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Injectable platelet-rich fibrin for the treatment of periodontal intrabony defects: A systematic review

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Systematic Review

Abstract:

Bone regeneration in periodontal defects is essential for tooth preservation and alveolar health. Among the materials most frequently used for regenerative procedures is sticky bone, a combination of injectable platelet-rich fibrin (i-PRF) and a bone graft. This combination, widely applied in periodontology, may improve clinical and radiographic parameters; however, solid clinical evidence remains limited. This systematic review aimed to evaluate the current evidence regarding the clinical and radiographic effectiveness of i-PRF as an adjunct in bone regeneration procedures compared with other biomaterials or conventional PRF. Randomized Clinical Trials (RCTs) evaluating the use of i-PRF or sticky bone compared with isolated bone grafts (demineralized freeze-dried bone allograft, hydroxyapatite, and xenografts) or conventional PRF were included. The search was conducted in PubMed/MEDLINE, Scopus, Web of Science, Embase, the Cochrane Library, and additional sources up to October 2025. Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool. Data synthesis was performed narratively, grouping studies according to intervention type and assessing outcomes. Five studies were included from an initial 646 records, totaling 135 participants. Four of the five studies (80%) demonstrated statistically superior clinical (Probing pocket depth reduction, clinical attachment level gain) and radiographic (bone fill) outcomes for the i-PRF group. One study (20%) found no significant differences between groups. Three studies also reported notable improvements in graft handling (sticky bone formation) when i-PRF was used. Current evidence suggests a potential benefit of i-PRF in optimizing bone regeneration outcomes; however, methodological heterogeneity and the limited number of RCTs constrain the formulation of strong clinical recommendations. This review was registered in the PROSPERO database (International Prospective Register of Systematic Reviews).

Keywords: platelet-rich fibrin, periodontitis, bone regeneration, alveolar bone loss, injectable platelet-rich fibrin, systematic review

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Introduction

Periodontitis, according to the current classification of periodontal diseases, is characterized as a chronic, multifactorial, inflammatory disease, influenced by environmental risk factors such as harmful habits and systemic conditions[1-3]. As the disease progresses, it compromises the supporting periodontium, which includes the periodontal ligament, alveolar bone, and root cementum, ultimately leading to the formation of intrabony defects and, in advanced stages, tooth loss[4].

Periodontal intrabony defects are traditionally categorized by the number of remaining bony walls (one to three). It is widely accepted that regenerative potential is directly related to the amount of preserved bone tissue: more contained defects, such as three-wall defects, generally show a better prognosis and greater predictability in periodontal regenerative procedures[5,6]. For the management of these defects, guided bone regeneration (GBR) is an established surgical approach that aims to achieve controlled reconstruction of bone-loss sites[7]. The core principle of GBR is selective cell exclusion, in which barrier membranes block the migration and proliferation of epithelial and connective tissue cells into the defect. This preserves space and allows slower-growing cells, specifically osteoblasts derived from surrounding bones, to repopulate the site, promoting new bone deposition and predictable healing[8].

Bone healing is an inherently complex biological process that begins with clot formation and progresses through sequential phases of inflammation, proliferation, maturation, and bone remodeling[9]. The outcome of this process may lead to two distinct biological responses: repair or regeneration. Repair is defined by the replacement of lost tissue with nonspecific fibrous connective tissue, frequently resulting in fibrosis and scar formation[10,11]. In contrast, regeneration represents the ideal biological outcome, characterized by the complete replacement of damaged tissue with new tissue that is morphologically and functionally identical to the original, thereby restoring full architecture and function[11].

To enhance bone formation and maximize regenerative potential, GBR often employs biomaterials. These are defined as natural or synthetic substances developed to interact with biological systems to improve, replace, or optimize tissue or organ

function[12]. Biomaterials are commonly classified according to their origin autogenous, allogeneic, xenogeneic, alloplastic, or synthetic[13]. They may also be categorized by their physical and absorptive properties, specifically as inorganic/mineralized or organic/demineralized, and by whether they are absorbable or non-absorbable by the body[14].

