Review article

The application of injectable platelet-rich fibrin in regenerative dentistry: A systematic scoping review of In vitro and In vivo studies

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\textbf{A B S T R A C T}

\textit{Background:} Ongoing research in the dental field has begun to focus on the use of injectable platelet-rich fibrin (I-PRF) as a regenerative tool with the potential to prompt tissue regeneration. In this regard, this systematic scoping review aimed to collect, map, and appraise the \textit{in vitro} and \textit{in vivo} studies regarding the role of I-PRF in oral and hard tissue regeneration in relation to oral and maxillofacial structures.

\textit{Methods:} A systematic electronic search of Medline, Scopus, Web of Science, and Embase databases was performed from 2000 to December 2021 using a combination of keywords. All \textit{in vitro} and \textit{in vivo} studies, written in English and concerning the potential role of I-PRF in regenerative dentistry were considered.

\textit{Results:} In total, 18 \textit{in vitro} studies, 5 animal studies, 6 case reports, and 31 clinical studies have evaluated the effect of I-PRF on oral and maxillofacial soft and hard tissue regeneration. The investigated studies verified the anti-inflammatory, anti-microbial efficacy and the positive effects of I-PRF application for wound, periodontal, bone, cartilage, and pulp regeneration, as well as acceleration in tooth movement during orthodontic treatment.

\textit{Conclusions:} Current literature approves the feasibility of I-PRF application as a promising regenerative adjunct to dental procedures.

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\textsuperscript{1} These authors contributed equally to this work.
\end{footnotesize}
1. Introduction

One of the greatest challenges that researchers are facing today is producing a biomaterial, which can be employed to enhance tissue regeneration with maximum predictability [1]. Though our knowledge on tissue healing process is still insufficient, it is clear that platelets can play a significant role in the tissue regenerative procedures [2].

The mechanisms of platelets in regeneration were demonstrated in the 1970s [3]. Platelets produce growth factors in their alpha-granules, which are accountable for cell division, differentiation, induction, and migration, and for neovascularization and collagen synthesis. Hence, they are known as potentiated cells for regeneration which can facilitate tissue regeneration [4].

Various platelet-rich concentrates, such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), have been proposed and utilized for tissue regeneration in several in vitro and in vivo studies [3]. Nevertheless, PRF has many benefits over PRP, including easy handling, low cost, and the lack of anticoagulant or bovine thrombin, which reduces biochemical alteration and risks associated with the use of bovine thrombin [5]. For about three decades, PRF has been used for regenerative purposes in dentistry [6]. Additionally, PRF has the potential to be used in fields other than dentistry, such as maxillofacial surgery and orthopedic surgery [7–9].

In 2014, by adjusting spin centrifugation forces, injectable platelet-rich fibrin (I-PRF) was developed. The blood centrifuged in non-glass centrifugation tubes at lower centrifugation speeds resulted in a flowable PRF called I-PRF [10]. I-PRF is a newly formed platelet concentrate enriched with leukocytes which can promote both soft and hard tissue regeneration phenomena [10,11]. Since I-PRF remains liquid for roughly 15 min, it will provide dental practitioners with a further practical form of PRF [12]. Following application, the human liquid fibrinogen in I-PRF is gradually transformed to a growth factor-rich PRF clot, which releases continuously over 10–14 days [13].

Up to now, several in vitro and in vivo studies have been carried out concerning the role of I-PRF in the enhancement of wound healing, the acceleration of orthodontic tooth movement, and the regeneration of bone, periodontal, cartilage, and pulp tissues [14–21]. On this basis, I-PRF is able to enhance the potential of intrinsic tissue regeneration by inducing human mesenchymal stem cells (MSCs) proliferation and migration, and by triggering osteogenic differentiation of MSCs [21,22]. I-PRF has also been reported to have greater anti-inflammatory and anti-microbial activity against many pathogens, which can contribute to faster tissue regeneration [23,24]. On the other hand, I-PRF is commonly used in regenerative dentistry as an injectable biomaterial, as a carrier for various biomolecules, or in conjunction with other biomaterials for a variety of clinical applications. Clinicians have recently used this method to facilitate the agglomeration or coating of biomaterials in order to improve the healing process of both soft and hard tissues [25–27].

Given the aforementioned advantages of utilizing I-PRF and since there is a lack of a comprehensive review regarding the application
of I-PRF in regenerative dentistry, this systematic scoping review aimed to map the current literature and to review the articles published to date concerning the potential role of I-PRF in regenerative dentistry where this injectable autologous biomaterial is used to promote soft and hard tissue regeneration.

2. Material and methods

2.1. Development of a protocol

The protocol followed in this study was adopted from the guidelines of the Joanna Briggs Institute on systematic scoping reviews [28]. A research question comprising the inclusion criteria for the participants, intervention, comparison, outcome, and study design (PICOS) was defined prior to starting the review, which is shown in Table 1.

2.2. Information sources and search strategy

A systematic electronic search of four databases (Medline, Scopus, Web of Science, and Embase) was performed, which is illustrated in Table 2. Articles published from 2000 up to December 1, 2021 were considered. An extra hand search was performed on bibliographies of retrieved papers as well as other related published systematic and narrative reviews for possible inclusion in the study.

2.3. Eligibility criteria

Only peer-reviewed, published articles pertaining to our PICOS question were considered in this review (Table 1). Studies in other languages other than English were excluded from our review considering the linguistic competency of the research team.

2.4. Selection of studies

Records retrieved by the systematic search were independently screened by four reviewers (NF, DJ, and PF, SS) according to the inclusion and exclusion criteria (Fig. 1). After initial screening through titles and abstracts, the full texts of the retrieved abstracts were independently screened by the reviewers. Disagreements were resolved by discussion among the research team (SH, RFS, and LT). Finally, articles, which met the inclusion criteria and linguistic capacities of the research team, were included for data extraction and analysis.

2.5. Data extraction

Data extraction was carried out based on the inclusion criteria. A custom-made data collection form was established to collect information from the final selection of studies. Data including the authors name, year of publication, type of studies, characteristics of cells/drugs/animals/humans, preparation method of I-PRF, and details of the interventions, methods, and outcome measures were compiled in Tables 3–6.

3. Results and discussion

3.1. Selection of studies

In total, the initial search strategies generated 837 articles. After duplicate removal, 509 abstracts remained for title and abstract evaluation. A total of 431 papers were excluded due to mismatch with our search criteria and 78 articles were retained for final full text review. Finally, 60 articles including 18 in vitro studies, 5 animal studies, 6 case reports, and 31 clinical studies, which have so far

### Table 1

| Domain               | Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|----------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Participants         | Cells, microorganisms, and tissues related to dental, oral and maxillofacial structures | Dermal cells and tissues                                                             |
| Intervention         | Using liquid- or injectable-PRF developed by low-speed centrifugation concept for cell proliferation, migration, viability, morphology, mineralization, differentiation, preventing microorganism growth, healing damaged tissues, and drug delivery in dental, oral and maxillofacial structures | Using other kinds of platelet concentrates only such as PRGF, CGF, PRP, FBF, A-PRF, C-PRF, ALB-PRF, PRF exudates, PRF lyase |
| Comparison           | – No treatment or receiving other treatments                                        | –                                                                                |
| Outcome              | Cell and microorganism behavior, and tissue response after treatment                | Narrative reviews, systematic reviews with or without meta-analysis, letters to the editors, short communications |
| Study Design         | In-vitro studies, ex-vivo studies, animal studies, non-comparative studies, case reports, case series and prospective/retrospective clinical trials | –                                                                                |

| Database            | Search strategy                                                                 | Hits |
|---------------------|---------------------------------------------------------------------------------|------|
| Medline             | (((((Injectable platelet rich fibrin[Title/Abstract]) OR (liquid platelet rich fibrin[Title/Abstract]) OR (Flowable platelet rich fibrin[Title/Abstract])) OR (PRF[Title/Abstract])) OR (injectable[Title/Abstract]) AND platelet rich fibrin[Title/Abstract])) OR (liquid[Title/Abstract] AND platelet rich fibrin[Title/Abstract])) OR (Flowable[Title/Abstract] AND platelet rich fibrin[Title/Abstract])) OR (Injectable[Title/Abstract] AND PRF[Title/Abstract])) OR (liquid[Title/Abstract] AND PRF[Title/Abstract])) OR (Flowable[Title/Abstract] AND PRF[Title/Abstract])) OR (injectable[Title/Abstract] AND PRF[Title/Abstract])) OR (liquid[Title/Abstract] AND PRF[Title/Abstract])) | 167  |
| Scopus              | (TITLE-ABS-KEY ("Injectable platelet rich fibrin") OR TITLE-ABS-KEY ("liquid platelet rich fibrin") OR TITLE-ABS-KEY ("flowable platelet rich fibrin") OR TITLE-ABS-KEY ("injectable" AND "platelet rich fibrin") OR TITLE-ABS-KEY ("liquid" AND "platelet rich fibrin") OR TITLE-ABS-KEY ("flowable" AND "PRF") OR TITLE-ABS-KEY ("PRF")) AND PUBYEAR > 2000 | 237  |
| Web of Science      | TOPIC: (injectable platelet rich fibrin) OR TOPIC: (liquid platelet rich fibrin) OR TOPIC: (Flowable platelet rich fibrin) OR TOPIC: (PRF) OR TOPIC: (injectable AND platelet rich fibrin) OR TOPIC: (liquid AND platelet rich fibrin) OR TOPIC: (Flowable AND platelet rich fibrin) OR TOPIC: (injectable AND PRF) OR TOPIC: (liquid AND PRF) OR TOPIC: (Flowable AND PRF) | 251  |
| Embase              | (injectable platelet rich fibrin:ab,ti OR liquid platelet rich fibrin:ab,ti OR flowable platelet rich fibrin:ab,ti OR "PRF") OR (injectable:ab,ti AND platelet rich fibrin:ab,ti) OR (liquid:ab,ti AND platelet rich fibrin:ab,ti) OR (flowable:ab,ti AND platelet rich fibrin:ab,ti) OR (injectable:ab,ti AND prf:ab,ti) OR (liquid:ab,ti AND prf:ab,ti) OR (flowable:ab,ti AND prf:ab,ti) | 182  |
evaluated the effect of I-PRF on soft and hard tissue regeneration related to oral and maxillofacial structures, were selected. The selected studies were classified under the following subheadings: wound healing and anti-inflammatory efficacy \((n = 9)\), anti-microbial efficacy \((n = 4)\), periodontal regeneration \((n = 13)\), bone regeneration \((n = 22)\), cartilage regeneration \((n = 7)\), orthodontic tooth movement \((n = 5)\), and pulp regeneration and drug delivery \((n = 3)\). Studies by Mu et al. \([29]\), Dohle et al. \([30]\), and Rafiee et al. \([31]\) touched upon two regenerative potentials of I-PRF; therefore, they were included in two categories. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram 2020 in Fig. 1 depicts the flow of included studies through each phase of the review process. Additionally, Fig. 2 illustrates a progressive increase in the frequency of publications from 2017 to 2021.

3.2. I-PRF preparation method

The I-PRF preparation method differs according to the centrifugation time and speed, centrifuge device, and the site from which sample is collected \([32]\).

3.2.1. Centrifugation time and speed

Most of the included studies used an optimum centrifugation speed of 700 rate per minute \(\text{rpm}\) for obtaining I-PRF, based on the notion that the number of platelets, inflammatory factors, and cytokine significantly increases with a reduction in relative centrifugal force \(\text{RCF}\) \([10,33]\).

In studies evaluating the wound healing, anti-inflammatory, and anti-microbial efficacy of I-PRF, the process of I-PRF preparation was almost the same, in that blood collected in tubes devoid of anticoagulant was centrifuged at a speed of 700 rpm for three minutes with a centrifugal device. Only Kiziltoprak et al. \([34]\) used a protocol of 2300 rpm for three minutes, and Jasmine et al. \([35]\) implemented a method of 1000 rpm for five minutes. The method of I-PRF preparation was mostly similar for bone regeneration purposes in which I-PRF was attained by centrifuging the tubes at 700 rpm for three minutes. The exceptions were the study by Valladão et al. \([36]\) in which I-PRF was acquired after centrifuging two non-ridged tubes holding 8 ml blood at 2700 rpm for three minutes in a centrifugal machine, the research by Kyyak et al. \([37]\) which centrifuged the tubes at 1200 rpm for eight minutes, Irdem et al.
Table 3
A summary of the included in-vitro studies regarding the application of I-PRF in regenerative dentistry.

| In vitro Studies                                                                 | Authors (Year)         | Category                        | Aim of study                                                                 | Cells/Drugs                                                                 | 1-PRF preparation method | Site of 1-PRF harvest | Main Methods and Results                                                                                                                                 |
|---------------------------------------------------------------------------------|------------------------|---------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Anti-microbial Activity:                                                                                                                                  |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G1) Staphylococcus epidermis ATCC 12.228 + I-PRF                                                                                                           |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G2) Staphylococcus epidermis ATCC 35.984 + 1-PRF                                                                                                           |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G3) Staphylococcus epidermis + I-PRF                                                                                                                     |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G4) Staphylococcus aureus + I-PRF                                                                                                                       |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Anti-biofilm Activity:                                                                                                                                  |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G1) non-biofilm producer (Staphylococcus epidermis ATCC 12.228) + I-PRF                                                                                  |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G2) Weak biofilm producer (Staphylococcus epidermis ATCC 35.984) + I-PRF                                                                                 |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G3) Moderate biofilm producer (Staphylococcus epidermis) + I-PRF                                                                                          |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G4) Strong biofilm producer (Staphylococcus aureus) + I-PRF                                                                                                |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Anti-microbial Assay by Broth Microdilution Method:                                                                                                       |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | MIC of I-PRF for non-biofilm producing bacteria → 80 ml/ml                                                                                               |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | MIC of I-PRF for weak, moderate and strong producing bacteria → 160 ml/ml                                                                            |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | MBC of I-PRF for non-biofilm producing bacteria → 160 ml/ml                                                                                               |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | MBC of I-PRF for weak, moderate and strong producing bacteria → 240 ml/ml                                                                            |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Live/Dead Microbial Assay:                                                                                                                                |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | I-PRF at MIC → > 50% bacterial cells necrosis                                                                                                             |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Anti-bacterial Assay by Disc Diffusion Method:                                                                                                             |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G1 → I-PRF > PRP and PRF (P < 0.05)                                                                                                                     |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | G2 → PRP > PRF and I-PRF (P < 0.05)                                                                                                                     |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Human Osteoblasts Viability Assay and Metabolic Activity by MTT Assay (On 3rd, 7th, and 10th Day):                                                            |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Day 3 → Increased viability, and metabolic activity (G2 > G1)                                                                                               |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Day 7 → The highest viability and metabolic activity (G2 > G1)                                                                                              |
|                                                                                  |                        |                                 |                                                                              |                                                                            |                          |                       | Day 10 → Viability and metabolic activity tend to decline.                                                                                                 |

