NAYARA TEIXEIRA DE ARAÚJO REIS

Uso de fibrina rica em plaquetas (PRF) no reparo ósseo: *revisão sistemática e meta-análise de estudos pré-clínicos*

Use of Platelet-Rich Fibrin (PRF) on bone repair: *a systematic review and meta-analysis of preclinical studies*

Dissertação apresentada à Faculdade de Odontologia da Universidade de Uberlândia, para obtenção do Título de Mestre em Odontologia na Área de Clínica Odontológica Integrada pelo programa de Pós-Graduação em Odontologia.

Uberlândia, 2021

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Orientadora: Prof.ª Dr.ª Priscilla Barbosa Ferreira Soares

Banca Examinadora:
Prof.ª Dr.ª Priscilla Barbosa Ferreira Soares
Prof. Dr. Luiz Renato Paranhos
Prof. Dr. Fábio Leite

Uberlândia, 2021

UNIVERSIDADE FEDERAL DE UBERLÂNDIA
Coordenação do Programa de Pós-Graduação em Odontologia
Av. Pará, 1720, Bloco 4L, Anexo B, Sala 35 - Bairro Umuarama, Uberlândia-MG, CEP 38400-902
Telefone: (34) 3225-8115/8108 - www.ppgoufu.com - copod@umuarama.ufu.br

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DEDICATÓRIA

Dedico esse trabalho à minha família: Minha mãe, meu pai, meus irmãos e minhas madrinhas por todo apoio e amor.

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“Recria tua vida, sempre, sempre.
Remove pedras e planta roseiras e faz doces. Recomeça.”

CORA CORALINA

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RESUMO

Esta revisão sistemática avaliou o potencial da PRF no reparo ósseo em animais e foi conduzida de acordo com o PRISMA. O protocolo foi registrado no PROSPERO (CRD [Blinding]). Foi realizada ampla pesquisa em 9 bancos de dados, incluindo literatura cinzenta. Todos os estudos avaliaram o uso da PRF (Fibrina Rica em Plaquetas) em defeitos ósseos criados em ratos comparado com coágulo (controle). A avaliação do biomaterial também foi realizada quando presente no estudo. O risco de viés foi avaliado pela ferramenta SYRCLE (Centro de Revisão Sistemática para Experimentação com Animais de Laboratório). A meta-análise para dados quantitativos foi realizada para estimar o efeito da PRF no reparo ósseo em ratos. A heterogeneidade (I^2) entre os estudos foi avaliada. A busca resultou em 685 estudos, 10 atenderam aos critérios de elegibilidade e 4 foram incluídos na avaliação quantitativa. A análise do risco de viés mostrou que a maioria dos estudos apresentou alto risco de viés. Os resultados da metanálise demonstraram resultados divergentes entre os estudos e sem diferença estatisticamente significativa para ambas as comparações: PRF com controle (SMD = 2.54; CI 95% = -0.80, 5.89; P = 0.14); e PRF com uso de biomateriais (SMD = -2.61; CI 95% = -5.96, 0.73; P = 0.13). Em geral, a heterogeneidade entre os estudos foi alta ($I^2 \geq 75,0\%$). O uso da PRF não demonstrou benefício nos defeitos ósseos quando comparado ao coágulo e ao uso de biomateriais.

PALAVRAS-CHAVE: Fibrina Rica em Plaquetas; Regeneração óssea; Osseointegração; Revisão sistemática

ABSTRACT

This systematic review evaluated the potential of PRF on bone repair in animals. This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The Protocol was registered on PROSPERO (CRD [Blinding]). It was wide search conducted in 9 databases including gray literature. All studies evaluated bone defects created in rats filled with PRF (Platelet Rich Fibrin) and clot (control). Biomaterial evaluation was also performed when present in the study. The risk of bias was assessed by the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) tool for animal studies. Meta-analysis for quantitative data was performed to estimate the effect of PRF on bone repair in rats. The heterogeneity (I^2) between the studies was assessed. The search resulted in 685 studies, 10 met the eligibility criteria and 4 were included in the quantitative assessment. Analysis of the risk of bias showed that most of studies showed high bias risk at performance and detection. Meta-analysis results demonstrated divergent results between the studies and the absence of a statistically significant effect for both comparison: PRF with control (SMD = 2.54; CI 95% = -0.80, 5.89; P = 0.14); and PRF in relation to use of biomaterials (SMD = -2.61; CI 95% = -5.96, 0.73; P = 0.13). In general, heterogeneity between studies was high ($I^2 \geq 75.0\%$). The use of PRF has demonstrated no benefit in bone defects when compared to the clot and the use of biomaterials.

KEYWORDS: Platelet-Rich Fibrin; Bone Regeneration; Osseointegration; Systematic Review

1. INTRODUÇÃO E REFERENCIAL TEÓRICO

Um dos maiores desafios é desenvolver aditivos cirúrgicos bioativos, que são utilizados para controlar a inflamação e acelerar o processo de cicatrização (Liu *et al.,* 2019). O processo de reparo tecidual é complexo e engloba a composição celular, os sinais químicos e toda a matriz extracelular para cicatrização (Matuska *et al.,* 2021). O processo de reparo tecidual ainda é pouco compreendido, porém é confirmado que as plaquetas exercem função essencial tanto no procedimento de hemostasia quanto da cicatrização da lesão (Sanghani-Kerai *et al.,* 2020).