Among biomaterials, autogenous bone grafts are considered the gold standard for bone regeneration because they carry no immunological risk and provide all three essential biological properties: osteogenesis, osteoinduction, and osteoconduction[15]. However, the need for a second surgical site is inherently associated with significant postoperative morbidity, a risk of donor-site complications, volumetric resorption, and limited availability. These disadvantages drive the search for alternative bone substitutes that minimize risks while optimizing regenerative outcomes[16].

The need to reduce morbidity associated with autogenous grafts while enhancing regenerative potential has encouraged the development of adjunctive biomaterials. In this context, platelet concentrates such as Platelet-Rich Fibrin (PRF) have emerged. As a second-generation autologous product, PRF consists of a tridimensional fibrin matrix capable of sustaining a gradual release of several growth factors. Among the most relevant bioactive molecules are platelet-derived growth factors (PDGF), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF), all of which modulate healing and angiogenesis[17-19].

Among the various formulations of platelet concentrates, injectable platelet-rich fibrin (i-PRF) stands out. Characterized by its liquid or non-coagulated state, i-PRF represents an evolution of the initial PRF concept[20]. It is obtained through the low-speed centrifugation concept (LSCC), which optimizes cellular distribution and maintains greater viability of stem cells and leukocytes. Its main advantage lies in its pre-coagulation state, allowing it to be injected directly into tissues or, more importantly for bone regeneration, mixed with graft granules to create a highly malleable composite known as “sticky bone”[21].

In summary, the regenerative potential and handling properties of i-PRF position it as a promising biological adjunct in GBR. However, despite favorable in vitro evidence and clinical reports, comparisons with different graft biomaterials and with conventional

PRF still require stronger consolidation in the literature. Therefore, the objective of this systematic review is to critically analyze and synthesize the available evidence to answer the following PICO question: What is the clinical and radiographic effectiveness of Injectable Platelet-Rich Fibrin (i-PRF) in the bone regeneration of periodontal defects compared with other graft biomaterials or conventional PRF?

Materials & Methods

Protocol and Registration

The present study was designed as a systematic review of the literature. The review protocol was prospectively submitted under the registration number (CRD420251163103) in the PROSPERO platform (International Prospective Register of Systematic Reviews). This review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2020) guidelines.

Research Question and Eligibility Criteria (PICO)

The research question was formulated according to the PICO framework, as shown in Table 1: "Comparative Efficacy of Injectable Platelet-Rich Fibrin (i-PRF) in Bone Regeneration Techniques: A Systematic Review." The PICO criteria are presented in Table 1.

Table 1 – PICO Criteria of the Research Question

PICO Component	Description
Population (P)	Patients (or sites) undergoing bone regeneration techniques in intrabony defects.
Intervention (I)	Use of Injectable Platelet-Rich Fibrin (i-PRF) as an adjunct or mixed with grafts.
Comparator (C)	Other biomaterials (e.g., bone graft alone—autogenous, allogeneic, xenogeneic, or alloplastic) are used alone or with other PRF formulations (e.g., L-PRF).
Outcome (O)	Clinical and radiographic efficacy (e.g., gain in bone height/volume, bone density, defect fill, PPD/CAL).

Inclusion Criteria: Randomized Controlled Trials (RCTs), either split-mouth or parallel-group design, in humans.

Exclusion Criteria: In vitro studies, animal studies, case reports, case series, letters to the editor, opinion articles, and systematic or narrative reviews.