(continued on next page)
### In vitro Studies

| Authors (Year) | Category | Aim of study | Cells/Drugs | I-PRF preparation method | Site of I-PRF harvest | Groups | Main Methods and Results |
|----------------|----------|--------------|-------------|--------------------------|-----------------------|--------|-------------------------|
| Shah et al.[66] (2021) | Bone Regeneration | To assess the response of osteoblast-like cell line (MG-63) coating of I-PRF on titanium disks. | - MG-63 osteoblastic cells | Homologous PRP on human osteoblasts (osteogenesis). | 700 rpm 3min | Orange layer | G1) Titanium Disks (n = 5) G2) Titanium Disks Coated with I-PRF (n = 5) |
|                     |          |              |             |                         |                       |        | MG-63 Osteoblastic Cells Proliferation by CCK-8 Assay (On the 1st, 7th, 14th, and 21st Day): G2 > G1 (P < 0.001) |
|                     |          |              |             |                         |                       |        | MG-63 Osteoblastic Cells Mineralization by Alizarin Red Staining (On 21st Day): G2 > G1 (P < 0.001) |
|                     |          |              |             |                         |                       |        | ALP Activity (On the 1st, 7th, 14th, 21st Day): G2 > G1 (P < 0.001) |
|                     |          |              |             |                         |                       |        | Human Osteoblasts Viability Assay, Migration by Scratch Assay, and Proliferation by MTT Assay (On 3rd, 7th and 10th Day): Day 3 → Increased viability, migration and proliferation for G2 Day 7 → Increased viability and proliferation (G2/G4 > G1/G3) Day 10 → Increased viability, proliferation and migration (G2/G4 > G1/G3) |
|                     |          |              |             |                         |                       |        | Osteogenic-related Gene Expression by RT-qPCR (On 3rd, 7th and 10th Day): Days 3 and 7 → Highest expression of alkaline phosphatase for G2/G4, highest BMP-2 expression for G2, increased expression of OCN for G2/G4, and lowest expression for G1. Day 10 → Increased expression of alkaline phosphatase for G1/G2, and increased expression of OCN for G2. |

Fernández-Medina et al. [64] (2019) | Bone Regeneration | To investigate the composition and bioactivity of four common clinical-grade hemoderivates prepared using standardized methods. | - Human osteoblasts | Homologous PRP on human osteoblasts (osteogenesis). | 700 rpm 3min | Upper layer | G1) Control G2) Clot (20%, 40%, 60%, 80% and 100% v/v) G3) A-PRF (20%, 40%, 60%, 80% and 100% v/v) G4) I-PRF (20%, 40%, 60%, 80% and 100% v/v) G5) P-PRF (20%, 40%, 60%, 80% and 100% v/v) G6) L-PRF (20%, 40%, 60%, 80% and 100% v/v) |
|                     |          |              |             |                         |                       |        | Growth Factor Release of IGF-1, VEGF, PDGF-BB, and BMP-2 by ELISA (On 1st, 3rd, 7th and 14th Days): Early time points → A significant cumulative release of IGF-1 and PDGF-BB for G3/G6, and a significant cumulative release of BMP-2 and VEGF for all groups. |
|                     |          |              |             |                         |                       |        | Human Osteoblasts Viability by Live/Dead Assay (At 24 and 72h), Metabolic Activity by Alamar Blue Assay (At 24 and 72h), and Migration by Scratch Assay (At 6 and 24h): Cell viability, metabolic activity and migration assay → Detrimental effect when the concentration of all groups was ≥ 60% |

(continued on next page)
| Authors (Year)       | Category                                      | Aim of study                                                                 | Cells/Drugs | I-PRF preparation method | Site of I-PRF harvest | Groups | Main Methods and Results                                                                                                                                 |
|---------------------|-----------------------------------------------|-------------------------------------------------------------------------------|-------------|--------------------------|-----------------------|--------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wang et al.[63] (2018) | Bone Regeneration                             | To investigate the effect of I-PRF on osteoblast behavior compared to traditional PRP. | Human Osteoblasts | 700 rpm 3 min           | Upper layer           | G1) Control
G2) PRP
G3) I-PRF | Human Osteoblasts Mineralization by Alizarin Red Staining (On 14th, and 21st Day): Day 21 → Superior mineralization properties for G4 compared to all groups.
Days 14 and 21 → A negative impact of A-PRF was demonstrated at high concentrations.  
Human Osteoblasts Viability by Live/Dead Assay (At 24 h): Viability → High survival rates of cells for all groups.  
Human Osteoblasts Migration Assay (At 24 h), Adhesion by DAPI Staining (At 2, 4 and 8 h), and Proliferation by CCK-8 Assay (On 1st, 3rd and 5th Day): Migration → G3 > G2 > G1 (P < 0.05)
Adhesion → No difference between all groups.
Proliferation → G3 > G2 > G1 on 3rd and 5th day (P < 0.05)  
Human Osteoblast Mineralization by ALP Assay (On 7th Day) and Alizarin Red Staining (On 14th Day): G3 > G2 > G1 (P < 0.05)  
Osteogenic-related Gene Expression by RT-qPCR on (3rd and 14th Day) and Immunohistochemical Staining of Osteocalcin (on 14th Day): Expression of ALP on 3rd day → G3 > G2 > G1
Expression of ALP, RUNX2 and OCN on 14th day → G3 > G2 > G1 (P < 0.05)
Expression of COL1 on 14th day → G3 > G2 > G1  
Histological Staining Analysis: 1) H&E, and 2) Immunohistochemical Staining of CD31, CD68, CD45 and Osteopontin (At 24h and on 7th Day): 7th day → Formation of lumina and microvesSEL-like structures in the I-PRF/co-culture complexes.  
Protein Quantification by ELISA, and Gene Expression by RT-qPCR (At 24h and on 7th Day): I-PRF + Co-culture of OEC and pOB → Angiogenic activation of OECs + Uregulation of wound healing associated factors (PDGF-BB, ICAM-1, and E-selectin) + Higher expression of the proangiogenic factor (continued on next page) |
| Dohle et al[30] (2018) | Bone Regeneration, Wound Healing and Anti-inflammatory Efficacy | To examine that the addition of I-PRF would result in an induction of wound healing processes and might positively influence the process of angiogenesis via inflammatory processes in the co-culture. | Human OECs
Human pOBs | 700 rpm 3 min | NR | G1) OEC
G2) pOB
G3) co-culture of OEC + pOB
G4) I-PRF
G5) I-PRF + OEC
G6) I-PRF + pOB
G7) I-PRF + co-culture of OEC + pOB | 1) H&E, and 2) Immunohistochemical Staining of CD31, CD68, CD45 and Osteopontin (At 24h and on 7th Day): 7th day → Formation of lumina and microvesSEL-like structures in the I-PRF/co-culture complexes.  
Protein Quantification by ELISA, and Gene Expression by RT-qPCR (At 24h and on 7th Day): I-PRF + Co-culture of OEC and pOB → Angiogenic activation of OECs + Uregulation of wound healing associated factors (PDGF-BB, ICAM-1, and E-selectin) + Higher expression of the proangiogenic factor (continued on next page) |
| Authors (Year)     | Category                | Aim of study                                                                 | Cells/Drugs | I-PRF preparation method | Site of I-PRF harvest | Groups                                                                 | Main Methods and Results                                                                                                                                                                                                 |
|-------------------|-------------------------|-------------------------------------------------------------------------------|-------------|--------------------------|------------------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zheng et al.[58]  (2020) | Periodontal Regeneration | To evaluate the biological effect of PRP and I-PRF on hPDLCs in vitro.       | hPDLCs      | 700 rpm 3 min            | Upper layer            | G1) hPDLCs + Growth medium G2) hPDLCs + Red I-PRF                    | Inflammatory Environment: Cell Proliferation: G1 = G2 = G4 > G3 (P < 0.05) Day 3 → G1 = G2 = G4 > G3 (P < 0.05) Day 7 → G2 > G1 > G4 (P < 0.05) After three days, gMSCs grown in 10% I-PRF had proliferated significantly less than the other groups. Osteogenic-related Gene Expression by RT-qPCR (on 14th Day): gMSCs Proliferation by CCK-8 Assay (On 1st, 3rd and 5th Day), and Migration by Transwell and Scratch Wound Healing Assay (At 24 h): Migration → G2 > G1 > G3 (P < 0.05) and Migration → G2 > G1 > G3 (P < 0.05) hPDLCs Mineralization by AlP Assay (On 7th Day) and Alizarin Red Staining (On 14th Day): G3 > G2 > G1 (P < 0.05) Osteogenic-related Gene Expression by RT-qPCR (on 14th Day): G3 > G2 > G1 (P < 0.05) Inflammatory- and Osteogenic-related Gene Expression in an Inflammatory Environment by RT-qPCR (on 14th Day): I-PRF → Significantly down-regulate the expression levels of p65, IL-1β and TNF-α, and significantly up-regulated expression levels of RUNX2, COL1, and OCN when compared to other groups. hPDLCs Proliferation by MIT Assay (At Baseline, and on 3rd and 5th Day): G2 > G1 > G3 (P < 0.05) hPDLCs Migration by Transwell Assay (At 24 h): G3 > G4 > G2/G1 (P < 0.05) hPDLCs Mineralization by AlP Assay (On 3rd Day) and Calcification Rate by Alizarin Red Staining (On 7th, 14th, and 21st Day): Mineralization → G4 > G3 > G2/G1 (P < 0.05) Calcification → G4 > G3 > G2/G1 on 21st day (P < 0.05) |
In vitro Studies

| Authors (Year) | Category | Aim of study | Cells/Drugs | I-PRF preparation method | Site of I-PRF harvest | Groups | Main Methods and Results |
|---------------|----------|--------------|-------------|--------------------------|-----------------------|--------|--------------------------|
| Fujikoa-Kobayashi [45] (2020) | Periodontal Regeneration | To compare the growth factor release of C-PRF with that of I-PRF, and to investigate the regenerative properties of C-PRF and I-PRF on human gingival fibroblasts. | - hGFs | - | 300 g 5 min (5702 Eppendorf, Hamburg, Germany) | Upper layer G1) hGFs G2) hGFs + I-PRF G3) hGFs + C-PRF | An overall decrease in the expression of all investigated osteogenic genes was observed in I-PRF-containing media in comparison with the controls. Expression of RUNX2 → G1 = G2 > G3 = G4 (P < 0.05) Expression of SPARC → G1 = G2 > G4 > G3 (P < 0.05) Growth Factor Release of PDGF-AA, PDGF-BB, PDGF-AB, TGF-β, VEGF, EGF, and IGFB-1 by ELISA (On 1st, 3rd, 7th and 10th Days): Over 10 days → The increase in the release of PDGF-AA, TGF-β1, and EGF from C-PRF compared with those from I-PRF were the most pronounced. hGFs Viability by Live/Dead Assay (At 24 h): Both C-PRF and I-PRF demonstrated excellent cell viability and biocompatibility. hGFs Migration Assay (At 24 h): G3 > G2 > G1 hGFs Proliferation Assay (On 1st, 3rd, and 5th Day): Day 1 → G3 = G2 > G1 Day 3 → G3 > G2 > G1 Day 5 → G3 > G2 > G1 Gene Expression by RT-qPCR (On 3rd Day): TGF-β → G3 = G2 > G1 PDGF → G3 > G1 Immunohistochemical Staining of COL1 (On 14th Day): G3 > G2 > G1 hGFs Cell Viability by Live/Dead Assay (At 24 h): Both PRP and I-PRF demonstrated excellent cell viability and biocompatibility. hGFs Migration Assay (At 24 h): G3 > G2 > G1 (P < 0.05) G6 > G5 > G4 (P < 0.05) G9 > G8 > G7 (P < 0.05) hGFs Proliferation by CCK-8 Assay (On 1st, 3rd and 5th Day): Day 1 → No difference between all groups. Day 3rd and 5th → I-PRF significantly increased cell numbers when compared to the other groups. hGFs Adhesion Assay by DAPI Staining (continued on next page) |
| Wang et al. [16] (2017) | Periodontal Regeneration | To evaluate the effect of I-PRF on hGFs cultured on smooth and roughened titanium implant surfaces compared to PRP. | - hGFs | - | 700 g 3 min (Duo Centrifuge, Nice, France) | Upper layer G1) hGF + TCP (Control) G2) hGF + TCP + PRP G3) hGF + TCP + I-PRF G4) hGF + PT (Control) G5) hGF + PT + PRP G6) hGF + PT + I-PRF G7) hGF + SLA (Control) G8) hGF + SLA + PRP G9) hGF + SLA + I-PRF | hGFs Cell Viability by Live/Dead Assay (At 24 h): Both PRP and I-PRF demonstrated excellent cell viability and biocompatibility. hGFs Migration Assay (At 24 h): G3 > G2 > G1 (P < 0.05) G6 > G5 > G4 (P < 0.05) G9 > G8 > G7 (P < 0.05) hGFs Proliferation by CCK-8 Assay (On 1st, 3rd and 5th Day): Day 1 → No difference between all groups. Day 3rd and 5th → I-PRF significantly increased cell numbers when compared to the other groups. hGFs Adhesion Assay by DAPI Staining (continued on next page) |
### Table 3 (continued)

| Authors (Year) | Category | Aim of study | Cells/Drugs | I-PRF preparation method | Site of I-PRF harvest | Groups | Main Methods and Results |
|----------------|----------|--------------|-------------|--------------------------|-----------------------|--------|--------------------------|
| Chai et al.[19] (2019) | Pulp Regeneration | To compare the cellular regenerative activity of hDPCs when cultured with either liquid PRF or traditional PRP. | - hDPCs | 700 rpm 3 min or NR | Upper layer | G1) hDPCs  
G2) hDPCs + PRP  
G3) hDPCs + I-PRF  
Inflammatory Environment:  
G1) hDPCs  
G2) hDPCs + LPS  
G3) hDPCs + I-PRF  
Regeneration- and ECM-related Gene Expression by RT-qPCR:  
G3 > G2/G1 (P < 0.05)  
G6 > G5/G4 (P < 0.05)  
G9 = G8 = G7 (P < 0.05)  
Immunohistochemical Staining of COL1 (On 7th Day):  
G3 > G2 > G1 (P < 0.05)  
G6 > G5/G4 (P < 0.05)  
G9 = G8/G7 (P < 0.05) |