A capacidade regenerativa das plaquetas foi apresentada na década de 70 (Ross *et al.,* 1974), quando foi descoberta que elas contêm fatores de crescimento encarregados pela produção de colágeno, mitose celular, crescimento de vasos sanguíneos, recrutamento de outras células que migram para o local da lesão e indução de diferenciação celular (Kavitha *et al.,* 2020).

A fibina rica em plaquetas (PRF) são concentrados de segunda geração de plaquetas com fatores de crescimento caracterizada como matriz de fibrina (Canullo *et al.,* 2021) e tem diversas vantagens como a praticidade de preparo sem precisar de manipulação química do sangue, o que a torna exclusivamente autóloga e sem contaminação (Al-Mahdi *et al.,* 2021). Na odontologia, uma das formas usadas clinicamente da PRF é nas cirurgias orais, pois atuam como aditivos cirúrgicos bioativos que são aplicados localmente para estimular o reparo da lesão (Farmani *et al.,* 2021).

Os leucócitos e fatores de crescimento são os componentes fundamentais das plaquetas para realizar os processos de cicatrização e reparação, que colaboram na diferenciação, proliferação, migração e metabolismo celular (Baghele *et al.,* 2019). Os fatores de crescimento têm a função de estimular e atrair células para a região lesionada, favorecendo a mitose celular e induzindo angiogênese e osteogênese (Canullo *et al.,* 2021). Além disso, esses fatores de crescimento, depois da ativação das plaquetas presas na matriz de fibrina, impulsionam resultado mitogênico das células do periósteo para atingir a cicatrização óssea (Kavitha *et al.,* 2020).

A PRF apresenta potencial de reparação óssea e tecidos moles, sem apresentar reações inflamatórias, com capacidade de ser usada da forma isolada ou combinada com enxertos ósseos, desenvolvendo assim, a hemostasia, o crescimento ósseo e maturação (Blatt *et al.,* 2021). O uso da PRF pode ser isolado ou combinado com biomateriais, apresentando resultados positivos em ambas as técnicas (Al-Mahdi *et al*., 2021). Atualmente, a fibrina rica em plaquetas aparenta ser uma técnica minimamente invasiva que está sendo bem aceita, com baixos riscos e resultados clínicos satisfatórios (Canullo *et al.,* 2021).

Em razão das comprovações de efetividade da PRF no reparo ósseo e por já existir um protocolo de uso em humanos, mas não existir um protocolo padrão de uso da PRF em defeitos ósseos em ratos, será necessário avaliar os artigos existentes na literatura e estabelecer assim um protocolo adequado, para depois realizar mais estudos laboratoriais padronizados que utilizam PRF nos defeitos ósseos em ratos e comprovar o efeito da PRF para diversos tratamentos que ainda não são usados clinicamente envolvendo cicatrização óssea, como a osteonecrose.

Desta forma, o objetivo deste trabalho é, por meio de revisão sistemática, avaliar o efeito da PRF em defeitos ósseos em ratos. A justificativa pela preferência do estudo em ratos é por já realizar e continuar trabalhos com esse animal. O estabelecimento de um protocolo de uso da PRF em ratos é de grande importância para pesquisas futuras, podendo ser gerado diversos trabalhos pré clínicos, e ser levado para uso clínico.

CAPÍTULO / ARTIGO

Artigo enviado para revista Archieves of oral biology

Use of Platelet-Rich Fibrin (PRF) on bone repair: a systematic review and meta-analysis of preclinical studies

Nayara Teixeira de Araújo Reis[a], João Lucas Carvalho Paz[a], Luiz Renato Paranhos[b], Ítalo de Macedo Bernardino[c], Camilla Christian Gomes Moura[d], Priscilla Barbosa Ferreira Soares[e] *

[a] Postgraduate Program in Dentistry, School of Dentistry, Federal University of Uberlândia, 38400-902, Uberlândia, MG, Brazil. E-mail address: nayarateixeiraa@ufu.br; joao.lucast66@gmail.com

[b] Department of Preventive and Community Dentistry, School of Dentistry, Federal University of Uberlândia, 38400-902, Uberlândia, MG, Brazil. E-mail address: paranhos.lrp@gmail.com

[c] Department of Dentistry, School of Dentistry, State University of Paraiba, 58429-500, Campina Grande, PB, Brazil. E-mail address: italo.macedo50@gmail.com

[d] Department Endodontics and Dental Materials, School of Dentistry, Federal University of Uberlândia, 38400-902, Uberlândia, MG, Brazil. E-mail address: camillamoura@ufu.br

[e] Department of Periodontology and Implantology, School of Dentistry, Federal University of Uberlândia, 38400-902, Uberlândia, MG, Brazil. E-mail address: pbfsoares@yahoo.com.br

* Corresponding author at: Department of Periodontology and Implantology, School of Dentistry, Federal University of Uberlândia, 38400-902, Bloco 4L, Uberlândia, Minas Gerais, Brazil. Phone/ Fax: +55 (34) 3225-8106. E-mail address: pbfsoares@yahoo.com.br

Highlights

- No significant difference between the groups: PRF and control; PRF and biomaterials
- The use of PRF has no benefit in bone defects when compared to the clot
- The analyzes of bone repair were performed by Histomorphometry or MicroCT

ABSTRACT

Objective: This systematic review evaluated the potential of PRF on bone repair in animals.