Search Sources

The search strategy was developed and adapted for each database, employing a combination of controlled terms (Medical Subject Headings – MeSH) and free terms, with the aim of maximizing sensitivity. The search was structured into three main concepts, exemplified in the PubMed search: The first concept (Intervention) included terms related to Injectable Platelet-Rich Fibrin (e.g., “Injectable Platelet-Rich Fibrin,” “i-PRF,” “Sticky Bone”). The second concept (Population, Comparison, and Outcome) encompassed broad terms associated with periodontal bone regeneration and its components (e.g., “intrabony defects,” “periodontitis,” “Guided Bone Regeneration,” “Bone Grafts,” “Allografts,” “Wound Healing”). Finally, the third concept applied a high-sensitivity filter specific for identifying Randomized Clinical Trials (RCTs). The complete and detailed search strategy used for each database is fully presented in the Supplementary Material (Appendix 1).

Search Strategy

Tailored search strategies were applied to each of the selected databases: EMBASE, PubMed/MEDLINE, SCOPUS, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). Additionally, gray literature searches were conducted in Google Scholar, OpenGrey, and MedNar. All electronic searches were completed up to October 2025. The reference manager used was EndNote Web®.

Article Selection Process and Data Extraction

The selection process was carried out independently by two reviewers (ALDC and CAS) in two phases, with the help of the Rayyan platform: (1) Initial screening of titles and abstracts; and (2) Full-text analysis of the preselected articles. Any disagreements between reviewers were resolved by consensus or by consulting a third reviewer (MPL). The selection process was detailed using a PRISMA Flowchart. A standardized spreadsheet in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) was

used.

Data extraction was performed independently by the same two reviewers using standardized forms. Extracted data included: Identification (Authors, year of publication, and DOI), methodology (parallel/split-mouth, number of patients, age and sex), details of the intervention (Test Group: i-PRF preparation protocol/centrifugation force, time, tube type/type of combined graft, mixing ratio, and final form of the biomaterial injection or "sticky bone") and comparator (Control Group: description of the treatment), defect details (type and location of the bone defect), outcomes (clinical and radiographic parameters assessed), results (follow-up period, main quantitative findings, and authors' conclusions), and other data regarding declared conflicts of interest.

Risk of Bias Assessment

The methodological quality and risk of bias of the included RCTs were independently assessed by two reviewers using the revised Cochrane Risk of Bias tool for Randomized Trials (RoB 2.0), with the aid of the Excel tool ROB2_IRPG_beta_v9.xlsm. Disagreements were resolved by consensus.

The tool evaluates five domains:

1. Bias arising from the randomization process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in the measurement of outcomes
5. Bias in the selection of the reported result

The overall judgment for each study was classified as "Low Risk of Bias," "Some Concerns," or "High Risk of Bias."

Data Synthesis (Qualitative Analysis – Without Meta-analysis)

A qualitative (descriptive) synthesis of the extracted results was planned, following the SWiM (Synthesis Without Meta-analysis) recommendations, due to the expected clinical and methodological heterogeneity among studies, such as variations in

i-PRF centrifugation protocols, types of grafts used, defect locations, and outcome measurement methods. A meta-analysis (quantitative statistical analysis) was therefore deemed inappropriate. Limitations will be addressed in the results section.

The narrative synthesis was structured as follows:

1. Outcome Grouping: Results will be grouped and presented separately for each predefined primary and secondary outcome.

2. Effect Reporting: For each outcome, both the direction and magnitude of the effect observed in the primary studies will be reported, along with the consistency of findings across RCTs.

3. Certainty Assessment: Findings will be interpreted in light of the Risk of Bias assessment (RoB 2.0), giving greater weight to evidence from RCTs classified as "Low Risk of Bias."