Rafiee et al.[83] (2020) | Upper layer | | | | | | |

(continued on next page)
### Table 3 (continued)

| Authors (Year) | Category | Aim of study | Cells/Drugs          | I-PRF preparation method | Site of I-PRF harvest | Groups                                                                 | Main Methods and Results |
|----------------|----------|--------------|----------------------|--------------------------|-----------------------|----------------------------------------------------------------------|--------------------------|
| Pulp Regeneration and Drug Delivery | To evaluate in-vitro drug delivery profile of two differently prepared triple antibiotic-containing I-PRF based scaffolds for pulp regeneration. | - Triple Antibiotic Mixture: 1- MET 2- CIP 3- MINO | 700 rpm 3 min 4 °C (MF-20R Centrifuge, Awel, China) | G1) I-PRF + Triple Antibiotic Mixture (MET, CIP, MINO) by immersion | Chromatographic Method Validation: Retention Time → MINO (2.3 min), CIP (2.6 min), MET (3.1 min). Maximum UV Absorances → CIP (268 nm), MET (278 nm), MINO (350 nm) |
| Rafiee et al.[31] (2020) | Pulp Regeneration, Drug Delivery, and Anti-microbial Efficacy | To evaluate the antimicrobial property of an I-PRF scaffold containing triple antibiotic mixture against an Actinomyces naeslundii and Enterococcus faecalis biofilm in an infected immature root canal model. | - Microbial Biofilm: 1) Actinomyces naeslundii 2) Enterococcus faecalis - Triple Antibiotic Mixture: 1- MET 2- CIP 3- MINO | 700 rpm 3 min 4 °C (Eppendorf Centrifuge, Hamburg, Germany) | Upper layer G1) Biofilm + Triple Antibiotic Mixture (MET, CIP, MINO) G2) Biofilm + I-PRF + Triple Antibiotic Mixture (MET, CIP, MINO) G3) Biofilm + I-PRF G4) Seven-day Biofilm Untreated (Control) G5) Microbial-free Untreated (Control) | Gene Expression by RT-qPCR: G2 → The highest antibacterial activity against Actinomyces naeslundii G1 and G2 → Had similar antibacterial property against Enterococcus faecalis G1, G2, and G3 → Revealed higher levels of antibacterial activity against E. faecalis than against Actinomyces naeslundii (P < 0.001) Actinomyces Naeslundii and Enterococcus Faecalis Viability by MTT Assay: G2 > G1 > G3 (P < 0.001) |

**Abbreviations:** I-PRF: Injectable Platelet Rich Fibrin, ATCC: American Type Culture Collection, RPM: Rate Per Minute, Min: Minute, NR: Not Reported, MIC: Minimal Inhibitory Concentration, MBC: Minimal Bactericidal Concentration, PRF: Platelet Rich Plasma, PRF: Platelet Rich Fibrin, ABSM: Allogenic Bone Substitute Material, XBSM: Xenogeneic Bone Substitute Material, RT-qPCR: Reverse Transcription quantitative Polymerase Chain Reaction, A-PRF: Advanced Platelet Rich Fibrin P-PRF: Pure Platelet Rich Plasma, c-PRF: Leukocyte- and Platelet Rich Plasma, IGF-1: Insulin-like Growth Factor-1, VEGF: Vascular Endothelial Growth Factor, PDGF: Platelet-derived Growth Factor, BMP: Bone Morphogenetic Protein, DAPI: 6-diamidino-2-phenylindole, CCK-8: Cell Counting Kit-8, ALP: Alkaline Phosphatase, RUNX-2: Runt-related Transcription Factor 2, OCN: Osteocalcin, COL1: Collagen Type 1, OEC: Outgrowth Endothelial Cell, pOB: Primary Osteoblast, CD: Cluster of Differentiation, ELISA: Enzyme-linked Immunosorbent Assay, KAM-1: Intercellular Adhesion Molecule 1, hpDLsCs: Human Periodontal Ligament Cells, LPS: LPS: Lipopolysaccharide, IL-1b: Interleukin 1 Beta, TNF-a: Tumor Necrosis Factor Alpha, gMSCs: Gingival Mesenchymal Stem Cells, SPARC: Secreted Protein Acidic And Cysteine Rich, IGF: Human Gingival Fibroblast, C-PRF: Concentrated Platelet Rich Fibrin, TCP: Tricalcium Phosphate, PT: Pickled Titanium, SLA: Sand-blasted, Large Grit, Acid-etched, ECM: Extracellular Matrix, hDPCs: Human Dental Pulp Cells, DMP-1: Dentin Matrix Acidic Phosphoprotein 1, DSPP: dentin Sialophosphoprotein, MET: Metronidazole, CIP: Ciprofloxacin, MINO: Minocycline
## Table 4

A summary of the included animal studies regarding the application of I-PRF in regenerative dentistry.

| Author (Year) | Category | Aim of study | Animals | I-PRF Preparation method | Site of I-PRF harvest | Groups | Main Methods and Results |
|---------------|----------|--------------|---------|--------------------------|----------------------|--------|-------------------------|
| Elsherbini et al.[14] (2020) | Wound Healing | To evaluate the effects of I-PRF and melatonin on wound healing in diabetic rats. | - 30 diabetic albino rats with surgical defect in their SMGs. | 700rpm, 3min, (Duo Centrifuge, Nice, France) | Upper layer | G1) Control (n = 10) G2) Melatonin (n = 10) G3) I-PRF (n = 10) | Malondialdehyde Levels Measurement (On 28th Day): Both I-PRF and melatonin → Reduction of malondialdehyde (P < 0.05). Histological Staining Analysis: 1) H&E Staining, and 2) Immunohistochemical Staining of Caspase-3, and VEGF (On 28th Day): - Both I-PRF and melatonin → Reduced caspase-3 and increased vascular endothelial growth factors (P < 0.05) → increased SMGs regenerative capacity when compared to diabetic group - Histomorphological structure of SMGs → Melatonin > I-PRF |
| Mu et al.[29] (2020) | Bone Regeneration, Wound Healing and Anti-inflammatory Efficacy | To assess the angiogenic and osteogenic capacity in rabbit sinus model grafted with DBBM particles soaked in I-PRF. | - 16 New Zealand rabbits (32 Sinuses) | 700rpm, 3min | Yellow | G1) DBBM (n = 16) G2) DBBM + I-PRF (n = 16) | Micro-CT Findings (At 8th Week Post-implantation): Bone volume over total volume and thickness of trabecular bone: G1 < G2 (P > 0.05) Laser Confocal Microscopy Photographs of Sequential Fluorochrome Staining (At 2nd, 4th, and 7th Week Post-implantation) together with 2) VG Staining (At 8th Week Post-implantation): - 2nd week → G2 > G1 (P < 0.05) - 4th and 7th weeks → G1 = G2 (P > 0.05) - 8th week → Area of new bone formation: G2 > G1 (P < 0.05) Area of Bio-Oss: G1 > G2 (P < 0.05) Histological Staining Analysis: 1) VG Staining and 2) Immunohistochemical Staining of SDF-1 (At 4th Week Post-implantation): Number of trabecular bones and new bone formation volume, and SDF-1 positive area → G2 > G1 (P < 0.05) 3) H&E, TRAP, ALP, and Masson Trichrome Staining (At 4th Weeks Post-implantation): New bone formation: G2 > G1 > G3 > G4 > G5 (P < 0.05) Osteoclast’s activity → G5 had the least activity. |
| Mu et al.[67] (2020) | Bone Regeneration | To evaluate the effect of I-PRF modified with GPNs for rabbit sinus augmentation. | - New Zealand rabbits | 700rpm, 3min | Yellow | G1) Control (n = 10) G2) GPNs (n = 10) G3) GPNs + I-PRF (n = 10) | Micro-CT Findings (At 8 Weeks Post-implantation): Highest bone density → G5 Histological Staining Analysis (At 2nd and 8th Weeks Post-implantation): 1) H&E, Aniline Blue, and TRAP Staining: - Angiogenesis and osteogenesis → G1 < G2 < G3 < G4 < G5 (P < 0.05) - Osteoclast’s activity → G5 had the least activity. Micro-CT Findings (At 4th and 8th Weeks Post-implantation): 4th Week → - Bone volume, and trabecular numbers: G3 > G2 > G1 (P < 0.05) - Trabecular separation: G1 > G2 > G3 (P < 0.05) 8th Week → - Bone volume: G3 > G2 > G1 (P < 0.05) - Trabecular number, and trabecular separation: (continued on next page)
| Author (Year)          | Category                | Aim of study                                                                 | Animals                                                                 | I-PRF Preparation method | Site of I-PRF harvest | Groups                                                                 | Main Methods and Results                                                                 |
|-----------------------|-------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------|------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Aydin Sert et al. [43] (2020) | Periodontal Regeneration | To evaluate the effect of I-PRF in rats with experimental periodontitis.     | - 24 Wistar albino rats with ligature-induced periodontitis             | 3300 rpm 2 min           | Upper layer            | G1) SRP (n = 8) G2) SRP + I-PRF (n = 8) G3) I-PRF (n = 8)          | G3 = G2 = G1 (P > 0.05)                                                                 |
|                       |                         |                                                                              |                                                                         |                           |                        |                                                                        | Histological Staining Analysis: 1) VG Staining (At 4th and 8th Weeks Post-implantation): | 4th Week → New bone area, new bone height, and the angle between the membrane and the implant: G3 > G2 > G1 (P < 0.05) 8th Week → New bone area, new bone height, and the angle between the membrane and the implant: G3 > G2 > G1 (P < 0.05) 2) H&E Staining (At 4th Weeks Post-implantation): 4th Week → Area of vessels, number of vessels, and average area of vessels: G3 > G2 = G1 (P < 0.05) |
|                       |                         |                                                                              |                                                                         |                           |                        |                                                                        | Micro-CT Findings (On 31th days): Bone volume, bone levels (mesial/distal) → G1 = G2 = G3 (P > 0.05). Bone mineral density → I-PRF > SRP + I-PRF > SRP (P < 0.0001). |

Abbreviations: I-PRF: Injectable Platelet Rich Fibrin, SMG: Submandibular Salivary Gland, RPM: Rate Per Minute, Min: Minute, G: Group, H&E: Hematoxylin and Eosin, VEGF: Vascular Endothelial Growth Factor, DBBM: Deproteinized Bovine Bone Mineral, NR: Not Reported, Micro-CT: Micro-Computed Tomography, VG: Van Gieson, SDF-1: Stromal Cell-derived Factor 1, H&E: Hematoxylin and Eosin, TRAP: Tartrate-resistant Acid Phosphatase, ALP: Alkaline Phosphatase, GNP: Gelatin Nanoparticle, SRP: Scaling and Root Planning, TNF-a: Tumor Necrosis Factor Alpha, IFN-ɤ: Interferon Gamma, IL-1β: Interleukin 1 Beta.
### Table 5: A summary of the included case reports regarding the application of I-PRF in regenerative dentistry.

