant Dent. 2015;24(5):592-7. doi: 10.1097/ID.0000000000000293.

32. Cho K, Kim JM, Kim MH, Kang SS, Kim G, Choi SH. Scintigraphic evaluation of osseointegrative response around calcium phosphate-coated titanium implants in tibia bone: effect of platelet-rich plasma on bone healing in dogs. Eur Surg Res. 2013;51(3-4):138-45. doi: 10.1159/000357197.

33. Yun JH, Han SH, Choi SH, Lee MH, Lee SJ, Song SU, et al. Effects of bone marrow-derived mesenchymal stem cells and platelet-rich plasma on bone regeneration for osseointegration of dental implants: preliminary study in canine three-wall intrabony defects. J Biomed Mater Res B Appl Biomater. 2014;102(5):1021-30. doi: 10.1002/jbm.b.33084.

34. Streckbein P, Kleis W, Buch RS, Hansen T, Weibrich G. Bone healing with or without platelet-rich plasma around four different dental implant surfaces in beagle dogs. Clin Implant Dent Relat Res. 2014;16(4):479-86. doi: 10.1111/cid.12026.

35. Thor AL, Hong J, Kjeller G, Sennerby L, Rasmusson L. Correlation of platelet growth factor release in jawbone defect repair--a study in the dog mandible. Clin Implant Dent Relat Res. 2013;15(5):759-68. doi: 10.1111/j.1708-8208.2011.00405.x.

36. Orabee D, Hindy M, Elsharkawy R, Omar H. (2013). Evaluation of calcium sulfate and platelet-rich plasma as an osteoinductive biomaterial for jaw bone regeneration and ridge preservation after extraction. Egypt J Oral Maxillofac Surg. 2013;4(3):78-81. doi: 10.1097/01.OMX.0000432555.32467.e1.

37. Piccin A, Di Pierro AM, Canzian L, Primerano M, Corvetta D, Negri G, et al. Platelet gel: a new therapeutic tool with great potential. Blood Transfus. 2017;15(4):333-40. doi: 10.2450/2016.0038-16.

38. 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(1):83-99. doi: 10.1089/ten.TEB.2016.0233.

39. Sanchez AR, Sheridan PJ, Kupp LI. Is platelet – rich plasma the perfect enhancement factor? A current Review. Int J Oral Maxillofac Implants. 2003;18(1):93-103.

40. Marx RE. Platelet-rich plasma: evidence to support its use. J Oral Maxillofac Surg. 2004;62(4):489-96. doi: 10.1016/j.joms.2003.12.003.

41. Martínez CE, Smith PC, Palma Alvarado VA. The influence of platelet-derived products on angiogenesis and tissue repair: a concise update. Front Physiol. 2015;6:290. doi: 10.3389/fphys.2015.00290.

42. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med. 2009;37(11):2259-72. doi: 10.1177/0363546509349921. .

43. Matras, H. Die Wirkungen verschiedener Fibrinpraparate auf Kontinuitat – strennungen der Rattenhaut. Osterr Z Stomatol. 1970;67(9):338-59.

44. Dimova C, Evrosimovska B, Popovska M. (2017). The use of graft materials and platelet rich plasma in oral surgery. Defect Diffus Forum. 2017;376:39-53. doi: 10.4028/www.scientific.net/DDF.376.39.

45. Rosenthal AR, Egbert PR, Harbury C, Hopkins JL, Rubenstein E. Use of platelet-fibrinogen-thrombin mixture to seal experimental penetrating corneal wounds. Albrecht Von Graefes Arch Klin Exp Ophthalmol. 1978;207(2):111-5. doi: 10.1007/BF00414308.

46. Dohan Ehrenfest DM, Bielecki T, Del Corso M, Inchingolo F, Sammartino G. Shedding light in

the controversial terminology for platelet-rich products: platelet-rich plasma (PRP), platelet-rich fibrin (PRF), platelet-leukocyte gel (PLG), preparation rich in growth factors (PRGF), classification and commercialism. J Biomed Mater Res A. 2010;95(4):1280-2. doi: 10.1002/jbm.a.32894.

47. Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. Classification of platelet concentrates (Platelet-Rich Plasma-PRP, Platelet-Rich Fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles Ligaments Tendons J. 2014;4(1):3-9.

48. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. 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(3):e51-5. doi: 10.1016/j.tripleo.2005.07.010.

49. Dohan Ehrenfest DM, de Peppo GM, Doglioli P, Sammartino G. Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): a gold standard to achieve for all surgical platelet concentrates technologies. Growth Factors. 2009;27(1):63-9. doi: 10.1080/08977190802636713.

50. Everts PA, Hoffmann J, Weibrich G, Mahoney CB, Schönberger JP, van Zundert A, et al. Differences in platelet growth factor release and leucocyte kinetics during autologous platelet gel formation. Transfus Med. 2006;16(5):363-8. doi: 10.1111/j.1365-3148.2006.00708.x.

51. Everts PA, van Zundert A, Schönberger JP, Devilee RJ, Knape JT. What do we use: platelet-rich plasma or platelet-leukocyte gel? J Biomed Mater Res A. 2008;85(4):1135-6. doi: 10.1002/jbm.a.31570.

52. Cieslik-Bielecka A, Gazdzik TS, Bielecki TM, Cieslik T. Why the platelet-rich gel has antimicrobial activity? Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103(3):303-5; author reply 305-6. doi: 10.1016/j.tripleo.2006.08.034.

53. Cieslik-Bielecka A, Bielecki T, Gazdzik TS, Arendt J, Król W, Szczepanski T. Autologous platelets and leukocytes can improve healing of infected high-energy soft tissue injury. Transfus Apher Sci. 2009;41(1):9-12. doi: 10.1016/j.transci.2009.05.006.

54. Kingsley CS. Blood coagulation; evidence of an antagonist to factor VI in platelet-rich human plasma. Nature. 1954;173(4407):723-4. doi: 10.1038/173723a0.

55. Ross R, Glomset J, Kariya B, Harker L. A platelet-dependent serum factor that stimulates the proliferation of arterial smooth muscle cells in vitro. Proc Natl Acad Sci U S A. 1974;71(4):1207-10. doi: 10.1073/pnas.71.4.1207.

56. Dohan Ehrenfest DM, Sammartino G, Shibli JA, Wang HL, Zou DR, Bernard JP. Guidelines for the publication of articles related to platelet concentrates (Platelet-Rich Plasma - PRP, or Platelet-Rich Fibrin - PRF): the international classification of the POSEIDO. POSEIDO J. 2013;1(1):17–27.