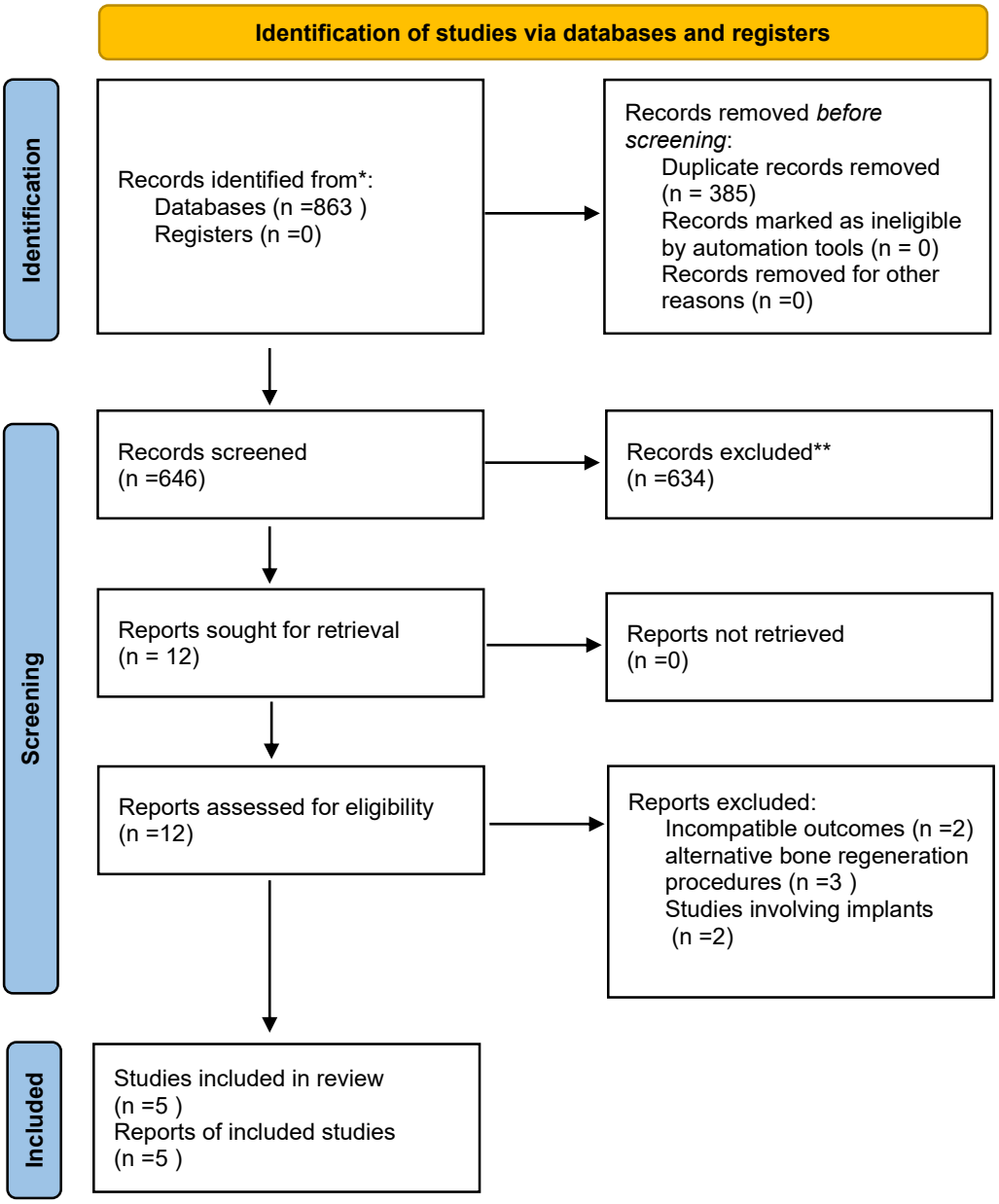
4. Heterogeneity Exploration: A detailed discussion will address the potential sources of heterogeneity, such as differences in intervention concentrations, treatment duration, follow-up time, or population characteristics.