| Case Reports | Author (Year) | Category | Aim of study | Participants | Site of harvest | Top layer | Intervention | Main Methods and Results |
|--------------|---------------|----------|--------------|--------------|----------------|-----------|--------------|--------------------------|
| Gasparro et al.[51] (2019) | Wound Healing | To evaluate the effect of I-PRF in the treatment of PCM of the oral cavity refractory to corticosteroid therapy. | - An individual with PCM of the oral cavity refractory to corticosteroid therapy. | - 700 rpm 3 min (Duo Centrifuge, Nice, France) | Top layer I-PRF | Pain Evaluation by VAS (After 6 Months): The pain gradually reduced until the score of zero at the fourth infiltration, and the patient remained free of pain during the whole study period. Clinical Evaluation (After 1 Year): The tooth was successfully reattached and maintained mobility and function. | Pain Evaluation by VAS (After 6 Months): Pain gradually reduced until the score of zero at the fourth infiltration, and the patient remained free of pain during the whole study period. Clinical Evaluation (After 1 Year): The tooth was successfully reattached and maintained mobility and function. |
| Suresh[52] (2021) | Anti-inflammatory Efficacy | To evaluate the successful replantation of an avulsed permanent tooth with an increased extra oral dry time using I-PRF. | - A 21-year-old female with tooth number 11 missing. | - 700 rpm 3 min | - | Clinical and Radiographic Evaluation (Every 3 Months up to 1 Year): The tooth was successfully replanted with no pain and mobility and lesions. | Clinical and Radiographic Evaluation (Every 3 Months up to 1 Year): The tooth was successfully replanted with no pain and mobility and lesions. |
| Thanasrisuewong et al.[50] (2020) | Bone Regeneration | To evaluate the effect of GBR using I-PRF in combination with particulate bone graft and L-PRF for vertical and horizontal bone augmentation prior to implant placement. | - A 55-year-old Asian woman presented with a severe bone defect in the posterior mandible. | - 700 rpm 3 min Room temperature (PC-02 Centrifuge, Nice, France) | Red I-PRF + Bio-Oss + Mineral-Oss + L-PRF + Collagen Membrane | Radiographic Evaluation (After 8 Months): The result showed a remarkable achievement of vertical and horizontal bone augmentation appropriate for implant placement. Clinical Evaluation (After 9 Months): The GBR procedure resulted in good bone quality and quantity of the grafted site. Histological Staining Analysis (After 9 Months): 1) H&E Staining: The histology showed a new normal physiological bone formation in around the implant site as well as at the osteotomy site. (continued on next page) |
| Lorenz et al.[70] (2018) | Bone Regeneration | To evaluate the effect of customized titanium mesh filled with XBSM in combination with A-PRF and I-PRF for reconstruction of a severe tumor-related bone defect in the mandible of a former head and neck cancer patient. | - A 61-year-old female patient affected by squamous cell carcinoma in the anterior floor of the mouth, treated by tumor resection including a block-type resection of the mandible along with bilateral neck dissection. | - 700 rpm 3 min | - | Complete rehabilitation and restoration of the patient's oral function were achieved. Histological analysis of extracted bone biopsies confirmed that the new bone had a lamellar architecture. | Complete rehabilitation and restoration of the patient's oral function were achieved. Histological analysis of extracted bone biopsies confirmed that the new bone had a lamellar architecture. (continued on next page) |
### Table 5 (continued)

| Case Reports | Author (Year) | Category | Aim of study | Participants | Site of I-PRF harvest | I-PRF Preparation Method | I-PRF Method | Intervention | Site of intervention originated from the residual bone. | Main Methods and Results | Abbreviations |
|--------------|---------------|----------|--------------|--------------|-----------------------|---------------------------|--------------|-------------|---------------------------------------------------|--------------------------|----------------|
|             | Chenciner et al. [19] (2017) | Bone Regeneration | To assess the possibility for augmented bone in the alveolar ridge in a 35-year-old male patient diagnosed with severe chronic periodontitis | A 36-year-old male patient with chronic periodontitis | NR | Blended A-PRF | 3 min | Bone graft + A-PRF, + I-PRF, + Bio-Disc, + Collagen membrane, + A-PRF membrane, + RPM, + VAS | To evaluate the effect of a prefabricated bone construction that utilizes a combination of bone graft material + A-PRF, + BPRF, + RPM and A-PRF. |Clinical and Radiographic Evaluation (At 15 Month): significant reduction in pocket depths and significant three-dimensional alveolar bone fill at the treatment site. | I-PRF: Injectable Platelet Rich Fibrin, PCM: Plasma Cell Mucositis, RPM: Rate Per Minute, Min: Minute, G: Group, VAS: Visual Analog Scale, GBR: Guided Bone Regeneration, H&E: Hematoxylin and Eosin, A-PRF: Advanced Platelet Rich Fibrin, VE: 4000, Ample Scientific Champion F-33D, EBA20, Dynamica Velocity 14R, or TC-SPINPLUS-6 Digital Desktop, except for the study by Fujioka-Kobayashi on I-PRF [45] which used horizontal centrifugation with the Eppendorf Centrifuge. Although the most common commercially available centrifugation systems are fixed-angled, they are less effective in cell layer separation compared to the horizontal systems [46]. In horizontal systems, the cells are more efficiently separated between the lowest and the highest RCF, leading to the most optimized differentiation of blood contents. Moreover, the cells in fixed-angled centrifugation are more prone to trauma due to the outward-downward force during angled centrifugation systems [44-47]. According to a recent study by Miron et al. [44], the horizontal centrifugation method significantly increases the number of platelets and leukocytes in I-PRF up to 3.5 times more than the fixed-angle centrifugation. |
|              | Lei et al. [91] (2019) | Periodontal Regeneration | To evaluate the effect of I-PRF on regenerative periodontal therapy utilizing a combination of bone graft + A-PRF and A-PRF. | A 18-year-old male with expulsion of the frontal region of the upper jaw, alveolar ridge | NR | Blended A-PRF | 3 min | Bone graft + A-PRF, + I-PRF, + Bio-Disc, + Collagen membrane, + RPM | To assess the possibility for augmentation of the alveolar ridge in the frontal region of the upper jaw, alveolar ridge utilizing a combination of bone graft (Duo Centrifuge, Nice, France) and I-PRF. |Clinical and Radiographic Evaluation (After 4 Months): uneventful. The control CBCT scan showed good organization of new bone in all of the aforementioned obtained layers compared to the baseline [49]. Almost all included studies reported investigating the I-PRF obtained from the upper layer of the tube known as the yellow I-PRF. |

3.2.2. Centrifuge device: Horizontal versus fixed-angle centrifugation

There are two main types of devices used to centrifuge blood for I-PRF preparation: either fixed-angle or horizontal centrifuge devices. While the most common centrifugation system used for PRF preparation yet is the fixed-angle centrifugation system, the horizontal centrifugation system is a more favorable method in research laboratories [44]. The majority of PRF centrifuges historically used horizontal centrifugation, yet few have adapted those protocols for the production of PRF [44]. On this basis, the in vitro and in vivo studies on I-PRF included in this paper reported using the fixed-angle method with either Duo, IntraSpin, MF-20R, PC-02, Eppendorf Centrifuge, VE-4000, Ample Scientific Champion F-33D, EBA20, Dynamica Velocity 14R, or TC-SPINPLUS-6 Digital Desktop, except for the study by Fujioka-Kobayashi on I-PRF [45] which used horizontal centrifugation with the Eppendorf Centrifuge.


Table 6
A summary of the included clinical studies regarding the application of I-PRF in regenerative dentistry.

| Author (Year)               | Category     | Aim of study                                                                 | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups                          | Main Methods and Results                                                                 |
|-----------------------------|--------------|-------------------------------------------------------------------------------|--------------|--------------------------|------------------------|---------------------------------|------------------------------------------------------------------------------------------|
| Saglam et al.[54] (2021)    | Wound Healing| To compare the effects of I-PRF with those of corticosteroids in the treatment of erosive oral lichen planus. | - 24 Patients with bilateral erosive oral lichen planus | 700 rpm 3 min         | NR                      | G1) Methylprednisolone Acetate (n = 24)  
G2) I-PRF (n = 24) | Pain Evaluation by VAS (At Baseline, 1st, 2nd and 6th Months):  
G1 = G2  
Quality of Life Evaluation by OHIP-14 (At Baseline, 1st, 2nd and 6th Months):  
G1 = G2  
Lesion Size Evaluation (At Baseline, 1st, 2nd and 6th Months):  
G1 = G2  
Lesion Area Measurement and Morphological Changes Evaluation by Thongprasom Score (At 4th Week):  
Lesion extension → G1 = G2 (reduction of 59.8% for G2 and 59.2% for G1)  
Pain Evaluation by VAS (At 4th Week):  
Pain → G1 = G2 (reduction of 47.6% for G2 and 40% for G1)  
Wound Healing Evaluation by H2O2 Test, MSS, LTH Indices (On 3rd, 7th, and 14th days and 1st month),  
Bleeding Status (On 3rd and 7th days) and Palatal Tissue Thickness (At Baseline, 1st month, and 3rd month):  
- Epithelialization on the 14th day → G1 < G2, G3 (P < 0.05)  
- MSS scores at the 14th day and 1st month → G2 < G1, G3 (P < 0.05)  
- LTH levels at the 3rd, 7th, and 14th day and 1st month → G2 > G1, G3 (P > 0.05)                                                                 |
| Bennardo et al.[53] (2021) | Wound Healing| To compare the efficacy of I-PRF and triamcinolone acetone injective therapies in patients with symptomatic oral lichen planus. | - 9 patients with symptomatic oral lichen planus | 700 rpm 3 min         | Yellow                   | G1) Triamcinolone Acetone (n = 9)  
G2) I-PRF (n = 9) | Lesion Area Measurement and Morphological Changes Evaluation by Thongprasom Score (At 4th Week):  
Lesion extension → G1 = G2 (reduction of 59.8% for G2 and 59.2% for G1)  
Pain Evaluation by VAS (At 4th Week):  
Pain → G1 = G2 (reduction of 47.6% for G2 and 40% for G1)  
Wound Healing Evaluation by H2O2 Test, MSS, LTH Indices (On 3rd, 7th, and 14th days and 1st month),  
Bleeding Status (On 3rd and 7th days) and Palatal Tissue Thickness (At Baseline, 1st month, and 3rd month):  
- Epithelialization on the 14th day → G1 < G2, G3 (P < 0.05)  
- MSS scores at the 14th day and 1st month → G2 < G1, G3 (P < 0.05)  
- LTH levels at the 3rd, 7th, and 14th day and 1st month → G2 > G1, G3 (P < 0.05)                                                                 |
| Kızıltoprak and Uslu[34] (2020) | Wound Healing| To evaluate the effects of AFG and I-PRF on palatal wound healing and postoperative discomfort. | -36 healthy individuals with the need of FGG | 2300 rpm 3 min         | Yellow                   | G1) Control (n = 12)  
G2) AFG (n = 12)  
G3) I-PRF (n = 12) | Wound Healing Evaluation by H2O2 Test, MSS, LTH Indices (On 3rd, 7th, and 14th days and 1st month),  
Bleeding Status (On 3rd and 7th days) and Palatal Tissue Thickness (At Baseline, 1st month, and 3rd month):  
- Epithelialization on the 14th day → G1 < G2, G3 (P < 0.05)  
- MSS scores at the 14th day and 1st month → G2 < G1, G3 (P < 0.05)  
- LTH levels at the 3rd, 7th, and 14th day and 1st month → G2 > G1, G3 (P < 0.05)                                                                 |

(continued on next page)
| Author (Year) | Category | Aim of study | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results |
|--------------|----------|--------------|--------------|--------------------------|-----------------------|--------|----------------------------|
| Nageh et al.[55] (2021) | Inflammatory Efficacy | To evaluate clinically and radiographically the management of internal inflammatory root resorption in permanent anterior teeth using I-PRF. | - 10 healthy patients with 13 anterior teeth diagnosed with internal inflammatory root resorption | 700 rpm 3 min - (VE-4000 Centrifuge, Texas, USA) | Upper layer | G1) I-PRF | - Bleeding → G1 < G2, G3 (P < 0.05) - Tissue thickness → G1 = G2 = G3 (P > 0.05) Postoperative Discomfort Evaluation by VAS (on 3rd, 7th, and 14th days and 1st month): VAS at the 7th day → G2 < G1, G3 Internal Inflammatory Root Resorption and Periapical Lesions Evaluation by CBCT (At Baseline, and 3rd, 6th, 12th Months): The mean volume of internal inflammatory root resorption and periapical lesions decreased (P < 0.05) Histological Staining Analysis: Masson's Trichrome Stains + Osteocalcin Antibody (At 4th Week): No significant difference between the residual crest heights of both groups (P > 0.05) Radiographic Evaluation by Panoramic Radiography (At 4th Week): The improvement in both groups looked similar. Radiographic Evaluation by CBCT (At a Period of 6 Months): Vertical bone gain → G1 > G2 (P = 0.008) Histological Staining Analyzing: 1) H & E Staining |
| İşık et al.[39] (2021) | Bone Regeneration | To evaluate the effect of the screw test pole technique using particulate allograft with I-PRF on vertical bone augmentation and to compare this with autogenous block bone graft. | - 13 patients with bilateral partial edentulousness with insufficient bone height for insertion of short dental implants in 1 ml upper layer | 2700 rpm 2 min - (EBA20 Centrifuge, Tuttingen, Germany) | G1) Autogenous Block Bone Graft (n = 13) G2) Allograft + I-PRF (n = 13) | Radiographic Evaluation by CBCT (At a Period of 6 Months): Vertical bone gain → G1 > G2 (P = 0.008) Histological Staining Analyzing: 1) H & E Staining (continued on next page) |
### Table 6 (continued)