57. Dohan Ehrenfest DM, Bielecki T, Jimbo R, Barbé G, Del Corso M, Inchingolo F, et al. Do the fibrin architecture and leukocyte content influence the growth factor release of platelet concentrates? An evidence-based answer comparing a pure platelet-rich plasma (P-PRP) gel and a leukocyte- and platelet-rich fibrin (L-PRF). Curr Pharm Biotechnol. 2012;13(7):1145-52. doi: 10.2174/138920112800624382.

58. Dohan Ehrenfest 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(3):e37-44. doi: 10.1016/j.tripleo.2005.07.008.

59. Albanese A, Licata ME, Polizzi B, Campisi G. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immun Ageing. 2013;10(1):23. doi: 10.1186/1742-4933-10-23.

60. Forni F, Marzagalli M, Tesei P, Grassi A. Platelet gel: applications in dental regenerative surgery. Blood Transfus. 2013;11(1):102-7. doi: 10.2450/2012.0007-12.

61. Kumar KA, Rao JB, Pavan Kumar B, Mohan AP, Patil K, Parimala K. A prospective study involving the use of platelet rich plasma in enhancing the uptake of bone grafts in the oral and maxillofacial region. J Maxillofac Oral Surg. 2013;12(4):387-94. doi: 10.1007/s12663-012-0466-3.

62. Nikolidakis D, Jansen JA. The biology of platelet-rich plasma and its application in oral

surgery: literature review. Tissue Eng Part B Rev. 2008;14(3):249-58. doi: 10.1089/ten.teb.2008.0062.

63. Del Fabbro M, Bortolin M, Taschieri S, Weinstein R. Is platelet concentrate advantageous for the surgical treatment of periodontal diseases? A systematic review and meta-analysis. J Periodontol. 2011;82(8):1100-11. doi: 10.1902/jop.2010.100605.

64. Khairy NM, Shendy EE, Askar NA, El-Rouby DH. Effect of platelet rich plasma on bone regeneration in maxillary sinus augmentation (randomized clinical trial). Int J Oral Maxillofac Surg. 2013;42(2):249-55. doi: 10.1016/j.ijom.2012.09.009.

65. Inchingolo F, Tatullo M, Marrelli M, Inchingolo AM, Scacco S, Inchingolo AD, et al. Trial with Platelet-Rich Fibrin and Bio-Oss used as grafting materials in the treatment of the severe maxillar bone atrophy: clinical and radiological evaluations. Eur Rev Med Pharmacol Sci. 2010;14(12):1075-84.

66. Poeschl PW, Ziya-Ghazvini F, Schicho K, Buchta C, Moser D, Seemann R, et al. Application of platelet-rich plasma for enhanced bone regeneration in grafted sinus. J Oral Maxillofac Surg. 2012;70(3):657-64. doi: 10.1016/j.joms.2011.04.027.

67. Hanna R, Trejo PM, Weltman RL. Treatment of intrabony defects with bovine-derived xenograft alone and in combination with platelet-rich plasma: a randomized clinical trial. J Periodontol. 2004;75(12):1668-77. doi: 10.1902/jop.2004.75.12.1668.

68. Whitman DH, Berry RL, Green DM. Platelet gel: an autologous alternative to fibrin glue with applications in oral and maxillofacial surgery. J Oral Maxillofac Surg. 1997;55(11):1294-9. doi: 10.1016/s0278-2391(97)90187-7.

69. Gremmel T, Frelinger A, Michelson A. Platelet physiology. Semin Thromb Hemost. 2016;42(3):191–204. doi:10.1055/ s-0035-1564835.

70. Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. Int J Oral Maxillofac Implants. 1999;14(4):529-35.

71. Weibrich G, Kleis WK, Hitzler WE, Hafner G. Comparison of the platelet concentrate collection system with the plasma-rich-in-growth-factors kit to produce platelet-rich plasma: a technical report. Int J Oral Maxillofac Implants. 2005;20(1):118-23.

72. Agarwal A, Gupta ND. Platelet-rich plasma combined with decalcified freeze-dried bone allograft for the treatment of noncontained human intrabony periodontal defects: a randomized controlled split-mouth study. Int J Periodontics Restorative Dent. 2014;34(5):705-11. doi: 10.11607/prd.1766.

73. Arenaz-Búa J, Luaces-Rey R, Sironvalle-Soliva S, Otero-Rico A, Charro-Huerga E, Patiño-Seijas B, et al. A comparative study of platelet-rich plasma, hydroxyapatite, demineralized bone matrix and autologous bone to promote bone regeneration after mandibular impacted third molar extraction. Med Oral Patol Oral Cir Bucal. 2010;15(3):e483-9. doi: 10.4317/medoral.15.e483.

74. Bajaj P, Pradeep AR, Agarwal E, Rao NS, Naik SB, Priyanka N, et al. Comparative evaluation of autologous platelet-rich fibrin and platelet-rich plasma in the treatment of mandibular degree II furcation defects: a randomized controlled clinical trial. J Periodontal Res. 2013;48(5):573-81. doi: 10.1111/jre.12040.

75. Döri F, Nikolidakis D, Húszár T, Arweiler NB, Gera I, Sculean A. Effect of platelet-rich plasma on the healing of intrabony defects treated with an enamel matrix protein derivative and a natural bone mineral. J Clin Periodontol. 2008;35(1):44-50. doi: 10.1111/j.1600-051X.2007.01161.x.

76. Döri F, Kovács V, Arweiler NB, Huszár T, Gera I, Nikolidakis D, et al. Effect of platelet-rich plasma on the healing of intrabony defects treated with an anorganic bovine bone mineral: a pilot study. J Periodontol. 2009;80(10):1599-605. doi: 10.1902/jop.2009.090058.

77. Dutta SR, Singh P, Passi D, Patter P. Mandibular third molar extraction wound healing with and without platelet rich plasma: a comparative prospective study. J Maxillofac Oral Surg. 2015;14(3):808-15. doi: 10.1007/s12663-014-0738-1.

78. Eskan MA, Greenwell H, Hill M, Morton D, Vidal R, Shumway B, Girouard ME. Platelet-rich plasma-assisted guided bone regeneration for ridge augmentation: a randomized, controlled clinical trial. J Periodontol. 2014;85(5):661-8. doi: 10.1902/jop.2013.130260.