Design: This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The Protocol was registered on PROSPERO (CRD [Blinding]). It was wide search conducted in 9 databases including gray literature. All studies evaluated bone defects created in rats filled with PRF (Platelet Rich Fibrin) and clot (control). Biomaterial evaluation was also performed when present in the study. The risk of bias was assessed by the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) tool for animal studies. Meta-analysis for quantitative data was performed to estimate the effect of PRF on bone repair in rats. The heterogeneity (I^2) between the studies was assessed.

Results: The search resulted in 685 studies, 10 met the eligibility criteria and 4 were included in the quantitative assessment. Analysis of the risk of bias showed that most of studies showed high bias risk at performance and detection. Meta-analysis results demonstrated divergent results between the studies and the absence of a statistically significant effect for both comparison: PRF with control (SMD = 2.54; CI 95% = -0.80, 5.89; p = 0.14); and PRF in relation to use of biomaterials (SMD = -2.61; CI 95% = -5.96, 0.73; p = 0.13). In general, heterogeneity between studies was high ($I^2 \geq 75.0\%$).

Conclusion: The use of PRF has demonstrated no benefit in bone defects when compared to the clot and the use of biomaterials.

Keywords: Platelet-Rich Fibrin; Bone Regeneration; Osseointegration; Systematic Review

1.Introduction

Platelet Rich Fibrin (PRF) is a natural scaffold composed by fibrin, platelets and some its fragments (Al-Mahdi *et al*., 2021), leukocytes, cytokines, and growth factors (Bahammam *et al*., 2021; Trimmel *et al*., 2021). The PRF is obtained by collecting and centrifuging the patient's blood without adding exogenous components (Choukroun *et al*., 2006b; Dohan *et al*., 2006b) and its characteristics are affected by the blood collection speed and centrifugation protocol (Dülgeroglu & Metineren, 2017; Miron *et al*., 2021).

The three-dimensional fibrin gel provided by PRF represents the final stage of coagulation cascade in which proteins arranged in different directions (Blatt *et al*., 2021; Hartlev *et al*., 2021) work as "molecular rails" favoring the cell migration. During the centrifugation process are released platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insuline-like growth factor I and II (IGFs); and alsocytokines as interleukin-4 (IL-4), interleukin-10 (IL-10), and transforming growth factor B (TGF-B) (Miron *et al*., 2021; Blatt *et al*., 2021) which are retained in fibrin mesh and slowly released at the tissue site where PRF is placed (Brazdeikytė *et al*., 2021; Farmani *et al*., 2021).

PRF have been indicated to accelerate the epithelial and connective healing including bone tissue (Li *et al*., 2013). Especially in dentistry, PRF may be useful in areas presenting bone defects, such as in periodontal disease, tooth loss (Anwandter *et al*., 2016), trauma (Gutmacher *et al*., 2017; Lin *et al*., 2017) or in patients who have systemic conditions that impair the bone healing such as diabetes, radiotherapy, osteomyelitis (do Lago *et al*., 2020). Several researches have been evaluated the effect of PRF alone (Raafat et al., 2018, Grecu et al., 2019) or associated with biomaterials (Oliveira et al., 2015; do Lago et al., 2020; Pavani et al., 2021) on bone defects, using small animal as preclinical models.

The use of rats as animal model allows several surgical approaches in the creation of the bone defect, being the calvaria (Oliveira *et al*., 2015; Abdullah, 2016; do Lago *et al*., 2020; Surmeli *et al*., 2021) and the long bone (Öncü *et al*., 2016; Akyildiz *et al*., 2018) the most used. However, there is no standardization of PRF protocols to rats or assertiveconclusions about their role in bone repair that can help other researchers to design their studies. Thus, the objective of the

present study is to perform a systematic review of the literature to assess and provide the best data on the potential of PRF for bone repair in rats.

2. Materials and methods

2.1. Protocol and registration

The protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Shamseer *et al*., 2015), and registered at the International Prospective Register of Systematic Reviews (PROSPERO) database, under the number CRD42020162319 (http://www.crd.york.ac.uk/PROSPERO). This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page *et al*., 2021), and was conducted according to the Joanna Briggs Institute (JBI) Manual (Munn *et al.,* 2020).

2.2. Study design and eligibility criteria

This systematic review was based on PICO (Patient, Intervention, Comparison, and Outcome) strategy that aimed to answer the following review question: "Can the use of PRF in bone defects in healthy rats induce bone repair compared to the clot?"

1. Population: Healthy rats
2. Intervention: Use of PRF in bone defects
3. Comparator: Clot and biomaterial
4. Outcome: Effect of PRF on bone repair

The inclusion criteria were only preclinical experimental (prospective) studies that report data on the use of PRF in bone defects, without restriction of year, language, and publication status (published, accepted/ahead of print articles).

Exclusion criteria included studies: 1) Not related to the topic; 2) Literature reviews; 3) Case report as well as case series; 4) Human studies; 5) Laboratorial Studies; 6) Pilot Study; 7) Letter Editor; 8) Editorials; 9) Indexes; 10) Congress Summary; 11) Reports; 12) *In vivo* studies with female rats; 13) In vitro studies; 14) In situ studies; 15) Absence of clot group; 16) Absence of PRF group.