| Author (Year)          | Category          | Aim of study                                                                 | Participants                                                                 | I-PRF Preparation Method | Site of I-PRF harvest | Groups                                                  | Main Methods and Results                                                                                                                                                                                                 |
|------------------------|-------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------|-----------------------|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Işık et al.[72] (2021) | Bone Regeneration | To assess augmentation success after GBR carried out simultaneously with implant placement using XBSM alone and in combination with liquid PRF. | - 40 partially edentulous patients with residual alveolar bone width of 4–5 mm | 700 rpm 3 min (EBA20 Centrifuge, Tuttingen, Germany) | Upper layer G1) Bovine-derived Xenograft (n = 20) G2) Liquid PRF Enriched Bovine-derived Xenograft (n = 20) | (After 6 Months): Percentage of newly formed bone → G2 > G1 (P < 0.001) Clinical Evaluation (After 12 months): The implants’ survival rates were 100% in both groups. Radiographic Evaluation by CBCT: 1) Augmentation Thickness (After a Period of 6 Months): G2 > G1 (P < 0.001) 2) Marginal Bone Loss Level (After 1st and 2nd Years): G2 < G1 (P < 0.001) Clinical Evaluation (After 6th month, 1st and 2nd Years): The implants’ survival rates were 100% for both groups. Radiographic Evaluation by CBCT and Periapical Radiography (At Baseline and After a Period of 6 Months): No significant difference in regenerated bone volume and density. |
| Thanasut et al.[40] (2021) | Bone Regeneration | To investigate effect of liquid and solid PRF on bone regeneration in repairing alveolar clefts with autologous ABSM. | - 13 patients with 15 alveolar cleft sites | 1000 rpm 10 min 25 °C (Dynamica Velocity 14 R Centrifuge, Victoria, Australia) | Yellow G1) Autologous ABSM (n = 7) G2) Autologous ABSM + Liquid PRF + PRF Membrane (n = 8) | Radiographic Evaluation by CBCT: Labial graft thickness → G3, Labial bone gain → G2 > G1 (P < 0.05) Bone resorption → No significant difference Radiographic Evaluation by CBCT (At a Period of 6 Months): Labial graft thickness → G3, Labial bone gain → G2 > G1 (P < 0.05) Bone resorption → No significant difference. |
| Wang et al.[73] (2021) | Bone Regeneration | To test whether or not a digital workflow for GBR with XBSM and I-PRF improved the thickness of the hard tissue compared to the conventional workflow. | - 26 patients with two or three wall horizontal bone defect in the anterior region | 700 rpm 3 min - (NR) | Upper yellow layer G1) XBSM + I-PRF (Conventional) (n = 14) G2) XBSM + I-PRF (Digital) (n = 12) | Radiographic Evaluation by CBCT (After a Period of 6 Months): Labial thickness of hard tissues, and bone gain → G2 > G1 (P < 0.05) Bone resorption → No significant difference. Radiographic Evaluation by CBCT (At a Period of 6 Months): Labial graft thickness → G3, Labial bone gain → G2 > G1 (P < 0.05) Bone resorption → No significant difference. |
| Wang et al.[74] (2021) | Bone Regeneration | To evaluate the impact of different GBR procedures on bone graft contour after wound closure in lateral ridge augmentation. | - 48 patients with 63 augmented sites with a two or three-wall horizontal | 700 rpm 3 min - (NR) | NR G1) XBSM+ Collagen Membrane G2) XBSM+ Collagen Membrane + Healing cap G3) XBSM+ I-PRF + Collagen | Radiographic Evaluation by CBCT (At a Period of 6 Months): Labial graft thickness → G3, Labial bone gain → G2. | (continued on next page)
### Table 6 (continued)

| Author (Year) | Category | Aim of study | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results |
|---------------|----------|--------------|--------------|--------------------------|-----------------------|--------|--------------------------|
| Rao et al. [27] (2020) | Bone Regeneration | To evaluate the effect of A-PRF and I-PRF along with iliac bone graft for secondary alveolar bone grafting and compared it with cases in which only iliac bone graft was used. | - 30 patients with alveolar cleft, with age group of ≥ 7 years, having complete unilateral cleft alveolus | 700 rpm 3 min - (NR) | Orange superficial layer | G1) Iliac bone graft (n = 15) G2) Iliac bone graft + A-PRF + I-PRF (n = 15) | - For both evaluations the data was clinically favorable in G2. IOAR Radiographic Evaluation by Bergland Criteria (At 3rd and 6th Month): G2 > G1 Periodontal Parameters Evaluation by PPD and Mobility indices (At 3rd and 6th month): Periodontal status improved in both groups but was more in G2 compared to G1. Radiographic Evaluation by CBCT (After a Period of 7.5 ± 1.0 Months): - The GBR produces an increase in bone thickness (P < 0.001) and height (P < 0.005). - Bone gain in horizontal defects → Maxilla > Mandible and Anterior > Posterior (P = 0.014 and 0.033, respectively) - No difference related to GBR location in vertical defects (P > 0.05) Radiographic Evaluation by CBCT (After a Period of 6 Months): - Significant new bone formation at mesial and distal regions of inserted implants (P < 0.05) - New bone was (continued on next page) |
| Valladão et al. [36] (2020) | Bone Regeneration | To describe the bone gain associated with GBR procedures combining membranes, bone grafts, and PRF [I-PRF and i-PRF] for vertical and horizontal bone augmentation. | - 18 patients who needed vertical or horizontal bone regeneration before installing dental implants | 2700 rpm 3 min - (IntraSpin, Florida, USA) | | G1) ABSM + XBSM + I-PRF + Collagen membrane + L-PRF membrane | | |
| Gülseren and Dereci [71] (2019) | Bone Regeneration | To evaluate the new bone formation after sinus floor augmentation with collagen plugs used as carriers for I-PRF. | - 12 patients who underwent sinus lifting procedures and dental implant placement (18 implants) | 700 rpm 3 min - (Duo Centrifuge, Nice, France) | | G1) Collagen Plugs Soaked with I-PRF + Implant | |
| Author (Year)               | Category                  | Aim of study                                                                 | Participants                                                                 | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results                                                                                                                                                                                                                     |
|---------------------------|---------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|-----------------------|--------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Kapa et al.[61] (2021)    | Periodontal Regeneration  | To evaluate the efficacy of sticky bone with I-PRF coated collagen membrane in the treatment of gingival recession. | - 16 patients with Miller’s Class I or II recession in the maxillary esthetic zone | 700 rpm 3–4 min          | NR                    | G1) Sticky Bone (I-PRF + Freeze-dried Bone Allograft) + I-PRF-coated Collagen Membrane Regenerated with I-PRF carried by collagen plugs in sinus floor augmentation. | Radiographic Evaluation by CBCT (At Baseline and After a Period of 6 Months): Increased labial plate thickness and GT Periodontal Parameters Evaluation by GT, RD, KTW and CRC (At Baseline and After a Period of 6 Months): - Increase in GT and KTW and decreased RD and PPD - 12 out of 16 treated cases achieved CRC. |
| Albonni et al.[62] (2021) | Periodontal Regeneration  | To clarify the clinical efficacy of using I-PRF as an adjunctive subgingival irrigation of SRP. | - 15 patients with bilateral periodontal pockets (≥ 5 mm) on a minimum of two teeth on each side | 700 rpm 3 min            | Yellow layer          | G1) Control (n = 338) G2) I-PRF (n = 338) | Periosteal Parameters Evaluation by PI, PPD, BOP and gingival recession Indices (At Baseline and After a Period of 3rd Month): No significantly difference in all clinical indices (P > 0.05) |
| Vučković et al.[59] (2020)| Periodontal Regeneration  | To evaluate the effect of I-PRF in conjunction with SRP in patients with chronic periodontitis. | - 24 patients with chronic periodontitis who had at least two sites with PPD ≥ 5 mm on contralateral side | 700 rpm 3 min Room temperature (Duo Centrifuge, Nice, France) | Upper layer            | G1) SRP (n = 24) G2) SRP + I-PRF (n = 24) | Periosteal Parameters Evaluation by CAL, GML, PPD, BOP, and PI Indices (At 3rd month): - A significant improvement in investigated clinical parameters for both G1 and G2 (P < 0.05) - CAL, GML, PPD, and BOP G2 > G1 (P = 0.003, 0.040, 0.006, and 0.000 respectively), - PI index G1 = G2 (P > 0.05) |
| Turer et al.[25] (2020)   | Periodontal Regeneration  | To determine whether the combined CTG with I-PRF with CAF improved root coverage of deep | - 72 patients with Miller class I and II gingival recession | 700 rpm 3 min Room temperature (Duo Centrifuge, Nice, France) | Upper layer            | G1) CAF + CTG (n = 36) G2) CAF + CTG + I-PRF (n = 36) | Periosteal Parameters Evaluation by PPD, CAL, RW, RD, ITH, GT, MRC and CRC (continued on next page) |
| Author (Year) | Category | Aim of study | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results |
|--------------|----------|--------------|--------------|--------------------------|-----------------------|--------|--------------------------|
| Miller Class I or II gingival recessions compared with CTG alone with CAF. | | | | | | | Indices (At Baseline, and 6th month): - A significant improvement in investigated clinical parameters for both G1 and G2 (P < 0.05) - RD and KTH → G2 > G1 (P = 0.050 and 0.017, respectively) - PPD, CAL, RW, GT, MRC, and CRC indices → G1 = G2 (P > 0.05) | Postoperative Painkiller Assumption, Morbidity and Esthetic Evaluation: - Significant difference between groups in VAS discomfort (P = 0.035) - Patients' and periodontist's VAS evaluation of root coverage, VAS bleeding, and postoperative painkiller consumption → G1 = G2 (P > 0.05) |
| Ozsagir et al. [60] (2020) | Periodontal Regeneration | To evaluate the effect of GT and KTW using I-PRF alone and with MN in individuals with thin periodontal phenotypes. | 33 systemically healthy patients with thin periodontal phenotypes | 700 rpm 3 min | NR | G1) I-PRF (n = 33) G2) I-PRF + MN (n = 33) | Periodontal Parameters Evaluation by GT and KTW Indices (At Baseline, 1st, 2nd, 3rd, 4th, 5th, and 6th month): - GT at 6th month-- Significant increase for both G1 and G2 (P < 0.001) - KTW at 6th month--G1 = G2 (P > 0.05) - However, in the intra-group comparisons, there was a significant difference between GT only in G2 (P < 0.001) at the 6th month. |
| Izol and Üner [17] (2019) | Periodontal Regeneration | To investigate the potential effects of I-PRF with Miller | 40 patients with Miller | 700 rpm 3 min | NR | | Periodontal Parameter (continued on next page) |
| Author (Year) | Category | Aim of study | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results |
|--------------|----------|--------------|--------------|--------------------------|----------------------|--------|--------------------------|
| Karadayi and Gursoytrak[76] (2021) | Cartilage Regeneration | To evaluate the efficacy of I-PRF on clinical symptoms of painful TMD, and to determine in which level of diseases, the I-PRF is more effective. | 36 patients with painful TMDs | 700 rpm 3 min | - (NR) | Top 3 ml | G1) Arthrocentesis (Wilkes' III)  
G2) Arthrocentesis (Wilkes' IV)  
G3) Arthrocentesis (Wilkes' V)  
G4) Arthrocentesis + I-PRF (Wilkes' III)  
G5) Arthrocentesis + I-PRF (Wilkes' IV)  
G6) Arthrocentesis + I-PRF (Wilkes' V)  
| G1) FGG (n = 20)  
G2) FGG + I-PRF (n = 20) | Evaluation by  
Gingival Recession Index (At Baseline and 3rd month):  
- At baseline → The mean initial exposed root surface was 4.7 ± 1.49 mm for G2, 4.1 ± 1.07 mm for G1, and 4.4 ± 1.31 mm for all subjects.  
- At 3rd month → The mean root surface coverage values were 3.5 ± 1.05 and 3.9 ± 0.78 mm in the G1 and G2, respectively.  
| Bera et al.[78] (2021) | Cartilage Regeneration | To evaluate the role of intra-articular injection of I-PRF along with arthrocentesis for the management of TMJ-OA. | 130 patients with OA | 700 rpm 3 min | - (NR) | NR | G1) Arthrocentesis (n = 67)  
G2) Arthrocentesis + I-PRF (n = 63) | Evaluation by  
VAS, Dysfunction Evaluation by Helkimo Clinical Dysfunction Index, and MMO  
Evaluation (At Baseline, Postoperative 10th Day, 30th Day, and 3rd Month):  
- VAS and Helkimo Clinical Dysfunction Score → A statistically significant difference in the all controls compared to baseline values  
- MMO → A statistically significant difference in the 2nd control compared to baseline values  
|
Table 6 (continued)