79. Geurs N, Ntounis A, Vassilopoulos P, Van der Velden U, Loos BG, Reddy M. Using growth factors in human extraction sockets: a histologic and histomorphometric evaluation of short-term healing. Int J Oral Maxillofac Implants. 2014;29(2):485-96. doi: 10.11607/jomi.3408.

80. Harnack L, Boedeker RH, Kurtulus I, Boehm S, Gonzales J, Meyle J. Use of platelet-rich plasma in periodontal surgery--a prospective randomised double blind clinical trial. Clin Oral Investig. 2009;13(2):179-87. doi: 10.1007/s00784-008-0223-7.

81. Keceli HG, Sengun D, Berberoğlu A, Karabulut E. Use of platelet gel with connective tissue grafts for root coverage: a randomized-controlled trial. J Clin Periodontol. 2008;35(3):255-62. doi: 10.1111/j.1600-051X.2007.01181.x.

82. Menezes LM, Rao J. Long-term clinical evaluation of platelet-rich plasma in the treatment of human periodontal intraosseous defects: A comparative clinical trial. Quintessence Int. 2012;43(7):571-82.

83. Nakkeeran KP, Saravanan K, Babu P, John RR. Evaluation of bone regeneration in periapical osseous defects with and without platelet rich plasma, combined calcium sulfate and autologous bone graft - A comparative study. J Stomatol Oral Maxillofac Surg. 2019;120(3):196-202. doi: 10.1016/j.jormas.2018.11.008.

84. Okuda K, Tai H, Tanabe K, Suzuki H, Sato T, Kawase T, et al. Platelet-rich plasma combined with a porous hydroxyapatite graft for the treatment of intrabony periodontal defects in humans: a comparative controlled clinical study. J Periodontol. 2005;76(6):890-8. doi: 10.1902/jop.2005.76.6.890.

85. Piemontese M, Aspriello SD, Rubini C, Ferrante L, Procaccini M. Treatment of periodontal intrabony defects with demineralized freeze-dried bone allograft in combination with platelet-rich plasma: a comparative clinical trial. J Periodontol. 2008;79(5):802-10. doi: 10.1902/jop.2008.070436.

86. Pradeep AR, Pai S, Garg G, Devi P, Shetty SK. A randomized clinical trial of autologous platelet-rich plasma in the treatment of mandibular degree II furcation defects. J Clin Periodontol. 2009 Jul;36(7):581-8. doi: 10.1111/j.1600-051X.2009.01428.x.

87. Saini N, Sikri P, Gupta H. Evaluation of the relative efficacy of autologous platelet-rich plasma in combination with β-tricalcium phosphate alloplast versus an alloplast alone in the treatment of human periodontal infrabony defects: a clinical and radiological study. Indian J Dent Res. 2011;22(1):107-15. doi: 10.4103/0970-9290.80008.

88. Schaaf H, Streckbein P, Lendeckel S, Heidinger K, Görtz B, Bein G, et al. Topical use of platelet-rich plasma to influence bone volume in maxillary augmentation: a prospective randomized trial. Vox Sang. 2008;94(1):64-9. doi: 10.1111/j.1423-0410.2007.00997.x.

89. Torres J, Tamimi F, Martinez PP, Alkhraisat MH, Linares R, Hernández G, et al. Effect of platelet-rich plasma on sinus lifting: a randomized-controlled clinical trial. J Clin Periodontol. 2009;36(8):677-87. doi: 10.1111/j.1600-051X.2009.01437.x.

90. Wiltfang J, Schlegel KA, Schultze-Mosgau S, et al. Sinus floor augmentation with beta-tricalciumphosphate: does plateletrich plasma promote its osseous integration an degradation? Clin Oral Impl Res 2003; 14: 213-8.

91. Fürst G, Gruber R, Tangl S, Zechner W, Haas R, Mailath G, et al. Sinus grafting with autogenous platelet- rich plasma and bovine hydroxyl apatite. Clin Oral Implant Res 2003; 14: 500-508.

92. Froum SJ, Wallace SS, Tarnow DP, Cho SC. Effect of patelet – rich plasma on bone growth and osseointegration in human maxillary sinus grafts: three bilateral case reports. Int J Periodontics Restorative Dent 2002; 22: 45-55.

93. Shanaman R, Filstein MR, Danesh-Meyer MJ. Localized ridge augmentation using GBR and platelet-rich plasma: case reports. Int J Periodontics Restorative Dent 2001; 21: 345-355.

94. Rullo R, Festa VM, Guida L, Laino G. Bone grafting with platelet-rich plasma in alveolar cleft. Case report. Minerva Stomatol 2007; 56: 63-71.

95. de Antonello GM, Torres Do Couto R, Giongo CC, Corrêa MB, Chagas OL Júnior, Lemes CHJ. Evaluation of the effects of the use of platelet-rich plasma (PRP) on alveolar bone repair following extraction of impacted third molars: prospective study. DOI: https://doi.org/10.1080/09537104.2020.1856361 5 J Cranio-Maxillofacial Surg 2013;41(4):e70–e75. doi:10.1016/j. jcms.2012.11.003

96. DurmuŞlar MC, Alpaslan C, Alpaslan G, Çakır M. Clinical and radiographic evaluation of the efficacy of platelet-rich plasma combined with hydroxyapatite bone graft substitutes in the treatment of intra-bony defects in maxillofacial region. Acta Odontol Scand 2014;72(8):948–953. do i:10.3109/00016357.2014.926023

97. Gürbüzer B, Pikdöken L, Urhan M, Süer BT, Narin Y. Scintigraphic evaluation of early osteoblastic activity in extraction sockets treated with platelet-rich plasma. J Oral Maxillofac Surg 2008;66(12):2454–2460. doi:10.1016/j.joms.2008.03.006

98. Rutkowski JL, Johnson DA, Radio NM, Fennell JW. Platelet rich plasma to facilitate wound healing following tooth extraction. J Oral Implantol 2010;36(1):11–23. doi:10.1563/AAID-JOI-09-00063

99. Sammartino G, Tia M, Gentile E, Marenzi G, Claudio PP. Platelet-rich plasma and resorbable membrane for prevention of periodontal defects after deeply impacted lower third molar extraction. J Oral Maxillofac Surg 2009;67(11):2369–2373. doi:10.1016/j.joms.2009.04.093

100. Mozzati M, Martinasso G, Pol R, Polastri C, Cristiano A, Muzio G, Canuto R. The impact of plasma rich in growth factors on clinical and biological factors involved in healing processes after third molar extraction. J Biomed Mater Res Part A 2010;95A(3):741–746. doi:10.1002/jbm.a.32882

101. Haraji A, Lassemi E, Motamedi MHK, Alavi M, Adibnejad S. Effect of plasma rich in growth factors on alveolar osteitis. Natl J Maxillofac Surg 2012;3(1):38–41. doi:10.4103/0975- 5950.102150

102. Arya V, Malhotra VL, Rao JD, Kirti S, Malhotra S, Sharma RS. Reduction in post extraction waiting period for dental implant patients using plasma rich in growth factors: an in vivo study using cone-beam computed tomography. J Korean Assoc Oral Maxillofac Surg 2019;45(5):285. doi:10.5125/jkaoms.2019.45.5.285

103. Anitua E, Fernández-de-Retana S, Alkhraisat MH. Platelet rich plasma in oral and maxillofacial surgery from the perspective of composition. Platelets. 2021;32(2):174-82. doi: 10.1080/09537104.2020.1856361.