2.3. Sources of information and search

The bibliographic search was completed in November 2019 and upgrade in March 2021. Electronic surveys were carried out in the databases Embase, MEDLINE (via PubMed), Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS), SciELO, LIVIVO, Scopus, Web of Science and citation databases Open Thesis and Open Grey were used to partially capture “gray literature”. These strategies were performed to minimize selection and publication bias.

The resources MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors), and Emtree (Embase Subject Headings) were used to select the search descriptors. Several combinations between the descriptors were made through boolean operators “AND” / “OR", respecting the syntax standards of each database. More details on search strategies and databases in Table 1.

2.4. Study selection

The selection of studies was carried out in four stages. In the first stage, the registers are identified after bibliographic search in the databases. The results obtained were exported to the EndNote Web ™ software (Thomson Reuters, Toronto, Canada), in which duplicates were removed. The remaining results were exported to Microsoft Word ™ 2019 (Microsoft ™ Ltd, Washington, USA), followed by the removal of duplicate articles manually. Two eligible reviewers (NTAR and JLCP) performed each phase independently, and disagreements inter-examiners were discussed with a third reviewer (LRP) to reach consensus.

In the second stage, the methodological analysis was performed by the titles. In the third stage, the abstracts of selected studies were read, and the exclusion criteria were applied. Title that matches the objectives of the study but did not have abstracts available were fully analyzed in the third stage. Thus, in the fourth stage, preliminary eligible studies had their full texts obtained and evaluated to verify whether they fulfilled the eligibility criteria. The references of the initially elegible articles were carefully assessed to check for studies that were possibly not detected in the main search strategy.

2.5. Data collection

Before data extraction, to ensure consistency among the reviewers, a calibration exercise was performed, in which data from three eligible studies were extracted together. After calibration, two reviewers (NTAR and JLCP) extracted data from eligible articles independently and blindly. In cases where there were divergences in data extraction, a third reviewer (LRP) analyzed the conflicts. The data extracted in this study were: Author, year of publication of the work, methodologies used, characteristics of the animals that comprised the sample (breed, number of animals used in the study, weight, and age), amount and form of blood collection, , bone repair time, control group and main outcomes. The ethical criteria involved in the studies, as well as the checklist used, were collected. The data were extracted from texts, tables, and images. In the case of missing data, the authors were contacted to inform what was not clear in the text.

2.6. Risk of bias

The bias risk analysis of the pre-clinal studies was accessed by two revisors (NTAR and JLCP) blindly and independently, as suggested by PRISMA checklist (Page *et al*., 2021). This was performed using SYRCLE RoB tool (Systematic Review Center for Laboratory Animal Experimentation) for animal intervention studies (Hooijmans *et al*., 2014). Both revisors accessed 10 checkpoints remaining. A third revisor (LRP) was invited to discuss the bias risk when no consensus was achieved. Ten pre-defined questions were accessed by revisors SYRCLE's risk of bias tool. Positive answer for question was marked as "YES", indicating low risk of bias; negative answer was marked as "NO", indicating high risk of bias. When the answer was not described on the text, it was marked as "UNCLEAR", indicating an unclear risk of bias.

2.7. Summary measures and data synthesis

The data collection process was carried out through analysis of the selected studies and presented in a descriptive/narrative manner. The analyzes of bone repair associated with the use of PRF were performed qualitatively and quantitatively for bone area by histomorphology (data presented in percentage)

or bone volume by MicroCT analysis (data presented in mm^3). Comparisons were made between groups that received PRF in bone defects and the group control (clot) in experimental time at 14 to 60 days with n = 4 and n = 6, and some groups biomaterial was applied.

Meta-analyzes for continuous outcomes were performed to estimate the effect of PRF on bone repair in rats. The differences in the outcome were reported through *forest plots*, considering the random-effects model to determine the standardized mean differences, 95% confidence intervals, and p-values (Histing *et al*., 2011; Higgins *et al*., 2012; DerSimonian & Laird, 2015). The heterogeneity between studies was assessed using the I^2 statistic and classified as follows: low ($I^2 \leq 25\%$), moderate ($I^2 = 50\%$) and high ($I^2 \geq 75\%$) (Higgins *et al*., 2003). It was not possible to evaluate the publication bias because there are no more than 10 studies to be grouped in a *funnel plot* (Egger *et al*., 1997). The software Review Manager version 5.4 (RevMan, Cochrane Collaboration) was used to perform all statistical analyzes.

3. Results

3.1. Study selection

During the first phase of study selection, 685 results were found distributed in nine electronic databases, including the “grey literature”. After removing the repeated/duplicate results, 432 articles remained for the analysis of titles and abstracts. After a detailed analysis, 102 studies were eligible for the full text analysis. The references of the 102 potentially eligible studies were evaluated carefully and no additional article was selected, resulting in 102 studies for the full text reading. After reading the full text, 92 studies did not fulfil the inclusion criteria and were eliminated, then 10 articles were assessed for qualitative analysis. Thus, 5 articles were selected for quantitative synthesis except for 1 study (Sindel *et al*., 2017) that was excluded at the time of the meta-analysis because the data presented a non-normal distribution and not parametric (mean range) that cannot be computed by meta-analysis. The studies of 21 days were not presented the mean values, median, standard deviation and short follow-up period. Therefore, only four articles were analyzed. The Figure 1 shows the

studies eliminated with respective reasons for exclusion and reproduces the process of search, identification, inclusion.