| Author (Year)        | Category                  | Aim of study                                                                 | Participants                                                                                     | I-PRF Preparation Method | Site of I-PRF harvest | Groups Main Methods and Results                                                                 |
|----------------------|---------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------|------------------------|--------------------------------------------------------------------------------------------------|
| Ghoneim et al.[77] (2021) | Cartilage Regeneration | To evaluate and compare the efficiency of intra-articular injection of I-PRF following arthrocentesis or arthrocentesis alone in treatment of patients with TMJ disc displacement with reduction. | - 40 patients with reducible anterior disc displacement | 700 rpm 3 min - (TC-SPINPLUS-6 Digital Desktop Centrifuge, Oakham, UK) | Top layer | G1) Arthrocentesis (n = 20) G2) Arthrocentesis + I-PRF (n = 20) | Months): - At 6th Month → G1 = G2 - At 12th Month → G2 > G1 (P < 0.0001) TMJ Pain Evaluation by VAS (After a Period of 6 Months): G1 = G2 (P < 0.05) MMO, Lateral Movements, and Clicking Evaluation (After a Period of 1 Week, and After 3 and 6 Months): - MMO, and lateral movements → G2 > G1 (P < 0.05) - Clicking → G1 > G2 (P < 0.05) |
| Torul et al.[79](2021) | Cartilage Regeneration | To compare the effectiveness of HA and I-PRF in the management of Wilkes stage III internal derangement, and to evaluate the biosupplementation capacity of I-PRF. | - 54 patients with Wilkes stage III internal derangement | 700 rpm 3 min - (Duo Centrifuge, Nice, France) | Top layer | G1) Arthrocentesis (n = 18) G2) Arthrocentesis + HA (n = 18) G3) Arthrocentesis + I-PRF (n = 18) | TMJ Pain Evaluation by VAS and Clicking (At Baseline, After a Period of 1 Week, and After a Period of 1 and 3 Months): G3 < G1 and G2 (P < 0.05) MMO Evaluation (At Baseline, After a Period of 1 Week, and After a Period of 1 and 3 Months): G3 > G1 and G2 (P < 0.05) |
| Yuce and Konerik[75] (2020) | Cartilage Regeneration | To evaluate the effect of intra-articular injection of I-PRF versus HA following arthrocentesis in patients suffering from TMJ pain and dysfunction. | - 47 patients (67 TMJs) with internal TMJ derangement | 700 rpm 3 min - (NR) | Top layer | G1) Arthrocentesis (n = 16) G2) Arthrocentesis + HA (n = 14) G3) Arthrocentesis + I-PRF (n = 17),5 | - Significant decreases in VAS and increases in MMO values were observed in all 3 groups during 12-month follow-up. TMJ Pain Evaluation by VAS: - At 9 months → G3 < G2 (P < 0.05) MMO Evaluation: - At 9 and 12 months → G3 > G2 (P < 0.05) |
| Gode et al.[41] (2019) | Cartilage Regeneration | To evaluate the effect of I-PRF on the viability of diced cartilage. | - 40 patients who underwent | 2700 rpm 2 min | Upper layer | G1) Diced cartilage (n = 20) | Cartilage Thickness Measured with | (continued on next page) |
| Author (Year)                          | Category                      | Aim of study                                                                 | Participants                                                                 | I-PRF Preparation Method               | Site of I-PRF harvest | Groups                          | Main Methods and Results                                                                 |
|---------------------------------------|-------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------|----------------------|---------------------------------|-------------------------------------------------------------------------------------------|
| Albilia et al. [18] (2018)            | Cartilage Regeneration        | To evaluate the effect of I-PRF in patients with TMJ pain and dysfunction.   | - 37 patients (48 TMJs) with painful internal derangement                    | 700 rpm 3 min - (Duo Centrifuge, Nice, France) | Yellow                | G1) I-PRF                        | Linear Soft Tissue Ultrasound (At the Postoperative 1st Week and the 3rd Month): - The mean cartilage graft thickness loss at 3rd month → 0.58 ± 0.21 mm in the G2 and 0.82 ± 0.35 mm in G1 - Volume → Significant loss in G1 - I-PRF was successful in reducing the resorption rate of diced cartilage on nasal dorsum by either increasing the viability or keeping its form. - 33 of 48 TMJs (69%) showed significant reduction in pain at 8 weeks, and at 3, 6, and 12 months. - The best responders to I-PRF were internal derangement stages Wilkes’ IV (78.5%) and V (100%), compared to Wilkes’ I (0%), II (47%), and III (33%).  |
| Zeitounlouian et al. [82] (2021)      | Orthodontic Tooth Movement    | To evaluate the efficacy of I-PRF regarding bone preservation and prevention of root resorption in | - 21 patients with Class II malocclusion with the extraction of the maxillary | 700 rpm 3 min - (NR)                  | NR                   | G1) Control (n = 21) G2) I-PRF (n = 21) | Bone Thickness, Bone Height, Root Length, and Dehiscence Evaluation by CBCT (Before (continued on next page)
Table 6 (continued)

| Author (Year)          | Category                        | Aim of study                                                                 | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results                                                                 |
|------------------------|---------------------------------|-------------------------------------------------------------------------------|--------------|--------------------------|-----------------------|--------|----------------------------------------------------------------------------------------|
| Karci and Baka[42](2021) | Orthodontic Tooth Movement      | To evaluate and compare the effects of local I-PRF injection and piezocision applications on tooth movement during canine distalization, as well as to evaluate any changes in the periodontal parameters. | patients undergoing orthodontic treatment. | 800 rpm | The middle layer | G1) Control (n = 12)  
G2) I-PRF (n = 12)  
G3) Control (n = 12)  
G4) Piezocision (n = 12) | and After Retraction:  
G1 = G2  
Orthodontic Tooth Movements  
Measurements and  
Dentoskeletal Changes by Evaluation by CBCT, and  
Lateral Cephalometric (Before Canine Retraction, and in 12th Week):  
G2 = G4 (P > 0.05)  
Periodontal Parameters  
Evaluation by PI, GI & PPD:  
G2 = G4 (P > 0.05) | 800 rpm 3 min (NR) | - 24 patients with Class II malocclusion with dental alveolar protrusion or moderate crowding |  |  |  |
| Zeitounlouian et al.[80] (2021) | Orthodontic Tooth Movement     | To investigate the effectiveness of I-PRF in accelerating maxillary canine retraction. | patients with Class II division I malocclusion required the extraction of both maxillary first premolars | 700 rpm | Yellow-orange top portion | G1) Control (n = 21)  
G2) I-PRF (n = 21) | Orthodontic Tooth Movement Measurement (Before Canine Retraction, at 1st, 2nd, 3rd, 4th, and 5th Month):  
- Canine retraction →  
G2 > G1 at 2nd, 3rd, and 4th month, with the difference being significant at 2nd month (P < 0.05)  
- Canine rotation and anchorage loss: G1 = G2 (P < 0.05) | 700 rpm 3 min (NR) | - 21 patients with Class II division I malocclusion required the extraction of both maxillary first premolars |  |  |  |
| Erdur et al.[81] (2021) | Orthodontic Tooth Movement      | To evaluate the efficiency of I-PRF in accelerating canine tooth movement and to examine levels of MMP-8, IL-1b, RANKL, and OPG in the GCF during orthodontic treatment. | patients with Class II division I malocclusion required the extraction of both maxillary first premolars | 700 rpm | Upper layer | G1) Control (n = 20)  
G2) I-PRF (n = 20) | Orthodontic Tooth Movement Measurement (Before Tooth Extraction, in 1st, 4th, 8th, and 12th Week):  
- Canine tooth movement at all time points→  
G2 > G1 (P < 0.001)  
GCF Collection (Before Tooth Extraction, in 1st, and 4th Week):  
- Stimulation in the levels of inflammatory cytokines→  
G2 > G1 (P < 0.001)  
- The levels of cytokines | 700 rpm 3 min Room temperature (Duo Centrifuge, Nice, France) | - 20 patients with Class II division I malocclusion required the extraction of both maxillary first premolars |  |  |  |
| Author (Year) | Category | Aim of study | Participants | I-PRF Preparation Method | Site of I-PRF harvest | Groups | Main Methods and Results |
|---------------|-----------|--------------|--------------|--------------------------|-----------------------|--------|-------------------------|
| Karakasali and Erdur [15] (2020) | Orthodontic Tooth Movement | To investigate the efficiency of I-PRF injection on maxillary incisor retraction rate. | - 40 patients with Class II Division I malocclusion required the extraction of both maxillary first premolars | 700 rpm 3 min Room temperature (Duo Centrifuge, Nice, France) 2–3 ml upper layer | G1) Control (n = 20) G2) I-PRF (n = 20) | changed in both groups between 1st and 4th week. - The IL-1β, MMP8, and RANKL values → G2 > G1 (P < 0.05) - The OPG values → G2 < G1 (P < 0.05) - The IL-1β, MMP8, and RANKL values → G2 > G1 (P < 0.05) - The OPG values → G2 < G1 (P < 0.05) | Orthodontic Tooth Movement Measurement (Before Incisor Retraction, in 1st, 2nd, 3rd, and 4th Week): - The average movements of incisors → G2 > G1 (P < 0.05) - No significant difference between the right and left sides in both groups at all time points (P < 0.05) - While the movement of incisors was significantly higher in G2 in the week following the PRF injection compared to the other weeks (P < 0.05), there were no significant difference in the control group at all-time points (P < 0.05). |

Abbreviations: I-PRF: Injectable Platelet Rich Fibrin, RPM: Rate Per Minute, Min: Minute, G: Group, VAS: Visual Analog Scale, OHIP-14: 14-item Oral Health Impact Profile, AFG: Autologous Fibrin Glue, FGG: Free Gingival Graft, H2O2: Hydrogen Peroxide, MSS: Manchester Scar Scale, LTH: Landry, Turnbull, and Howley, TMD: Temporomandibular Disorder, TMJ: Temporomandibular Joint, OAR: Osteoarthritis, HA: Hyaluronic Acid NR: Not Reported, A-PRF: Advanced Platelet Rich Fibrin, PPD: Periodontal Pocket Depth, CBR: Guided Bone Regeneration, c-PRF: Leukocyte- and Platelet Rich Fibrin, d-PTFE-Ti: Titanium-reinforced Non-resorbable High-density Polytetrafluoroethylene, ABSM: Allogenic Bone Substitute Material, XBSM: Xenogenic Bone Substitute Material, SRF: Scaling and Root Planning, CAL: Clinical Attachment Loss, GML: Gingival Margin Level, BOP: Bleeding on Probing, PI: Plaque Index, CTC: Connective Tissue Graft, CAF: Coronally Advanced Flap, RW: Recession Width, RD: Recession Depth, KTH: Keratinized Tissue Height, GT: Gingival Thickness, MRC: Mean Root Coverage, CRC: Complete Root Coverage, KTW: Keratinized Tissue Width, MN: Micro Needling, MMO: Maximum Mouth Opening, HA: Hyaluronic Acid, MMP-8: Matrix Metalloproteinase-8, IL-1b: Interleukin 1 Beta, RANKL: Receptor Activator of Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells Ligand, OPG: Osteoprotegerin, GCF: Gingival Crevicular Fluid.
3. Wound healing and anti-inflammatory efficacy

3.3. In vitro studies on wound healing and anti-inflammatory efficacy

To date, the investigation of I-PRF on the cells during oral tissue regeneration, inflammation, and wound healing has been evaluated in one in vitro [30], two animal studies [14,29], two case reports [51,52], and four clinical studies [34,53–55] (Fig. 3).

3.3.1. In vitro studies on wound healing and anti-inflammatory efficacy

In an in vitro study in 2018, Dohle et al. [30] assessed the effect of I-PRF matrices on inducing angiogenesis and wound healing through inflammatory processes in an in vitro co-culture. Based on the enzyme-linked immunosorbent assay (ELISA) and Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) tests, an increased expression of factors associated with wound healing (PDGF-BB, intracellular adhesion molecules (ICAM-1), and E-selectin) as well as upregulation of the proangiogenic growth factors (vascular endothelial growth factor (VEGF), bone morphogenetic protein (BMP-2), and alkaline phosphatase (ALP)) for vascular endothelial growth were reported. Thus, the angiogenic activation of human outgrowth endothelial cells was verified following the application of I-PRF.

3.3.2. Animal studies on wound healing and anti-inflammatory efficacy

In 2020, Elsherbini et al. [14] compared the wound healing efficacy of I-PRF with that of melatonin in diabetic rats following a surgical defect in their submandibular salivary glands (SMGs). It was concluded that while both I-PRF and melatonin increased SMGs’ regenerative capacity by significantly reducing caspase-3 (P < 0.001) and by increasing vascular endothelial growth factors (P = 0.001, 0.009 respectively), I-PRF showed inferior results with regards to SMGs’ histomorphological structure. In another animal study conducted in 2020, Mu et al. [29] evaluated the angiogenic potential in a rabbit sinus model, which was grafted using deproteinized bovine bone mineral (DBBM) particles dipped in I-PRF. The angiogenic capacity in the I-PRF combined with the DBBM group was reported to be greater than those in the DBBM group. A prolonged-release pattern was reported for the growth factors in the I-PRF combined with the DBBM group for nearly two weeks. The authors [29] reported that the DBBM did not inhibit factor release from I-PRF.

3.3.3. Case reports on wound healing and anti-inflammatory efficacy

In the case study by Gasparro et al. [51] published in 2019, the authors reported that despite a decreased perilesional inflammatory infiltrate after six months of I-PRF injection in a case of plasma cell mucositis, no complete healing of the lesion occurred. It was found that the patient became pain-free after the fourth infiltration, and the visual analog scale (VAS) score remained zero during the entire study. In summary, the authors concluded that while I-PRF showed promising results in accelerating wound healing and decreasing postoperative pain, autologous fibrin presented superior results in wound healing. In a recently published case report, Suresh [52] has evaluated the effect of I-PRF administration in the replantation of an avulsed permanent tooth with an increased extra-oral dry time in a 21-year-old female. The clinical and radiographic evaluations over a year showed that the tooth was successfully replanted with no pain and mobility and lesions.

3.3.4. Clinical studies on wound healing and anti-inflammatory efficacy

Four clinical studies evaluated the effect of I-PRF therapy on wound healing and anti-inflammatory parameters. In the clinical study by Kiziltoprak et al. [34] in 2020, palatal wound epithelialization following I-PRF application was evaluated by H2O2 bubbling test and soft tissue healing was assessed by Landry, Turnbull, and Howley (LTH) index. In addition, the Manchester scar scale (MSS), bleeding in palpation, and palatal tissue thickness were investigated for wound healing following the I-PRF application into the palatal area. Higher epithelialization and lower bleeding were found in the I-PRF group compared to the control (P < 0.05). However, it was reported that after one month, the autologous fibrin had lower MSS scores and higher LTH levels than the I-PRF groups (P < 0.05).
In general, autologous I-PRF can be suggested as a promising adjuvant to the dental and surgical therapeutic processes in increasing the number of growth factors inside the wound and reducing the bacterial count, and helping in wound healing and regeneration.

3.4. Anti-microbial efficacy

The anti-microbial efficacy of I-PRF in the oral environment has been investigated in four in vitro studies [24,31,35,56] (Fig. 3).