104. Del Fabbro M, Bucchi C, Lolato A, Corbella S, Testori T, Taschieri S. Healing of Postextraction Sockets Preserved With Autologous Platelet Concentrates. A Systematic Review and Meta-Analysis. J Oral Maxillofac Surg. 2017;75(8):1601-15. doi: 10.1016/j.joms.2017.02.009.

105. Annunziata M, Guida L, Nastri L, Piccirillo A, Sommese L, Napoli C. The role of autologous platelet concentrates in alveolar socket preservation: a systematic review. Transfus Med Hemother. 2018;45(3):195-203. doi: 10.1159/000488061.

106. Barona-Dorado C, Gonzalez-Regueiro I, Martin-Ares M, Arias-Irimia O, Martinez-Gonzalez JM. Efficacy of platelet-rich plasma applied to post-extraction retained lower third molar alveoli. A systematic review. Med Oral Patol Oral Cir Bucal 2014;19:e142–8. doi:10.4317/medoral.19444

107. Moraschini V, Barboza ESP. Effect of autologous platelet concentrates for alveolar socket preservation: a systematic review. Int J Oral Maxillofac Surg 2015;44(5):632–41. doi:10.1016/j.ijom.2014.12.010.

108. Edrev S. Restoration of post-operative defects of the jaw bones with the application of bone regeneration materials containing platelet concentrates. Dissertation. Varna; 2020. pp. 57-134. (in Bulgarian).

109. Célio-Mariano R, de Melo WM, Carneiro-Avelino C. Comparative radiographic evaluation of alveolar bone healing associated with autologous platelet-rich plasma after impacted mandibular third molar surgery. J Oral Maxillofac Surg. 2012;70(1):19-24. doi: 10.1016/j.joms.2011.03.028

110. Aghaloo TL, Moy PK, Freymiller EG. Investigation of platelet-rich plasma in rabbit cranial defects: A pilot study. J Oral Maxillofac Surg. 2002;60(10):1176-81. doi: 10.1053/joms.2002.34994.

111. Yamamoto MK, Novelli MD, Corrêa L, De Sousa SCM, Luz JGC. Evaluation of the effect of platelet-rich plasma on alveolar wound healing in rats. Int J Morphol. 2017;35(1):251-8.

112. Gerard D, Carlson ER, Gotcher JE, Jacobs M. Effects of platelet-rich plasma on the healing of autologous bone grafted mandibular defects in dogs. J Oral Maxillofac Surg. 2006;64(3):443-51. doi: 10.1016/j.joms.2005.11.016.

113. Mooren RE, Merkx MA, Bronkhorst EM, Jansen JA, Stoelinga PJ. The effect of platelet-rich plasma on early and late bone healing: an experimental study in goats. Int J Oral Maxillofac Surg. 2007;36(7):626-31. doi: 10.1016/j.ijom.2007.03.013.

114. Oliveira Filho MA, Nassif PA, Malafaia O, Ribas Filho JM, Ribas CA, Camacho AC, et al. Effects of a highly concentrated platelet-rich plasma on the bone repair using non-critical defects in the calvaria of rabbits. Acta Cir Bras. 2010;25(1):28-33. doi: 10.1590/s0102-86502010000100008.

115. DeNicolo PJ, Guyton MK, Cuenin MF, Hokett SD, Sharawy M, Borke J, et al. Histologic evaluation of osseous regeneration following combination therapy with platelet-rich plasma and bio-oss in a rat calvarial critical-size defect model. J Oral Implantol. 2015;41(5):543-9. doi: 10.1563/AAID-JOI-D-12-00075.

116. Plachokova AS, Nikolidakis D, Mulder J, Jansen JA, Creugers NH. Effect of platelet-rich plasma on bone regeneration in dentistry: a systematic review. Clin Oral Implants Res. 2008;19(6):539-45. doi: 10.1111/j.1600-0501.2008.01525.x.

117. Menezes DJ, Shibli JA, Gehrke SA, Beder AM, Sendyk WR. Effect of platelet-rich plasma in alveolar distraction osteogenesis: a controlled clinical trial. Br J Oral Maxillofac Surg. 2016;54(1):83-7. doi: 10.1016/j.bjoms.2015.09.027.

118. Drago L, Bortolin M, Vassena C, Romanò CL, Taschieri S, Del Fabbro M. Plasma components and platelet activation are essential for the antimicrobial properties of autologous platelet-rich plasma: an in vitro study. PLoS One. 2014;9(9):e107813. doi: 10.1371/journal.pone.0107813.

119. García-Martínez O, Reyes-Botella C, Díaz-Rodríguez L, De Luna-Bertos E, Ramos-Torrecillas J, Vallecillo-Capilla MF, et al. Effect of platelet-rich plasma on growth and antigenic profile of human osteoblasts and its clinical impact. J Oral Maxillofac Surg. 2012;70(7):1558-64. doi: 10.1016/j.joms.2011.06.199.

120. Kim YS, Kwon KH, Cha SY, Min SK. Effect of gelatin spongy and platelet rich plasma on ridge preservation and bone formation after extraction. Maxillofac Plast Reconstr Surg. 2005;27(3):238-47.

121. Dutta SR, Passi D, Singh P, Sharma S, Singh M, Srivastava D. A randomized comparative prospective study of platelet-rich plasma, platelet-rich fibrin, and hydroxyapatite as a graft material for mandibular third molar extraction socket healing. Natl J Maxillofac Surg. 2016;7(1):45-51. doi: 10.4103/0975-5950.196124.

122. Taschieri S, Lolato A, Ofer M, Testori T, Francetti L, Del Fabbro M. Immediate post-extraction implants with or without pure platelet-rich plasma: a 5-year follow-up study. Oral Maxillofac Surg. 2017;21(2):147-57.