3.2. Characteristics of eligible studies

The characteristics of the eligible studies are show in table 2. Three studies were conducted in Turkey (Sindel *et al*., 2017; Dülgeroglu & Metineren, 2017; Akyildiz *et al*., 2018), four in Brazil (Pola, 2013; Oliveira *et al*., 2015; Queiroz, 2019; do Lago *et al*., 2020), one in Saudi Arabia (Abdullah, 2016), one in Romenia (Grecu *et al.*, 2019) and one in Egypt (Raafat *et al*., 2018). The publications collected were 2013 to 2020 year. Out of the 10 selected studies, 7 collected PRF by Intracardiac puncture (Pola, 2013; Oliveira *et al*., 2015; Dülgeroglu & Metineren, 2017; Akyildiz *et al*., 2018; Grecu *et al.*, 2019; Queiroz, 2019; do Lago *et al*., 2020). The other three studies collected PRF by venous blood (Raafat *et al*., 2018), orbital sinus (Abdullah, 2016), and ventral tail artery (Sindel *et al*., 2017). The type of PRF (intervention) was fibrin clot form compared to the isolated clot (control and comparative). Studies also used biomaterials as hyaluronic acid (Sindel *et al*., 2017; Akyildiz *et al*., 2018), particulate autogenous bone and Bio-Oss (Oliveira *et al*., 2015; do Lago *et al*., 2020), simvastatin (Raafat *et al*., 2018), demineralized bone matrix (Sindel *et al*., 2017; do Lago *et al*., 2020), beta tri calcium phosphate bone graft material (Abdullah, 2016), anti-inflammatory non-steroidal (Queiroz, 2019).

The type of PRF, quantity, method of collection and period of bone repair evaluation were considered aspects of interest. The time and blood quantify used was not standardized because there are several possibilities for obtaining the PRF. No study reported a checklist to conduct the animal research. All applicable international, national, and/or institutional guidelines and ethical criteria for the care and use of animals were followed.

3.3. Risk of Bias within studies

The figure 2 shows the risk of bias analysis of the included studies. It was considered “NO”, when it was outside the established criteria and it was “UNCLEAR”, when it did not have enough information to answer the questions.

3.4. Outcomes of each study and meta-analyses

The Table 2 shows a summary of the parameters and specific results collected for the studies included in the qualitative analysis. Six studies (Pola, 2013; Oliveira *et al*., 2015; Sindel *et al*., 2017; Akyildiz *et al*., 2018; Raafat *et al*., 2018; do Lago *et al*., 2020) evaluated the bone area by histomorphometry (%) in a total of 288 samples from 289 rats. The studies Dülgeroglu & Metineren, 2017; Grecu *et al*., 2019; Queiroz, 2019 evaluated bone cells through histology (showed no units of measurement) in a total of 218 samples from 179 rats. Other studies evaluated bone volume by computed microtomography (MicroCT) (mm^3) using 218 samples from 183 rats (Abdullah, 2016; Queiroz, 2019). Considering the individual results of the included studies, the following statements can be made: 1) Six studies (Pola, 2013; Abdullah, 2016; Dülgeroglu & Metineren, 2017; Akyildiz *et al*., 2018; Grecu *et al*., 2019; Queiroz, 2019) reported that PRF alone improved bone repair; 2) All studies (Oliveira *et al*., 2015; Abdullah, 2016; Dülgeroglu & Metineren, 2017; Sindel *et al*., 2017; Akyildiz *et al*., 2018; Raafat *et al*., 2018; do Lago *et al*., 2020) evaluated the only PRF and observed bone repair similar compared to the clot and biomaterial; 3) Three studies (Oliveira *et al*., 2015; Sindel *et al*., 2017; Raafat *et al*., 2018) found no difference between isolated PRF and control group; 4) Four articles (Oliveira *et al*., 2015; Abdullah, 2016; Raafat *et al*., 2018; do Lago *et al*., 2020) showed that PRF with biomaterial is efficient in improvement bone repair.

The Figure 3 shows the results of the meta-analysis of studies that evaluated the effect of PRF on bone repair. Comparing PRF with the control, there were divergent results between the studies and no statistically significant effect (SMD = 2.54; CI 95% = -0.80, 5.89; p = 0.14). Analyzing the results of the PRF concerning the use of biomaterials, also there were divergent results between the articles and the absence of a statistically significant difference (SMD = -2.61; CI 95% = -5.96, 0.73; p = 0.13). In general, heterogeneity between studies was high ($I^2 \geq 75.0\%$).

4. Discussion

This study investigated the effectiveness of PRF for bone regeneration compared to clot in preclinical animal models. It has been used alone (Grecu *et al.*, 2019) or as graft complement (autogenous or non-autogenous) to reduce the healing period (Oliveira *et al*., 2015; Abdullah, 2016; Sindel *et al*., 2017; Akyildiz *et al*., 2018; Rafaat *et al*., 2018; do Lago *et al*., 2020). PRF is easily obtained and cost accessible (He *et al*., 2009; Pripatnanont *et al*., 2013; Kim *et al*., 2014; Sindel *et al*., 2017; Akyildiz *et al*., 2018) which makes it quite interesting. However, according to the comparisons obtained from included studies it was concluded that the use of PRF in bone defects in healthy rats is not superior to the clot (control group).