3.4.1. In vitro studies on anti-microbial efficacy

Jasmine et al. [35] evaluated the I-PRF anti-microbial and anti-biofilm activity against staphylococcus pathogens obtained from a patient with oral abscess. The bactericidal activity of I-PRF against both biofilm-producers and non-biofilm producers was revealed through broth microdilution as minimal bactericidal concentration (MBC) and minimal inhibitory concentration (MIC). A significant decrease in biofilm production was reported at MIC against weak, moderate, and strong biofilm producers (P < 0.05). All biofilm-producing bacteria were incapable of biofilm production at MBC concentration. In another work, Rafiee et al. [31] examined the antimicrobial property of I-PRF matrices encompassing a triple antibiotic mixture against Enterococcus faecalis and Actinomyces naeslundii biofilms in an immature root canal model. The results of gene expression by RT-qPCR revealed that the utmost antibacterial activity against Actinomyces naeslundii occurred in the group containing an I-PRF scaffold nurtured with a triple antibiotic mixture. Moreover, the findings of Actinomyces naeslundii and Enterococcus faecalis viability by MTT assay showed that the maximum and minimum antibacterial efficiency happened in the I-PRF group combined with triple antibiotic and I-PRF alone, respectively. I-PRF scaffold combined with triple antibiotic was shown to substantially reduce live bacteria up to about 92%. In a research by Kour et al. [56], the anti-microbial effect of I-PRF against two periodontal pathogens (Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans) was compared with PRP and PRF. The anti-microbial assay by disc diffusion method revealed that, in the case of Porphyromonas gingivalis, I-PRF had the widest zone of inhibition, which was significantly wider than that of PRP and PRF (P < 0.05). However, in the case of Aggregatibacter actinomycetemcomitans, PRP showed wider zone of inhibition, which was significantly wider than that of PRF and I-PRF (P < 0.05). Karde et al. [24] compared the anti-microbial property of I-PRF with other platelet concentrates, such as PRF and PRP obtained from chronic generalized marginal gingivitis patients. It was concluded that I-PRF has maximum anti-microbial efficacy compared with other platelet concentrates, therefore, demonstrating a superior regenerative potential.

In brief, I-PRF application showed favorable anti-microbial efficacy against both periodontal and cariogenic pathogens.
3.5. Periodontal regeneration

A total of five in vitro studies [11,32,45,57,58], one animal study [43], one case report [12], and six clinical studies [17,25,59–62] have investigated the influence of I-PRF on periodontal regeneration so far (Fig. 3).

3.5.1. In vitro studies on periodontal regeneration

In 2017, Wang et al. [11] compared the effect of I-PRF and PRP on human gingival fibroblasts cultured on titanium implant surfaces in an in vitro setting. According to the authors, both I-PRF and PRP showed excellent gingival fibroblast viability and biocompatibility, and increased migration, spreading, and surface area on tissue culture plastic and pickled titanium, but not acid-etching. I-PRF showed significantly higher transforming growth factor beta (TGF)-β, PDGF, messenger ribonucleic acid (mRNA), fibropectin, and Collagen type I compared with PRP. In 2020, Fujioka-Kobayashi et al. [45] compared the regenerative potential of I-PRF and concentrated platelet-rich fibrin (C-PRF) on human gingival fibroblasts. They reported a significant increase in growth factor release for the C-PRF obtained from the buffy coat layer following higher centrifugation protocols compared to the standard I-PRF. Additionally, it was shown that C-PRF had significantly higher gingival fibroblast migration, proliferation, gene expression, and collagen I synthesis. In another in vitro study in 2020, lozon et al. [57] studied the effect of I-PRF on proliferation and osteogenic differentiation of gingival mesenchymal stem cells. The authors reported that while the 5% I-PRF culture significantly increased cell proliferation after seven days, 10% I-PRF significantly reduced cell proliferation. Reduced expression of all osteogenic genes was reported for gingival mesenchymal stem cells in I-PRF cultures. Recently, Zheng et al. [58] and Thanasrisueb Wong et al. [32] evaluated the effect of I-PRF on human periodontal ligament cells in their in vitro research. Both studies reported enhanced cell proliferation, migration, biological differentiation, and mineralization following conditioning with I-PRF.

3.5.2. Animal studies on periodontal regeneration

In the only animal study carried out on periodontal regeneration capacity of I-PRF, Aydinyurt et al. [43] inspected the efficacy of I-PRF in rats with experimental periodontitis. The researchers claimed positive effects of subgingival I-PRF injection on periodontitis by decreasing bone loss and regulating the inflammatory process. However, according to the authors, the combination of I-PRF injection with scaling and root planning (SRP) did not yield any significant contribution to the treatment of periodontitis.

3.5.3. Case reports and clinical studies on periodontal regeneration

In the case study presented by Lei et al. [12], the effect of advanced platelet-rich fibrin (A-PRF)/I-PRF combined with bone grafts was investigated for guided bone regeneration in a patient with severe chronic periodontitis. Significant alveolar bone gains and reduced pocket depths were reported at the treatment site following a 15-month follow-up. Six clinical studies have so far evaluated the effect of I-PRF therapy on periodontal parameters. In 2019, Izol and Öner [17] examined the effect of I-PRF on root coverage in free gingival graft (FGG) surgery and reported that root surface biomodification with I-PRF promotes root coverage and increases new gingival tissue formation. In another investigation in 2020, Turer et al. [25] researched whether connective tissue graft combined with I-PRF affected root coverage of gingival recessions. The addition of I-PRF to the graft material resulted in a significant reduction of recession depth and an increase in keratinized tissue height compared to the connective tissue graft alone. However, no significant differences were reported between pocket depths, clinical attachment level, recession width, gingival thickness, mean and complete root coverage indices by both periodontal treatments after six months. Vučković et al. [59] compared SRP and I-PRF-added SRP in patients diagnosed with chronic periodontitis. Contrary to the findings of Aydinyurt et al.'s animal study [43], this study revealed that I-PRF combined with SRP significantly improved clinical attachment level, gingival margin level, probing pocket depth, and bleeding on probing indices compared to SRP alone. In another study, Ozsagir et al. [60] compared the effect of I-PRF alone and I-PRF combined with microneedling on gingival thickness and keratinized tissue width in thin periodontal phenotypes. The authors reported that both I-PRF and microneedling-combined I-PRF increased the gingival thickness with the increase being significantly greater in the combined therapy. Kapa et al. [61] have recently evaluated the efficacy of sticky bone with I-PRF coated collagen membrane along with the utilization of coronally advanced flap in the treatment of 16 patients with isolated Miller’s Class I or II recession in the maxillary esthetic zone over a period of six months. In this regard, radiographic evaluation by CBCT showed that the labial plate and gingival thickness increased in all cases over that period. Additionally, clinical evaluation demonstrated that all treated cases achieved an increase in gingival thickness and keratinized tissue width as well as a decrease in periodontal pocket and recession depths. Besides, 12 out of 16 treated cases achieved completed root coverage. Albonni et al. [62] have recently assessed the clinical efficacy of administration of I-PRF as an adjunctive subgingival irrigation of SRP in 15 patients suffering from periodontitis with bilateral periodontal pockets (>5 mm) on a minimum of two teeth on each side. Clinical evaluation regarding common periodontal parameters over a period of three months showed no significant differences regarding the adjunctive administration of I-PRF along with the utilization of SRP (P > 0.05).

In conclusion, while the in vitro studies [11,32,45,57,58] showed promising results in terms of periodontal regeneration potential of I-PRF, there is a lack of consensus on the effect of I-PRF on periodontal parameters evaluated in in vivo settings.

3.6. Bone regeneration

A total of 21 studies have so far evaluated the effect of I-PRF on bone regeneration in relation to the oral and maxillofacial structures. These studies are classified under the following subheadings: Seven in vitro studies [13,30,37,63–66], three animal studies [29,67,68], three case reports [50,69,70], and nine clinical studies [25,34,36–38,69–72] (Fig. 3).

3.6.1. In vitro studies on bone regeneration

A total of seven in vitro studies have evaluated I-PRF effects on bone regeneration using human osteoblasts. Wang et al.’s in vitro study [63] on PRP and I-PRF in 2018 was the first research on the effect of I-PRF cultivation on primary human osteoblasts’ proliferation, viability, differentiation, mineralization adhesion, and migration. The authors reported that I-PRF resulted in a 3-fold raise in human osteoblast migration in comparison with PRP. In addition, a significantly greater proliferation was induced by I-PRF compared to PRP on the third and fifth day; however, no differences were detected in terms of cell attachment. Furthermore, human osteoblast mineralization by ALP Assay and Alizarin red staining showed significantly higher alizarin red staining at 14 days and ALP staining at
seven days for I-PRF. In an in vitro study in 2018, Dohle et al. [30] assessed the effect of I-PRF on human primary osteoblasts in an in vitro co-culture, and found lumina and microvesSEL-like configurations within the I-PRF medium one week following the culture. In 2019, Fernández-Medina et al. [64] compared I-PRF with the other clinical-grade platelet-rich hemoderivatives (A-PRF, pure platelet-rich plasma (P-PRP), leukocyte and platelet-rich plasma (l-PRP)) on osteoblast behavior. The human osteoblast mineralization by Ali-zarin red staining at day 21 demonstrated superior mineralization properties for I-PRF compared to P-PRP, A-PRF, and l-PRF. However, an I-PRF concentration of > 60% had a detrimental effect on cell viability, metabolic activity, and migration assay. In another in-vitro research by Kyak et al. [13] in 2020, the effect of an allogeneic bone substitute material (ABSM) and a xenogeneic bone substitute mate-

rals (XBSM) with and without I-PRF was assessed on cell char-

acteristics of human osteoblasts. As reported by the authors, the human osteoblast proliferation, attachment, viability, and expression of differentiation and proliferation markers significantly increased in the I-PRF-added bone substitute material (BSM) compared to BSM without I-PRF. Nevertheless, XBSM combined with I-PRF showed inferior results compared to the allogeneic bone substitute-structure and ABSM-I-PRF in almost all parameters. To recapitulate, the authors suggested that the use of I-PRF in combination with BSM could enhance the healing process of human osteoblasts. Recently, Kyak et al. [37] investigated the effect of bovine bone substitute materials (XBSM) combined with I-PRF on the metabolic activity and viability of human osteoblasts. Their findings revealed an increased viability, improved alkaline phosphatase and bone morphogenetic protein 2 expression at earlier phases, and osteonectin expression at later periods when I-PRF was combined with XBSM. In another recent study, Murdiastuti et al. [65] compared the effect of I-PRF and freeze-dried homologous PRP on human osteoblasts and reported that the I-PRF group had the highest number of osteocytes. In 2021, Shah et al. [66] in a study evaluating the effect of osteoblast-like cell line (MG-63) coating of I-PRF on titanium disks, revealed that I-PRF coating of titanium disks resulted in increased proliferation, mineralization, and alkaline phosphatase production.

3.6.2. Animal studies on bone regeneration

Up to now, three animal studies have evaluated the regenerative effects of I-PRF on inducing bone formation. In two studies on I-PRF-induced maxillary bone regeneration, Mu et al. [29,67] assessed the effect of I-PRF modified with gelatin nanoparticles (GNPs) and DBBM for rabbit sinus augmentation. The authors found significantly greater bone creation surrounding the raised Schneiderian mem-

brane for the sinus cavities treated with GNPs-I-PRF hydrogels compared with GNPs gels and the control [67]. Similarly, Mu et al. [29] reported that I-PRF combined with DBBM led to new bone creation in the Schneiderian membrane zone and the basal bone wall. At four weeks, the group treated with GNPs-I-PRF was reported to have significantly higher values for the number of trabecular bones and new bone formation volume [67]. However, lower trabecular separation was reported for GNPs-I-PRF compared with control groups and GNPs. It was concluded that bone resorption was significantly decreased by treating the sinus cavities with GNPs-I-PRF hydrogels [67]. Moreover, Mu et al. [29] concluded that despite the augmented vascular formation and bone remodeling at the early stages of healing using I-PRF incorporated DBBM, the bone volume did not significantly change in a long-term period. Recently, Yuan et al. [68] evaluated the angiogenesis, osteogenesis, and bone mass reduction using deproteinized bovine bone mineral (DBBM), gelatin nanoparticles (GNPs), and I-PRF in male beagle dogs. The researchers showed that the GNPs combined with I-PRF significantly enhanced angiogenesis and woven bone, and reduced osteoclast activity in extraction sockets 2 weeks following the operation. Significant cor-

ticalization on the alveolar ridge crest was also reported at 8 weeks post-operation.

3.6.3. Case reports on bone regeneration

To date, three case studies [50,69,70] have evaluated the oral and maxillofacial bone regeneration capacities of bone graft combined with I-PRF. Of these case studies, one assessed bone gain in the maxilla, and the other two examined mandibles. In a case study by Chenevez et al. [69], carried out in 2017, a combination of bone graft material, I-PRF, and A-PRF was used to examine the potential for ridge augmentation in maxillary frontal area. A four-month follow-up with clinical and cone-beam computed tomography (CBCT) scan examinations revealed new bone formation suitable for dental implant placement in the 18-year-old male patient who suffered from tooth 11 expulsion and alveolar ridge partial fracture. In another case reported in 2018, Lorenz et al. [70] investigated the effect of customized titanium mesh filled with XBSM in combination with I-PRF and A-PRF to restore a severe mandibular defect caused by tumor in a 61-year-old head and neck cancer patient. The 8-month clinical and histopathological examination of extracted bone biopsies obtained from the former squamous cell carcinoma patient showed new bone formation in the augmented site. In 2020, Thanasri-suebwong et al. [50] evaluated a combination of I-PRF, particulate bone graft, and leukocyte and platelet-rich fibrin (l-PRF) for horizontal and vertical bone augmentation before implant placement in a patient with severe bone defect in posterior mandible. A 9-month clinical evaluation showed favorable results in bone quality and quantity of the graft site both vertically and horizontally which was appropriate for implant placement.

In summary, all three case reports [50,69,70] assessing the effect of bone graft in combination with A-PRF, I-PRF, and l-PRF sub-

stantiated that infiltration with PRF improved the quality of the bone graft material in both maxilla and mandible.