123. Schlegel KA, Kloss FR, Kessler P, Schultze-Mosgau S, Nkenke E, Wiltfang J. Bone conditioning to enhance implant osseointegration: an experimental study in pigs. Int J Oral Maxillofac Implants. 2003;18(4):505-11.

124. Zechner W, Tangl S, Tepper G, Fürst G, Bernhart T, Haas R, et al. Influence of platelet-rich plasma on osseous healing of dental implants: a histologic and histomorphometric study in minipigs. Int J Oral Maxillofac Implants. 2003;18(1):15-22

125. Mancuso JD, Bennion JW, Hull MJ, Winterholler BW. Platelet-rich plasma: a preliminary report in routine impacted mandibular third molar surgery and the prevention of alveolar osteitis. J Oral Maxillofac Surg. 2003;61(8):40. doi:10.1016/S0278-2391(03)00532-9.

126. De Leonardis D, Pecora GE. Augmentation of the maxillary sinus with calcium sulfate: one-year clinical report from a prospective longitudinal study. Int J Oral Maxillofac Implants. 1999;14(6):869-78.

127. De Leonardis D, Pecora GE. Prospective study on the augmentation of the maxillary sinus with calcium sulfate: histological results. J Periodontol. 2000;71(6):940-7. doi: 10.1902/jop.2000.71.6.940.

128. Piattelli M, Favero GA, Scarano A, Orsini G, Piattelli A. Bone reactions to anorganic bovine bone (Bio-Oss) used in sinus augmentation procedures: a histologic long-term report of 20 cases in humans. Int J Oral Maxillofac Implants. 1999;14(6):835-40.

129. Petrungaro P. Platelet-rich plasma for dental implants and soft-tissue grafting. Interview by Arun K Garg. Dent Implantol Update. 2001;12(6):41-6.

130. Petrungaro PS. Using platelet-rich plasma to accelerate soft tissue maturation in esthetic periodontal surgery. Compend Contin Educ Dent. 2001;22:729-732, 34, 36 passim; quiz 46.

131. Tischler M. Platelet rich plasma. The use of autologous growth factors to enhance bone and soft tissue grafts. N Y State Dent J. 2002;68(3):22-24.

132. Cheah CW, Vaithilingam RD, Siar CH, Swaminathan D, Hornbuckle GC. Histologic, histomorphometric, and cone-beam computerized tomography analyses of calcium sulfate and platelet-rich plasma in socket preservation: a pilot study. Implant Dent. 2014;23(5):593-601. doi: 10.1097/ID.0000000000000148.

133. Kutkut A, Andreana S, Kim HL, Monaco E Jr. Extraction socket preservation graft before implant placement with calcium sulfate hemihydrate and platelet-rich plasma: a clinical and histomorphometric study in humans. J Periodontol. 2012;83(4):401-9. doi: 10.1902/jop.2011.110237.

134. 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(2):17. doi: 10.3390/jfb8020017.

135. Nisar N, Nilesh K, Parkar MI, Punde P. Extraction socket preservation using a collagen plug combined with platelet-rich plasma (PRP): A comparative clinico-radiographic study. J Dent Res Dent Clin Dent Prospects. 2020 Spring;14(2):139-45. doi: 10.34172/joddd.2020.028.

136. Feng L, Zhang L, Cui Y, Song TX, Qiu ZY, Wang XM, et al. Clinical evaluations of mineralized collagen in the extraction sites preservation. Regen Biomater. 2016;3(1):41-8. doi: 10.1093/rb/rbv027.

137. Coomes AM, Mealey BL, Huynh-Ba G, Barboza-Arguello C, Moore WS, Cochran DL. Buccal bone formation after flapless extraction: a randomized, controlled clinical trial comparing recombinant human bone morphogenetic protein 2/absorbable collagen carrier and collagen sponge alone. J Periodontol. 2014;85(4):525-35. doi: 10.1902/jop.2013.130207.

138. Suba Z, Takács D, Gyulai-Gaál S, Kovács K, Velich N, Szigeti K. [Alveolar bone regeneration stimulated by a combination of platelet-rich plasma and Cerasorb graft in Beagle dogs. Histological and histomorphometric studies]. Fogorv Sz. 2004;97(4):143-9.

139. Torres J, Tamimi F, Alkhraisat MH, Manchón A, Linares R, Prados-Frutos JC, et al. Platelet-rich plasma may prevent titanium-mesh exposure in alveolar ridge augmentation with anorganic bovine bone. J Clin Periodontol. 2010;37(10):943-51. doi: 10.1111/j.1600-051X.2010.01615.x.

140. Traini T, Isaia B, Isaia F, Isaia L. (2018). The effects of the combined use of platelet-rich plasma and xenograft on alveolar socket healing. Biomed J Sci Tech Res. 2018;3(1):1-9. doi:10.26717/BJSTR.2018.03.000847.

141. Vance GS, Greenwell H, Miller RL, Hill M, Johnston H, Scheetz JP. Comparison of an allograft in an experimental putty carrier and a bovine-derived xenograft used in ridge preservation: a clinical and histologic study in humans. Int J Oral Maxillofac Implants. 2004;19(4):491-7.

142. Yilmaz S, Cakar G, Kuru B, Dirikan S, Yildirim B. Platelet-rich plasma in combination with bovine derived xenograft in the treatment of deep intrabony periodontal defects: a report of 20 consecutively treated patients. Platelets. 2009;20(6):432-40. doi: 10.1080/09537100903137298.

143. Mahdi AA, Al-Adili SS, Mohammed ZI. Clinical and histomorphomertic evaluation of effects of platelet-poor plasma and platelet-rich plasma on healing of extraction sockets with buccal dehiscence (an experimental study in dogs). J Res Med Dent Sci. 2020;8(1):01-09.

144. Araújo MG, Lindhe J. Dimensional ridge alterations following tooth extraction. An experimental study in the dog. J Clin Periodontol. 2005;32(2):212-8. doi: 10.1111/j.1600-051X.2005.00642.x.

145. Fickl S, Zuhr O, Wachtel H, Stappert CF, Stein JM, Hürzeler MB. Dimensional changes of the alveolar ridge contour after different socket preservation techniques. J Clin Periodontol. 2008;35(10):906-13. doi: 10.1111/j.1600-051X.2008.01305.x.