Only three studies found superior results to the PRF when compared to the clot, and both evaluated the repair process in long bones (Dülgeroglu & Metineren, 2017; Akyildiz *et al*., 2018; Raafat *et al*., 2018). It is widely known that the healing process in long bones requires both osteoblastic and chondroblastic cells, with endochondral ossification predominating (Marsell & Einhorn, 2011; Saluja *et al.*, 2011). This process involves the presence of hard callus, which probably had a delay in its maturation in the PRF group, causing more fibrosis and less new bone formation on 6 weeks, despite de favorable results initially (Akyildiz *et al*., 2018). Similarly, Rafaat *et al*. (2018) also found superior results for the PRF group only in the first analysis period, equaling to the control group in the subsequent period. The other studies evaluated bone repair in calvaria, which is subject to the process of intramembranous ossification, and to less movement than the tibia or femur, probably resulting in a modified repair pattern when subjected to bone defects. Thus, with these data, it is possible to observe the differences and similarities in the results of the studies of this review.

It is important to address that the methods for obtaining PRF varied among the studies included in this review (table 2). There was no standardization regarding the rotation time, speed, or the radius of the centrifuge used. The sum of these factors defines the G force applied to the tubes inside the centrifuge (Dohan E *et al*., 2018; Tovar *et al*., 2021). The fibrin architecture is related to the G force and the centrifugation time applied to the tube (Dohan E *et al*., 2018; Tovar *et al*., 2021). The G-force was not mentioned in any study included in this

review compromising an adequate discussion regarding the effect of fibrin structure on bone healing.

The size of the defect can also impact the result of the histomorphometry analysis. It is necessary to create critical defects, which does not heal spontaneously in a certain period (Messora *et al.*, 2007; Sohn *et al*., 2010; Al-Mahdi *et al*., 2021), however the defects size varied in the included studies, as well as the periods of analysis. In this way, an adequate analysis of the PRF alone is difficult.On the other hand, when associated with biomaterials, Three studies showed that the PRF promised results (Oliveira *et al*., 2015; Abdullah, 2016; do Lago *et al*., 2020).

The graft materials used to improve bone regeneration varied considerably between the studies included in this review (Oliveira *et al*., 2015; Abdullah, 2016; Sindel *et al*., 2017; Akyildiz *et al*., 2018; Rafaat *et al*., 2018; do Lago *et al*., 2020). Beta tricalcium phosphate (β-TCP) (Abdullah, 2016), deproteinized bovine bone mineral (DBBM) commercially named Bio-Oss (Oliveira *et al*., 2015; do Lago *et al*., 2020), hyaluronic acid (Sindel *et al*., 2017; Akyildiz *et al*., 2018) and simvastatin coupled to gelatin granules (Rafaat *et al*., 2018) were solely compared to PRF or in association. Inorganic particulate biomaterials as β-TCP and Bio-Oss provide a scaffold for neovascularization and cell penetration which depends on porosity of the material (Abdullah, 2016; do Lago *et al*., 2020). These materials possess osteoconductive properties which may be improved by the sustained and gradual release of growth factors by PRF (do Lago *et al*., 2020).

Particularly, β-TCP dissolves after grafting, providing high concentration of calcium and phosphate, which may be related to the greater bone regeneration observed by *MCT* analysis in PRF/ β-TCP groups compared to PRF alone in the first 2 weeks (Abdullah, 2016; Hartlev *et al*., 2021; Miron *et al*., 2021). However, differences in the volume and density of the newly formed bone between PRF and PRF/ b-TCP groups were not significant at 3, 4, and 6 postoperative weeks (Abdullah, 2016), indicating that presence of β-TCP was no longer significant. Contrary to β-TCP, Bio-Oss did not present complete reabsorption of its particles, presenting histological sections with residual particles on 4 and 8 weeks of analysis (do Lago *et al*., 2020; Blatt *et al*., 2021).

This did not prevent the association between Bio-Oss/PRF from being superior to PRF alone in both analyzed periods (Oliveira *et al*., 2015).

HA occurs naturally in initial bone callus and has osteoconductive properties, which justifies its comparison to PRF in two studies (Sindel *et al*., 2017; Akyildiz *et al*., 2018). However, the results of such research are opposite. While one attributes better results to the PRF when compared to HA (Sindel *et al*., 2017), the other shows total superiority of the latter (Akyildiz *et al*., 2018). It is not possible to make direct comparisons, because they differ in relation to the region chosen for the creation of the bone defect and in relation to the periods of analysis. Simvastatin, a drug commonly used to reduce cholesterol levels, but which has also recently been evaluated as an osteoinductor agent associated with different carriers (Elavarasu *et al*., 2012; Raafat *et al*., 2018) was also compared to PRF sole or in association. The latter significantly increased the maturation of collagen in two months after surgery, indicating a stimulatory effect of both on osteoblasts.