3.6.4. Clinical studies on bone regeneration

Nine clinical studies [27,36,38–40,71–74] have so far investigated oral and maxillofacial bone regeneration following I-PRF application. In a retrospective clinical study conducted in 2019, Gülsen and De-recci [71] examined bone formation following sinus floor elevation with I-PRF carried by collagen plugs. Radiographic evaluation by CBCT showed significant mesial and distal bone formation in the inserted implants after six months (P < 0.05). New bone regeneration was detected in sinus floor augmentation using I-PRF, which was carried via collagen plugs. In another retrospective clinical study in 2020, Valladão et al. [36] investigated the combination of I-PRF/l-

PRF, bone grafts, and membranes for bone augmentation in patients with horizontal or vertical bone defects needing dental implants. Radiographic evaluation by CBCT following 7.5 ± 1.0 months showed that the combination of bone graft with PRF significantly increased bone thickness and height following treatment (P < 0.001 and P < 0.005, respectively). In a prospective clinical study conducted in 2020, Rao et al. [27] evaluated the effect of A-PRF and I-PRF in combination with iliac bone graft in patients with complete uni-lateral cleft alveolus. Radiographic evaluation by Bergland criteria and periodontal parameters assessment by periodontal pocket depth (PPD) and mobility indices at third and sixth month revealed more clinically favorable results in the iliac bone graft + A-PRF + I-PRF
group compared to the patients who only received an iliac bone graft. Generally, all three clinical studies verified the positive effects of injectable PRF application in bone gain as an adjunct to bone graft materials in both maxilla and mandible. In a clinical study by Irdem et al. [38] in 2021, the effectiveness of the DBBM combined with liquid PRF was assessed on new bone formation in patients with bilateral maxillary sinus atrophy in need of maxillary sinus augmentation. It was found that the combination of DBBM with liquid-PRF did not significantly affect new bone formation. Işık et al. [39] compared the effectiveness of particulate allograft combined with I-PRF and autogenous block bone graft on vertical bone augmentation. It was reported that while the particulate allograft material combined with I-PRF is rich in osteoblast cells compared to autogenous block bone graft, it resulted in similar vertical bone gain. In another study by Işık and colleagues [72] on guided bone regeneration simultaneous with implant placement, greater augmentation thickness as well as less marginal bone loss was detected for the bovine-derived xenograft mixed with liquid PRF compared to the xenograft only group.

Thanasut et al. [40] inspected the efficacy of autologous ABSM with and without liquid and solid PRF in bone regeneration in alveolar clefts and found no significant differences in regenerated bone volume and density between autologous ABSM alone and combined with liquid PRF. In a digital workflow for guided bone regeneration using XBSM and I-PRF inspected by Wang et al. [73], a positive effect on the labial thickness of hard tissue was observed with XBSM and I-PRF. Moreover, the authors also investigated the effect of different guided bone regeneration procedures on graft contour in lateral ridge augmentation and found that labial graft thickness was greater when XBSM was combined with I-PRF [74].

In brief, all of the aforementioned in vitro and in vivo studies showed promising results in terms of bone regeneration following the administration of I-PRF. Only Fernández-Medina et al. [64] reported detrimental effects in cell viability, metabolic activity, and migration assay when the concentration of I-PRF was above 60%.

3.7. Cartilage regeneration

So far, seven clinical studies [18,41,75–79] have investigated the impact of I-PRF application on cartilage regeneration in relation to oral and maxillofacial structures (Fig. 3).

3.7.1. Clinical studies on cartilage regeneration

In 2018, Albilia et al. [18] assessed the effect of I-PRF in patients suffering from temporomandibular joint (TMJ) dysfunction and pain. After eight weeks, and at 3-, 6-, and 12-month follow-ups, the investigators noticed a significant decline in pain scores for responders to intra-articular injections of liquid PRF due to possible remodeling of damaged cartilage surfaces. In a study in 2019, Gode et al. [41] investigated the I-PRF effects on diced cartilage used for rhinoplasty dorsal camouflagé. Cartilage thickness measurements at one week and three months postoperative verified the success of I-PRF in decreasing the diced cartilage resorption rate on nasal dorsum by either increasing the viability or maintaining its form. In 2020, Yuce and Komerik [75] compared the effect of I-PRF intra-articular infiltration with that of hyaluronic acid (HA) in patients suffering from TMJ dysfunction and pain. Based on the findings, pain values significantly decreased in the arthrocentesis group combined with I-PRF in comparison to the HA-combined arthrocentesis at nine-month follow-up. Furthermore, maximum mouth opening values in the arthrocentesis group combined with the I-PRF were significantly greater compared to the arthrocentesis group combined with HA at 9 and 12 months postoperatively. In 2021, Karadayi et al. [76] compared the effectiveness of arthrocentesis in combination or without I-PRF for TMJ internal derangement. After three months of follow-up, the authors reported a substantial enhancement inVAS and Helkimo clinical dysfunction scores, as well as the maximum incisal opening of the patients treated with I-PRF-combined arthrocentesis compared to arthrocentesis alone. Recently, Bera et al. [78] assessed the effect of arthrocentesis with intra-articular I-PRF injection in the treatment of TMJ osteoarthritis. It was found that while adding I-PRF to arthrocentesis did not alleviate TMJ pain following 6 months of treatment, its repeated injections did positively impact maximal mouth opening. In another study, Ghoneim et al. [77] also compared the efficiency of arthrocentesis with and without intra-articular I-PRF injection in treating TMJ disc displacement with reduction. The authors found significant reduction in click sound and pain intensity and increase in lateral movement and maximal mouth opening when I-PRF was injected. Torul and colleagues [79] examined the effectiveness of I-PRF in the treatment of Wilkes stage III internal derangement and reported that injecting i-PRF following arthrocentesis is more effective than arthrocentesis alone or in combination with hyaluronic acid in the short period.

In conclusion, all seven studies [18,41,75–79] showed favorable trends with regards to cartilage regeneration and temporomandibular disorder treatment following I-PRF therapy.

3.8. Orthodontic tooth movement

To date, five clinical studies [15,42,80–82] have inspected the effect of I-PRF therapy on orthodontic tooth movement (Fig. 3).

3.8.1. Clinical studies on orthodontic tooth movement

In 2020, Karakasali and Erdur [15] assessed the efficiency of I-PRF injection in the retraction rate of the maxillary incisors. The study concluded the movements of incisors were significantly greater in the I-PRF group compared with the control group at all time intervals (P < 0.05). In another clinical research by Zeitounlouian et al. [80], the maxillary canine retraction was evaluated following I-PRF therapy. The authors reported a significantly greater canine retraction at the I-PRF site compared with the control site, which was observed only in the second month. Recently, Erdur et al. [81] carried out a research to examine the efficiency of canine tooth movement acceleration following I-PRF treatment and to investigate levels of interleukin 1 beta (IL-1β), matrix metalloproteinase-8 (MMP-8), receptor activator of nuclear factor kappa-B ligand (RANKL), and osteoprotegerin (OPG) in the gingival crevicular fluid during orthodontic treatment. The authors found a significantly increased rate of tooth movement for I-PRF, verified by the stimulation in the inflammatory cytokine levels (P < 0.001). In a recent study, Karci et al. [42] compared piezocision with I-PRF injection in tooth movement during canine distalization. It was concluded that while both applications accelerate tooth movement, they do not differ in terms of amount, speed, duration of tooth movement, or periodontal parameters.

In summary, these four clinical studies confirmed the favorable effects of I-PRF on accelerating maxillary anterior tooth movement during orthodontic treatment.

Furthermore, in another recent study by Zeitounlouian et al. [82] on the efficacy of I-PRF in preserving bone and preventing root resorption in orthodontic patients, it was found that I-PRF is not effective in preventing canine root resorption during canine retraction.
In addition, the investigators showed that the prevalence of dehiscence and fenestration was not reduced by I-PRF.

3.9. Pulp regeneration and drug delivery

Up to now, three in vitro studies [19,31,83] have evaluated the pulp regeneration and drug delivery potential of I-PRF.

3.9.1. In vitro studies on pulp regeneration and drug delivery

In 2019, Chai et al. [19] compared the cellular regenerative capacity of human dental pulp cells when cultivated with PRP or I-PRF. It was found that I-PRF substantially increases the migration of dental pulp cells compared to PRP. Moreover, a significantly higher alkaline phosphatase activity and expression of genes coding Collagen type I, Dentin matrix acidic phosphoprotein 1 (DMP-1), and Dentin sialophosphoprotein (DSP) were prompted by I-PRF when compared with PRP. In conclusion, it was suggested that I-PRF possesses a regenerative potential to stimulate reparative dentin and odontoblastic differentiation in human dental pulp cells. In 2020, Rafiee et al. [83] evaluated the in vitro drug delivery profile of two differently prepared Triple Antibiotic-containing I-PRF-based scaffolds for pulp regeneration. The results of I-PRF combined with Triple Antibiotic Mixture (metronidazole (MET), ciprofloxacin (CIP), minocycline (MINO)) verified a burst release within the initial 24 h which sustained for up to 14 days. However, I-PRF combined with Triple Antibiotic Mixture by integration did not show the appropriate characteristics for the sustainable release of the antibiotics. In another drug delivery study by Rafiee et al. [31] in 2020, the efficacy of I-PRF scaffold carrying triple antibiotic mixture was evaluated against Enterococcus faecalis and Actinomyces naeslundii biofilms in an infected root canal model. It was found that delivering Triple Antibiotic Mixture via I-PRF was the most efficient in reducing bacterial metabolic activities when compared with other delivery methods.

In summary, using the 700 rpm for 3 min protocol for I-PRF preparation, all of the studies verified promising results for pulp regeneration and drug delivery potential of I-PRF scaffolds except when combined with Triple Antibiotic Mixture by integration.

4. Future prospects

Although this injectable material is yet to be known by clinicians, there is growing evidence supporting its regenerative potentials. Consequently, to verify the applicability of I-PRF in regenerative procedures, many more intricate and high-quality randomized controlled trials (RCTs) should be performed to demonstrate whether this intervention would improve the clinical outcomes and satisfy the involved clinicians and patients in real clinical situations. Besides, in spite of the limited evidence regarding the effectiveness of I-PRF in other regenerative procedures, the authors believe that the feasibility of I-PRF should be further investigated through rigorous RCTs. In this regard, researchers have recently suggested the possibility of using I-PRF as a promising therapeutic in the treatment of oral mucositis [84].

Very recently, researchers have demonstrated a novel harvesting technique to isolate a concentrated liquid PRF directly from the buffy coat layer superior to the red blood cell layer following l-PRF protocols (2700 rpm for 12 min) [45,49]. They called this obtained liquid PRF as concentrated PRF (C-PRF). In other words, liquid PRF, which is created by a hard spin of blood lacking anticoagulants, forms an upper platelet-poor plasma (PPP) layer, a buffy coat layer (regarded as C-PRF), and the red blood cell layer [87]. In this regard, the findings by Miron et al. have shown that while conventional I-PRF techniques concentrate platelets by 2–3-fold and leukocyte by 1.5-fold from the 1- to 1.2-ml plasma layer compared to baseline concentrations in whole blood, harvesting 0.3–0.5 ml of C-PRF within the buffy coat can increase platelets and leukocytes yield over 10-fold [49].

As discussed earlier, the administration of I-PRF has recently caught extreme attention due to its regenerative, anti-inflammatory, and antibacterial potentials. Furthermore, I-PRF exhibit high cellular contain, growth factors, and cytokines [85]. Since this biomaterial is applied directly to the treatment site, it has high bioavailability. This property makes the growth factors and cytokines affect the treatment site more effectively. In addition, the gradual release of its growth factors and cytokines is another advantage of I-PRF which can significantly regenerate tissues over time [85]. However, I-PRF degrade within a two-week period that limits their long-term application [86]. In order to overcome the aforementioned disadvantage of I-PRF, Fujioka-Kobayashi et al. [86] have lately developed a novel type of PRF called albumin-PRF (Alb-PRF), which is created by combining the liquid PRF layer with the heated albumin layer to form a long-lasting biomaterial capable of releasing growth factors and cytokines for up to 4 months. In fact, it has been shown that heating the platelet-poor plasma forms an albumin gel which generates Alb-PRF when it is mixed back with C-PRF [87]. The lower degradation rate of Alb-PRF in comparison with I-PRF, makes Alb-PRF a more stable biomaterial for longer periods [86]. Since there is limited evidence regarding the prospective relevance of Alb-PRF in regenerative dentistry, the authors deem it necessary that many more preclinical/clinical studies be conducted in order to prove the favorable characteristics of this biomaterial in regenerative procedures. Pre-clinical studies have shown that C-PRF demonstrates an anti-inflammatory activity in murine macrophages and mesenchymal cells, and has a potent inhibitory effect on osteoclastogenesis [87,88]. Although a massive increase in platelets and leukocytes count has been reported for C-PRF compared to the conventional I-PRF [49], no clinical study has investigated the supplementary regenerative value of C-PRF in oral and maxillofacial structures compared to the traditional I-PRF protocol. Thus, further research is suggested to verify the proposed regenerative potential of this novel C-PRF in clinical settings.

5. Conclusion

One of the main goals of platelet concentrate therapy is to provide a source of growth factors to promote tissue regeneration. Current literature confirms the ability of I-PRF to fulfill this goal and approves the feasibility of I-PRF application as a promising regenerative adjunct to dental procedures. Among the favorable effects of I-PRF are reducing the bacterial count, increasing the amount of growth factors inside the wound, helping with wound healing, and accelerating orthodontic tooth movement as well as periodontal, bone, cartilage, and pulp regeneration. There is a lack of consensus on the effect of I-PRF on periodontal parameters evaluated in vivo settings. Further randomized clinical trials are recommended to validate the proposed benefits.
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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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