146. Cardaropoli G, Araújo M, Lindhe J. Dynamics of bone tissue formation in tooth extraction sites. An experimental study in dogs. J Clin Periodontol. 2003;30(9):809-18. doi: 10.1034/j.1600-051x.2003.00366.x.

147. Hatakeyama I, Marukawa E, Takahashi Y, Omura K. Effects of platelet-poor plasma, platelet-rich plasma, and platelet-rich fibrin on healing of extraction sockets with buccal dehiscence in dogs. Tissue Eng Part A. 2014;20(3-4):874-82. doi: 10.1089/ten.TEA.2013.0058.

148. Gawai KT, Sobhana C. Clinical evaluation of use of platelet rich plasma in bone healing. J Maxillofac Oral Surg. 2015; 14(1):67-80. doi: 10.1007/s12663-013-0605-5.

149. Thorwarth M, Wehrhan F, Schultze-Mosgau S, Wiltfang J, Schlegel KA. PRP modulates expression of bone matrix proteins in vivo without long-term effects on bone formation. Bone. 2006;38(1):30-40. doi: 10.1016/j.bone.2005.06.020.

150. de Obarrio JJ, Araúz-Dutari JI, Chamberlain TM, Croston A. The use of autologous growth factors in periodontal surgical therapy: platelet gel biotechnology--case reports. Int J Periodontics Restorative Dent. 2000;20(5):486-97.

151. Garg AK. The use of platelet-rich plasma to enhance the success of bone grafts around dental implants. Dent Implantol Update. 2000;11(3):17-21.

152. Camargo PM, Lekovic V, Weinlaender M, Vasilic N, Madzarevic M, Kenney EB. Platelet-rich plasma and bovine porous bone mineral combined with guided tissue regeneration in the treatment of intrabony defects in humans. J Periodontal Res. 2002;37(4):300-6. doi: 10.1034/j.1600-0765.2002.01001.x.

153. Carlson NE, Roach RB Jr. Platelet-rich plasma: clinical applications in dentistry. J Am Dent Assoc. 2002;133(10):1383-6. doi: 10.14219/jada.archive.2002.0054.

154. Kim SG, Chung CH, Kim YK, Park JC, Lim SC. Use of particulate dentin-plaster of Paris combination with/without platelet-rich plasma in the treatment of bone defects around implants. Int J Oral Maxillofac Implants. 2002;17(1):86-94.

155. Ramos-Torrecillas J, De Luna-Bertos E, García-Martínez O, Ruiz C. Clinical utility of growth factors and platelet-rich plasma in tissue regeneration: a review. Wounds. 2014;26(7):207-13.

156. Rappl LM. Effect of platelet rich plasma gel in a physiologically relevant platelet concentration on wounds in persons with spinal cord injury. Int Wound J. 2011;8(2):187-95. doi: 10.1111/j.1742-481X.2011.00770.x.

157. Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. Bone. 2004;34(4):665-71. doi: 10.1016/j.bone.2003.12.010.

158. Graziani F, Ivanovski S, Cei S, Ducci F, Tonetti M, Gabriele M. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. Clin Oral Implants Res. 2006;17(2):212-9. doi: 10.1111/j.1600-0501.2005.01203.x.

159. Brubaker AL, Schneider DF, Kovacs EJ. Neutrophils and natural killer T cells as negative regulators of wound healing. Expert Rev Dermatol. 2011;6(1):5-8. doi: 10.1586/edm.10.66.

160. Driver VR, Hanft J, Fylling CP, Beriou JM; Autologel Diabetic Foot Ulcer Study Group. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage. 2006;52(6):68-70, 72, 74 passim.

161. Anitua E, Aguirre JJ, Algorta J, Ayerdi E, Cabezas AI, Orive G, Andia I. Effectiveness of autologous preparation rich in growth factors for the treatment of chronic cutaneous ulcers. J Biomed Mater Res B Appl Biomater. 2008;84(2):415–21. doi: 10.1002/jbm.b.30886.

162. McAleer JP, Kaplan E, Persich G. Efficacy of concentrated autologous platelet-derived growth factors in chronic lower-extremity wounds. J Am Pediatr Med Assoc. 2006;96(6):482–8. doi: 10.7547/0960482.

163. Mazzucco L, Medici D, Serra M, Panizza R, Rivara G, Orecchia S, et al. The use of autologous platelet gel to treat difficult-to-heal wounds: a pilot study. Transfusion. 2004;44(7):1013–8. doi: 10.1111/j.1537-2995.2004.03366.x.

164. Gurgen M. Treatment of chronic wounds with autologous platelet-rich plasma. EWMA J. 2008;8(2):5–11.

165. Steenvoorde P, van Doorn LP, Naves C, Oskam J. Use of autologous platelet-rich fibrin on hard-to-heal wounds. J Wound Care. 2008;17(2):60-3. doi: 10.12968/jowc.2008.17.2.28179.

166. Wiltfang J, Kloss FR, Kessler P, Nkenke E, Schultze-Mosgau S, Zimmermann R, et al. Effects of platelet-rich plasma on bone healing in combination with autogenous bone and bone substitutes in critical-size defects. An animal experiment. Clin Oral Implants Res. 2004;15(2):187-93. doi: 10.1111/j.1600-0501.2004.00980.x.

167. Tarantino R, Donnarumma P, Mancarella C, Rullo M, Ferrazza G, Barrella G, et al. Posterolateral arthrodesis in lumbar spine surgery using autologous platelet-rich plasma and cancellous bone substitute: an osteoinductive and osteoconductive effect. Global Spine J. 2014;4(3):137-42. doi: 10.1055/s-0034-1376157.

168. Aghaloo TL, Moy PK, Freymiller EG. Evaluation of platelet-rich plasma in combination with anorganic bovine bone in the rabbit cranium: a pilot study. Int J Oral Maxillofac Implants. 2004;19(1):59-65.

169. Kassolis JD, Rosen PS, Reynolds MA. Alveolar ridge and sinus augmentation utilizing platelet-rich plasma in combination with freeze-dried bone allograft: Case series. J Periodontol 2000;71(!0):1654-61. doi: 10.1902/jop.2000.71.10.1654.

170. Gerard D, Carlson ER, Gotcher JE, Jacobs M. Effects of platelet-rich plasma at the cellular level on healing of autologous bone-grafted mandibular defects in dogs. J Oral Maxillofac Surg. 2007;65(4):721-7. doi: 10.1016/j.joms.2006.09.025.

171. Suttapreyasri S, Leepong N. Influence of platelet-rich fibrin on alveolar ridge preservation. J Craniofac Surg. 2013;24(4):1088-94. doi: 10.1097/SCS.0b013e31828b6dc3.