Results

Study Selection and PRISMA Flow

The initial electronic search and gray literature screening yielded 863 articles. After removing 385 duplicates, 646 studies were screened by title and abstract, leaving 12 articles that proceeded to full-text assessment for eligibility. Ultimately, 5 studies were selected for qualitative synthesis. The main reasons for full-text exclusion were: incompatibility with the PICO population or outcomes, use of additional bone regeneration procedures, or inclusion of implant-related interventions. The complete identification and study selection process is detailed in the PRISMA Flowchart (Figure 1).

Figure 1 – Prisma flowchart



Characteristics of the Included Studies

A total of 5 studies were included in the final synthesis. Their detailed characteristics are summarized in Table 01. The total number of participants was 135 patients; although some studies reported only the number of periodontal defects treated, all of them employed a parallel-group study design.

Periodontal clinical parameters were assessed in all studies, and considerable variability was identified regarding intervention protocols, follow-up durations, and

surgical techniques. These variations were accounted for during the planning of the Narrative Synthesis (SWiM) to explore clinical and methodological heterogeneity.

Table 2 - data synthesis

Study	**Alshoiby et al., 2023**	**Chaudhary et al., 2023**	**Salem et al., 2023**	**Singh et al., 2023**	**Salama et al., 2025**
Study design	Parallel	Parallel	Split-mouth	Parallel (3 groups)	Parallel
Total subject number (male/female)	20 (5/15)	34 (18/16)	15 (not specified)	21(10/11)	30 (not specified)
Systemic condition	Excluded smokers, pregnant or lactating, and uncontrolled diabetes	Excluded smokers, pregnant or lactating, and uncontrolled diabetes	Excluded smokers, pregnant or lactating and uncontrolled diabetes	Excluded smokers, pregnant or lactating and uncontrolled diabetes	Excluded smokers, pregnant or lactating and uncontrolled diabetes
Intervention	i-PRF + DFDBA	i-PRF + Hydroxyapatite (HA)	i-PRF + DFDBA	Sticky bone (SB)	Sticky Bone (SB) + Repeated i-PRF injection
Comparator	DFDBA Alone	HA Alone	A-PRF + DFDBA	PRF + Bone graft (BG) Open flap debridement (OFD)	Xenograft (XE)
Inicial condition	Stage III periodontitis	Tree wall intrabony defects under stage III periodontitis	two or tree wall intrabony defects	two or tree wall intrabony defects	two or tree wall intrabony defects
Follow-up	9 months	9 months	6 months	12 months	9 months
Probing Pocket Depth (PPD)	i-PRF + DFDBA: 3.20 ± 0.63 DFDBA: 3.70 ± 1.16 p: 0.325	i-PRF + HA: 3.59±0.71 HA: 4.06±0.66 p: 0.054	i-PRF + DFDBA: 2±0 A-PRF + DFDBA: 2.4±0.50 p: 0.005*	SB: 3.12 ± 0.35 PRF + BG: 3.87 ± 0.35 p: 0 .012* OFD:4.80 ± 0.44	SB + i-PRF: 2.93±0.06 XE: 3.66±0.25 p:<0.001**
Clinical attachment level (CAL)	i-PRF + DFDBA: 3.40 ± 0.97 DFDBA: 4.00 ± 2.26 p: 1.000	i-PRF + HA: 3.71±0.77 HA: 4.24±0.97 p: 0.088	i-PRF + DFDBA: 6±1.51 A-PRF + DFDBA: 7.66±1.29 p: 0.003*	SB: 3.37 ± 0.51 PRF + BG: 4.37 ± 0.74 p: = 0.001 OFD: 6.40 ± 0.54	SB + i-PRF: 2.09±0.07 XE: 2.50±0.37 p:<0.001**
Radiografic linear defect depth (RLDD)	i-PRF + DFDBA: 3.58 ± 0.66 DFDBA: 3.89 ± 1.57 p: 0.572	i-PRF + HA: 5.58±1.28 HA: 6.12±1.33 p: 0.020*	i-PRF + DFDBA: 1.16±0.58 A-PRF + DFDBA: 1.4±0.60 p: 0.293	SB: 1.43 ± 0.36 PRF + BG: 3.83 ± 0.31 p: = <0 .001** OFD: 0.66 ± 0.23	SB + i-PRF: 1.72±0.12 XE: 2.12±0.45 p:<0.001**