Although clinical trials are the more appropriate method to evaluate new biomaterials in terms of acceleration and stimulation of bone formation there is still insufficient data to carry out adequate systematic reviews, with low risk of bias. Surprisingly, the data obtained from studies using rats as an animal model also lack of adequate description regarding method of blood collection and storage, centrifuging protocol, preparation of PRF and standardization of the defect. Therefore, based on the limitations of current literature PRF did not provide significant benefits for bone repair showing unpredictable effects. Further animal studies with greater standardization of factors are necessary to makea strong recommendation for its use in humans in others different studies using PRF. This systematic approach with meta-analysis is essential to guide and support these future studies.

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Credit authorship contribution statement

Nayara Teixeira de Araújo Reis: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Project administration, Visualization, Supervision. **João Lucas Carvalho Paz:** Validation, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing. **Luiz Renato Paranhos:** Methodology, Validation, Writing - review & editing, Supervision, Project administration. **Ítalo de Macedo Bernardino:** Formal analysis, Validation, Writing - review & editing. **Camilla Christian Gomes Moura:** Writing - original draft, Writing - review & editing. **Priscilla Barbosa Ferreira Soares:** Conceptualization, Validation, Writing - review & editing, Supervision, Project administration. All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of Competing Interest

The authors have nothing to declare.

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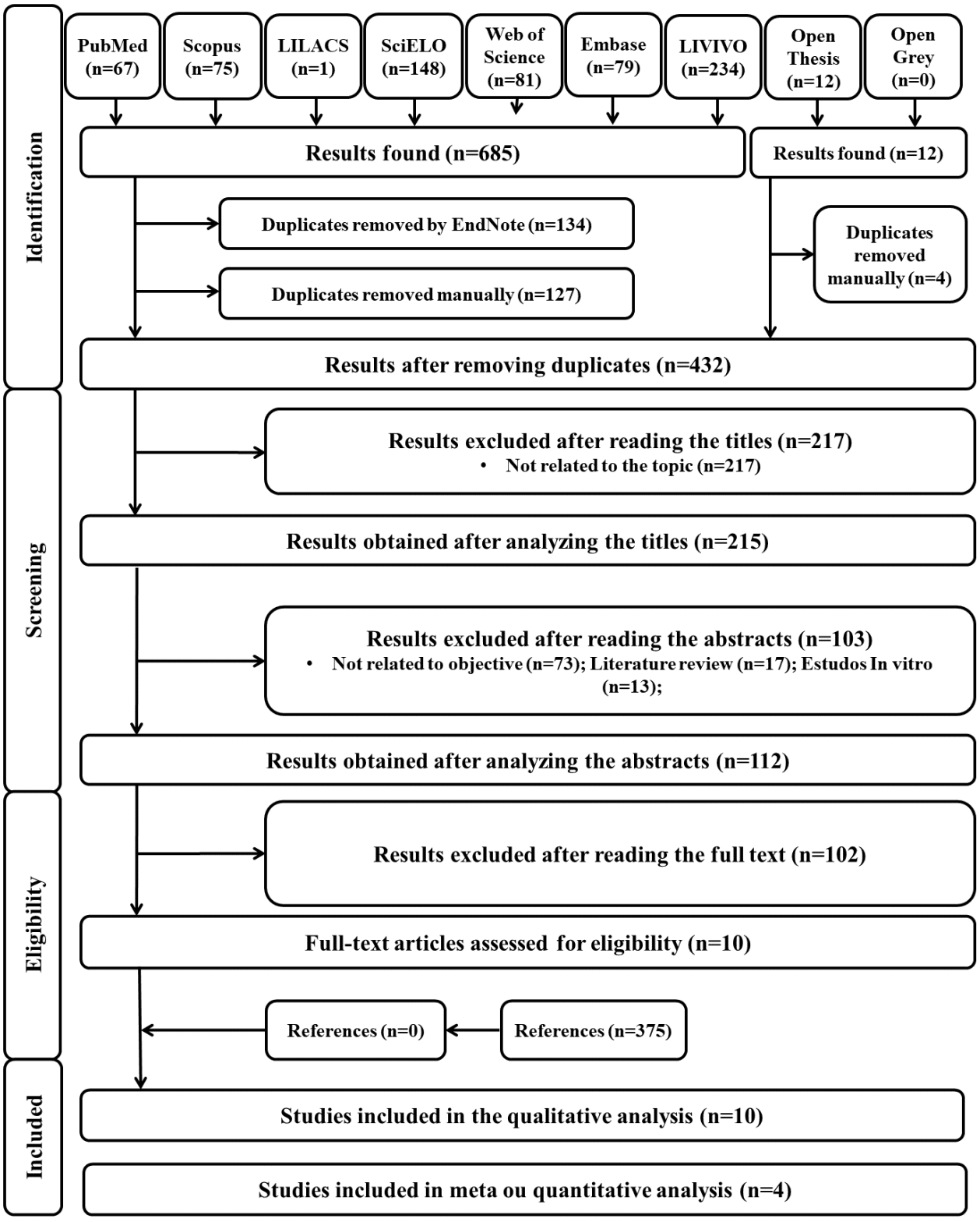

Figure. 1. Flowchart for identifying eligible studies.