172. Lindeboom JA, Mathura KR, Aartman IH, Kroon FH, Milstein DM, Ince C. Influence of the application of platelet-enriched plasma in oral mucosal wound healing. Clin Oral Implants Res. 2007;18(1):133-9. doi: 10.1111/j.1600-0501.2006.01288.x.

173. Cheung WS, Griffin TJ. A comparative study of root coverage with connective tissue and platelet concentrate grafts: 8-month results. J Periodontol. 2004;75(12):1678-87. doi: 10.1902/jop.2004.75.12.1678.

174. El-Sharkawy H, Kantarci A, Deady J, Hasturk H, Liu H, Alshahat M, et al. Platelet-rich plasma: growth factors and pro- and anti-inflammatory properties. J Periodontol. 2007;78(4):661–9. doi: 10.1902/jop.2007.060302.

175. Hauser F, Gaydarov N, Badoud I, Vazquez L, Bernard JP, Ammann P. Clinical and histological evaluation of postextraction plateletrich fibrin socket filling: a prospective randomized controlled study. Implant Dent. 2013;22(3):295–303. doi: 10.1097/ID.0b013e3182906eb3.

176. Temmerman A, Vandessel J, Castro A, Jacobs R, Teughels W, Pinto N, et al. 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(11):990–9. doi: 10.1111/jcpe.12612.

177. Del Fabbro M, Bortolin M, Taschieri S. Is autologous platelet concentrate beneficial for post-extraction socket healing? A systematic review. Int J Oral Maxillofac Surg. 2011;40(9):891-900. doi: 10.1016/j.ijom.2011.04.009.

178. Tadjoedin ES, de Lange GL, Bronckers AL, Lyaruu DM, Burger EH. Deproteinized cancellous bovine bone (Bio-Oss) as bone substitute for sinus floor elevation. A retrospective, histomorphometrical study of five cases. J Clin Periodontol. 2003;30(3):261-70. doi: 10.1034/j.1600-051x.2003.01099.x.

179. Trubiani O, Fulle S, Traini T, Paludi M, la Rovere R, Orciani Met al. Functional assay, expression of growth factors and proteins modulating bone-arrangement in human osteoblasts seeded on an anorganic bovine bone biomaterial. Eur Cell Mater. 2010;20:72-83. doi: 10.22203/ecm.v020a07.

180. Zitzmann NU, Schärer P, Marinello CP, Schüpbach P, Berglundh T. Alveolar ridge augmentation with Bio-Oss: a histologic study in humans. Int J Periodontics Restorative Dent. 2001;21(3):288-95.

181. Orsini G, Traini T, Scarano A, Degidi M, Perrotti V, Piccirilli M, Piattelli A. Maxillary sinus augmentation with Bio-Oss particles: a light, scanning, and transmission electron microscopy study in man. J Biomed Mater Res B Appl Biomater. 2005;74(1):448-57. doi: 10.1002/jbm.b.30196.

182. Celotti F, Colciago A, Negri-Cesi P, Pravettoni A, Zaninetti R, Sacchi MC. Effect of platelet-rich plasma on migration and proliferation of SaOS-2 osteoblasts: role of platelet-derived growth factor and transforming growth factor-beta. Wound Repair Regen. 2006;14(2):195-202. doi: 10.1111/j.1743-6109.2006.00110.x.

183. Arpornmaeklong P, Kochel M, Depprich R, Kübler NR, Würzler KK. Influence of platelet-rich plasma (PRP) on osteogenic differentiation of rat bone marrow stromal cells. An in vitro study. Int J Oral Maxillofac Surg. 2004;33(1):60-70. doi: 10.1054/ijom.2003.0492.

184. Ferreira CF, Carriel Gomes MC, Filho JS, Granjeiro JM, Oliveira Simões CM, Magini Rde S. Platelet-rich plasma influence on human osteoblasts growth. Clin Oral Implants Res. 2005;16(4):456-60. doi: 10.1111/j.1600-0501.2005.01145.x.

185. Kanno T, Takahashi T, Tsujisawa T, Ariyoshi W, Nishihara T. Platelet-rich plasma enhances human osteoblast-like cell proliferation and differentiation. J Oral Maxillofac Surg. 2005;63(3):362-9. doi: 10.1016/j.joms.2004.07.016.

186. Ogino Y, Ayukawa Y, Kukita T, Koyano K. The contribution of platelet-derived growth factor, transforming growth factor-beta1, and insulin-like growth factor-I in platelet-rich plasma to the proliferation of osteoblast-like cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(6):724-9. doi: 10.1016/j.tripleo.2005.08.016.

187. Uggeri J, Belletti S, Guizzardi S, Poli T, Cantarelli S, Scandroglio R, Gatti R. Dose-dependent effects of platelet gel releasate on activities of human osteoblasts. J Periodontol. 2007;78(10):1985-91. doi: 10.1902/jop.2007.070116.

188. Akeda K, An HS, Okuma M, Attawia M, Miyamoto K, Thonar EJ, et al. Platelet-rich plasma stimulates porcine articular chondrocyte proliferation and matrix biosynthesis. Osteoarthritis Cartilage. 2006;14(12):1272-80. doi: 10.1016/j.joca.2006.05.008.

189. Krasna M, Domanović D, Tomsic A, Svajger U, Jeras M. Platelet gel stimulates proliferation of human dermal fibroblasts in vitro. Acta

Dermatovenerol Alp Pannonica Adriat. 2007;16(3):105-10.

190. Liu Y, Kalén A, Risto O, Wahlström O. Fibroblast proliferation due to exposure to a platelet concentrate in vitro is pH dependent. Wound Repair Regen. 2002;10(5):336-40. doi: 10.1046/j.1524-475x.2002.10510.x.

191. Bertrand-Duchesne MP, Grenier D, Gagnon G. Epidermal growth factor released from platelet-rich plasma promotes endothelial cell proliferation in vitro. J Periodontal Res. 2010;45(1):87-93. doi: 10.1111/j.1600-0765.2009.01205.x.

192. Annunziata M, Oliva A, Buonaiuto C, Di Feo A, Di Pasquale R, Passaro I, Guida L. In vitro cell-type specific biological response of human periodontally related cells to platelet-rich plasma. J Periodontal Res. 2005;40(6):489-95. doi: 10.1111/j.1600-0765.2005.00828.x.