Deproteinized Bovine-Derived Bone Mineral with 10% Collagen (DBDFA); Injectable Platelet-Rich Fibrin (I-PRF); Platelet-Rich Fibrin (PRF); Xenograft (XE); Hydroxyapatite (HA).*P<0.05, **P<0.001; Linear measurements in millimeters at the maximum follow-up.

Risk of Bias Assessment (RoB 2.0)

The summary of the Risk of Bias (RoB) evaluation is illustrated in the Risk of Bias Summary Chart (Figure 2).

Among the five studies included, one was classified as low risk of bias, one presented some concerns, and three were judged to have a high risk of bias. The main

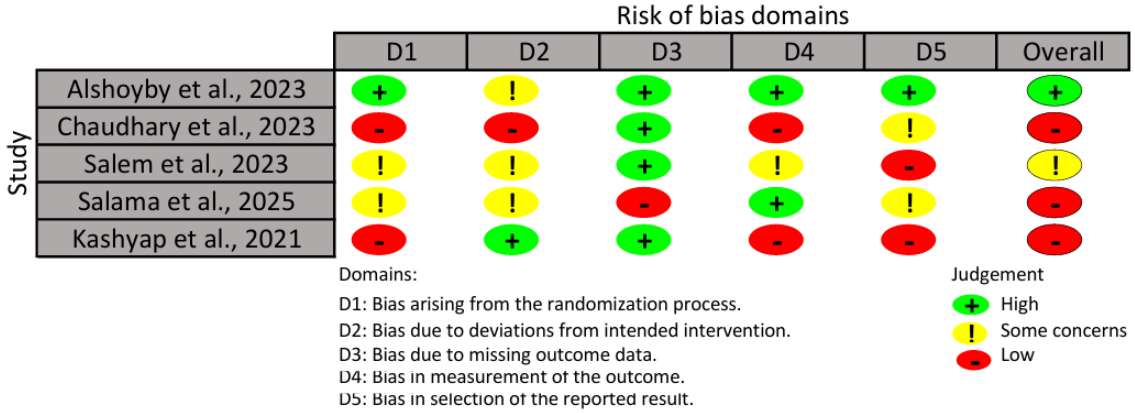
contributor to these higher-risk classifications was Domain 2 (Bias due to deviations from intended interventions), which was the most frequent reason for "High Risk" or "Some Concerns." In addition, Domain 5 (Bias in selection of the reported outcomes) showed recurrent suboptimal ratings, primarily due to the absence of pre-registered protocols and the potential omission of initially planned outcomes.

Narrative Synthesis of the Results (SWiM)

Regarding the primary outcomes, clinical attachment level (CAL) gain and probing pocket depth (PPD) reduction, most studies (4/5) reported significant improvements in periodontal parameters favoring the Intervention group (I) compared with the Comparator group (C). In terms of effect magnitude, studies showing a benefit of the intervention consistently reported greater CAL gains and deeper PPD reduction. Overall, these differences were interpreted as having small to moderate clinical relevance.

For the secondary outcomes, the risk of poorer radiographic defect resolution was, on average, 30–40% lower in the Intervention group (I) compared with the control group (C). Studies rated as having Some Concerns or High Risk of Bias tended to report larger magnitudes of bone gain in favor of the intervention, whereas low-risk studies generally presented more conservative results—although still supportive of the intervention.