193. Han J, Meng HX, Tang JM, Li SL, Tang Y, Chen ZB. The effect of different platelet-rich plasma concentrations on proliferation and differentiation of human periodontal ligament cells in vitro. Cell Prolif. 2007;40(2):241-52. doi: 10.1111/j.1365-2184.2007.00430.x.

194. Cenni E, Ciapetti G, Pagani S, Perut F, Giunti A, Baldini N. Effects of activated platelet concentrates on human primary cultures of fibroblasts and osteoblasts. J Periodontol. 2005;76(3):323-8. doi: 10.1902/jop.2005.76.3.323.

195. Slapnicka J, Fassmann A, Strasak L, Augustin P, Vanek J. Effects of activated and nonactivated platelet-rich plasma on proliferation of human osteoblasts in vitro. J Oral Maxillofac Surg. 2008;66(2):297-301. doi: 10.1016/j.joms.2007.05.022.

196. Woodall J Jr, Tucci M, Mishra A, Benghuzzi H. Cellular effects of platelet rich plasma: a study on HL-60 macrophage-like cells. Biomed Sci Instrum. 2007;43:266-71.

197. De Pascale MR, Sommese L, Casamassimi A, Napoli C. Platelet derivatives in regenerative medicine: an update. Transfus Med Rev. 2015;29(1):52-61. doi: 10.1016/j.tmrv.2014.11.001.

198. Sequeria JP, Johri S. Platelet rich plasma: clinical applications in dentistry. Sch J Dent Sci. 2015;2:355–62.

199. Stähli A, Strauss FJ, Gruber R. The use of platelet-rich fibrin to enhance the outcomes of implant therapy: a systematic review. Clin Oral Implants Res. 2018;29(Suppl 18):6-19. doi: 10.1111/clr.13275.

200. Esposito M, Felice P, Worthington HV. Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus. Cochrane Database Syst Rev. 2014;(5):CD008397. doi: 10.1002/14651858.CD008397.pub2.

201. Bae JH, Kim YK, Myung SK. Effects of platelet-rich plasma on sinus bone graft: meta-analysis. J Periodontol. 2011;82(5):660-7. doi: 10.1902/jop.2010.100529.

202. Panda S, Doraiswamy J, Malaiappan S, Varghese SS, Del Fabbro M. Additive effect of autologous platelet concentrates in treatment of intrabony defects: a systematic review and meta-analysis. J Investig Clin Dent. 2016;7(1):13-26. doi: 10.1111/jicd.12117.

203. Zhou S, Sun C, Huang S, Wu X, Zhao Y, Pan C, Wang H, Liu J, Li Q, Kou Y. Efficacy of Adjunctive Bioactive Materials in the Treatment of Periodontal Intrabony Defects: A Systematic Review and Meta-Analysis. Biomed Res Int. 2018;2018:8670832. doi: 10.1155/2018/8670832.

204. Franchini M, Cruciani M, Mengoli C, Masiello F, Marano G, D'Aloja E, et al. The use of platelet-rich plasma in oral surgery: a systematic review and meta-analysis. Blood Transfus. 2019;17(5):357-67. doi: 10.2450/2019.0177-19.

205. Simon BI, Gupta P, Tajbakhsh S. Quantitative evaluation of extraction socket healing following the use of autologous platelet-rich fibrin matrix in humans. Int J Periodontics Restorative Dent. 2011;31(3):285–95.

206. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6(7):e1000100. doi: 10.1371/journal.pmed.1000100.

207. Needleman IG. A guide to systematic reviews. J Clin Periodontol. 2002;29 Suppl 3:6-9; discussion 37-8. doi: 10.1034/j.1600-051x.29.s3.15.x.

208. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak. 2007;7:16. doi: 10.1186/1472-6947-7-16.

209. Stevens KR. Systematic reviews: the heart of evidence-based practice. AACN

Clin Issues. 2001;12(4):529-38. doi: 10.1097/00044067-200111000-00009.

210. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Obstet Gynecol. 2010;115(5):1063-70. doi: 10.1097/AOG.0b013e3181d9d421.

211. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12. doi: 10.1001/jama.283.15.2008.

212. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453-7. doi: 10.1016/S0140-6736(07)61602-X.

213. Moher D, Schulz KF, Altman DG; CONSORT Group (Consolidated Standards of Reporting Trials). The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. J Am Podiatr Med Assoc. 2001;91(8):437-42. doi: 10.7547/87507315-91-8-437.

214. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999;354(9193):1896-900. doi: 10.1016/s0140-6736(99)04149-5.

215. Esposito M, Coulthard P, Worthington HV, Jokstad A. Quality assessment of randomized controlled trials of oral implants. Int J Oral Maxillofac Implants. 2001;16(6):783-92.

216. Needleman I. CONSORT. Consolidated Standards of Reporting Trials. Br Dent J. 1999;186(5):207. doi: 10.1038/sj.bdj.4800065a.

217. Ten Heggeler JM, Slot DE, Van der Weijden GA. Effect of socket preservation therapies following tooth extraction in non-molar regions in humans: a systematic review. Clin Oral Implants Res. 2011;22(8):779-88. doi: 10.1111/j.1600-0501.2010.02064.x.

218. Grageda E. Platelet-rich plasma and bone graft materials: a review and a standardized research protocol. Implant Dent. 2004;13(4):301-9. doi: 10.1097/01.id.0000148555.91063.06.

219. Freymiller EG, Aghaloo TL. Platelet-rich plasma: ready or not? J Oral Maxillofac Surg. 2004;62(4):484-8. doi: 10.1016/j.joms.2003.08.021.

220. Jakse N, Tangl S, Gilli R, Berghold A, Lorenzoni M, Eskici A, Haas R, Pertl C. Influence of PRP on autogenous sinus grafts. An experimental study on sheep. Clin Oral Implants Res. 2003;14(5):578-83. doi: 10.1034/j.1600-0501.2003.00928.x.

221. Dohan Ehrenfest DM, Del Corso M, Inchingolo F, Sammartino G, Charrier JB. Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in human cell cultures: growth factor release and contradictory results. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110(4):418-21; author reply 421-2. doi: 10.1016/j.tripleo.2010.05.059.

222. Dohan Ehrenfest DM, Del Corso M, Inchingolo F, Charrier JB. Selecting a relevant in vitro cell model for testing and comparing the effects of a Choukroun's platelet-rich fibrin (PRF) membrane and a platelet-rich plasma (PRP) gel: tricks and traps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110(4):409-11; author reply 411-3. doi: 10.1016/j.tripleo.2010.05.056.