Figure 2 – Risk of bias domains



Discussion

The present study aimed to systematically evaluate the effect of Injectable Platelet-Rich Fibrin (i-PRF) as an adjunct to bone grafts in the treatment of periodontal intrabony defects (IBDs). The clear methodological and clinical heterogeneity of the included Randomized Controlled Trials (RCTs)—particularly due to the diversity of biomaterials used as comparators—posed a limitation and prevented the performance of a formal meta-analysis. Despite this methodological restriction, the narrative synthesis of the five RCTs revealed a consistent pattern. The combination of i-PRF with bone grafts demonstrated a significant additional benefit in periodontal regeneration compared with the use of grafts alone. This advantage was reflected in improvements in the primary clinical and radiographic outcomes. The only study reporting divergent findings was that of Alshoiby et al. (2023), which did not identify statistically significant differences between I-PRF + DFDBA and DFDBA alone, although both groups showed significant gains compared with baseline.

The potential adjuvant effects of i-PRF in periodontal regeneration are supported by robust laboratory evidence. Its primary biological advantage is linked to the sustained and gradual release of platelet-derived growth factors—such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and insulin-like growth factor (IGF). These factors are crucial for modulating chemotaxis, differentiation, and activity of osteogenic cells, as widely demonstrated in the literature [22,23]. Additionally, in vitro studies confirm that i-PRF enhances osteoblast migration and proliferation, offering a plausible explanation for the clinical improvements observed when it is combined with bone grafts [24,25]. From a clinical standpoint, this membrane is advantageous because it facilitates the formation of the sticky bone composite. The liquid fibrin matrix increases graft particle cohesion, providing the material with greater malleability and plasticity, which optimizes adaptation to the defect morphology and minimizes graft dispersion at the surgical site [25].

The clinical applicability of i-PRF extends beyond Periodontology, reaching multiple healthcare specialties. Its bioactive potential has been explored as a therapeutic adjunct in Dermatology [26], in the management of temporomandibular

disorders[27], and in oral medicine procedures[28]. In regenerative oral surgeries, it is widely used, with positive results reported in alveolar ridge augmentation, guided bone regeneration, and the enhancement of soft- and hard-tissue healing around periodontal structures [29,30].

Despite the alignment between clinical findings and laboratory evidence, it is essential to acknowledge that this systematic review is inherently affected by the methodological limitations of the primary literature. Three of the five included studies were classified as having a high overall risk of bias, particularly due to Domain 2 (bias due to deviations from intended interventions). This raises the possibility that the observed treatment effects may have been overestimated, especially for subjective or semi-subjective outcomes such as probing pocket depth (PPD) and clinical attachment level (CAL).

Another critical limitation is the short follow-up duration, which reached a maximum of 9–12 months in most studies. This period is insufficient to assess the long-term stability of bone gain, which is essential when evaluating regenerative outcomes. Finally, the pronounced clinical heterogeneity was exacerbated by the comparison of different classes of biomaterials (DFDBA, hydroxyapatite, xenograft, and bioactive glass) and by the variation in liquid PRF application protocols (sticky bone vs. direct I-PRF injection), which restricted the potential for direct and robust comparisons between interventions.

In conclusion, I-PRF may be considered a promising adjunct due to its osteoinductive potential, autologous nature, and low cost. However, its clinical indication should be adopted cautiously. Although liquid PRF demonstrates the capacity to enhance bone graft performance, its true clinical benefit—free from bias—remains inconclusive based on the currently available evidence. Therefore, new RCTs with greater methodological rigor (according to RoB 2.0), reduced performance bias (Domain 2), extended follow-up periods (>2 years), and standardized protocols for platelet concentrate preparation and comparator biomaterials are essential to generate high-certainty clinical recommendations.

Conclusion

i-PRF, when used as an adjunct to bone grafts, was shown to enhance the regeneration of periodontal intrabony defects, as demonstrated in the narrative synthesis. However, its effectiveness is intrinsically associated with low certainty of evidence due to methodological limitations in the primary studies. RCTs with higher methodological rigor (low risk of bias) and well-standardized comparator protocols are required to establish more definitive conclusions.

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