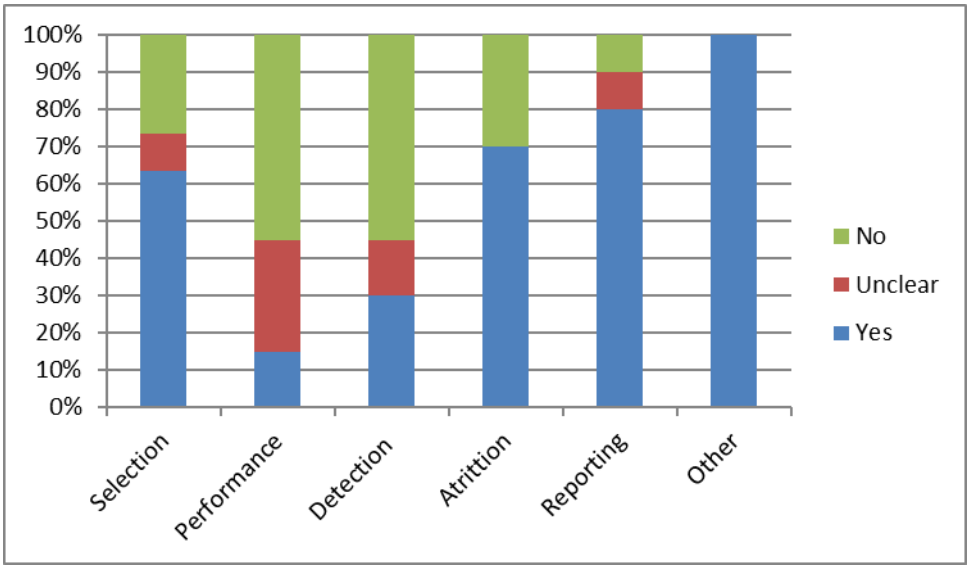

Figure. 2. Bias risk of the selected works

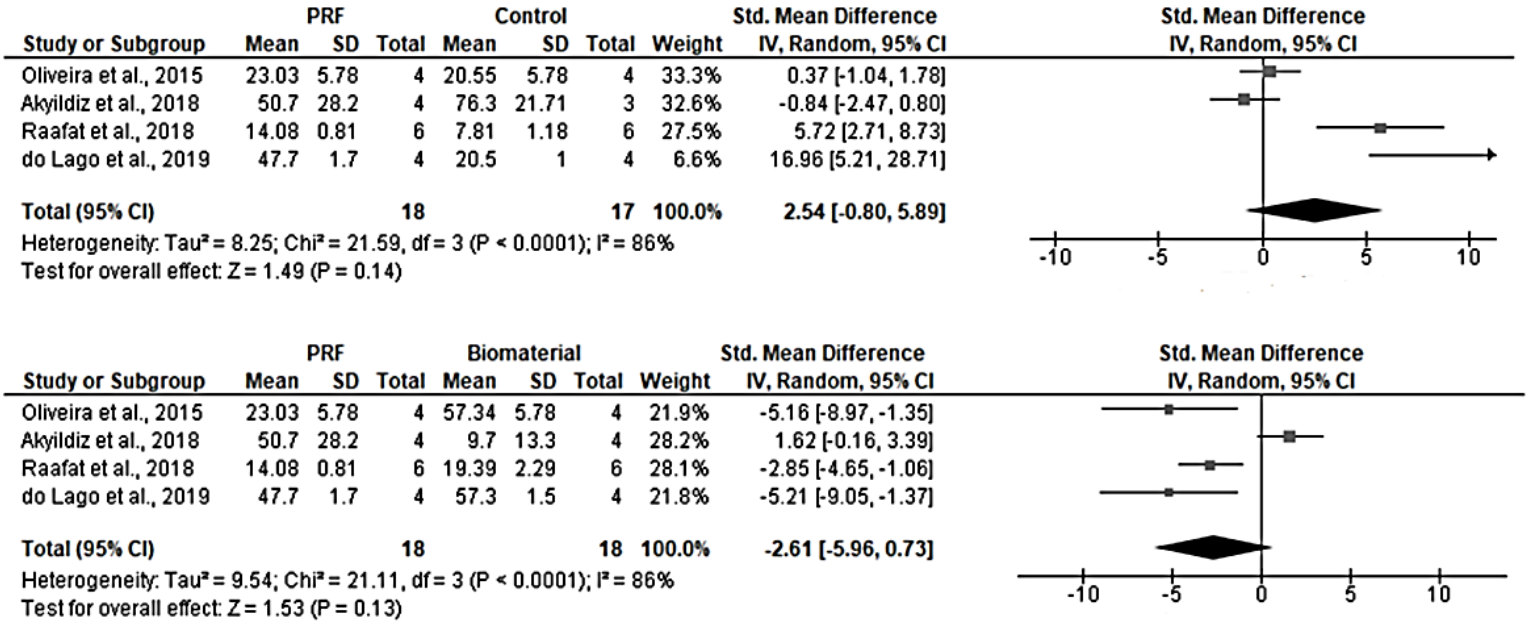

Figure. 3. *Forest plot* of estimates reported by eligible studies that assessed the effect of PRF on bone repair.

Table 1. Strategies for database search.

Database	Search Strategy (MARCH, 2021)
PubMed **http://www.ncbi.nlm.nih.gov/pubmed**	(("Rats" OR "Rat" OR "Rattus" OR "Rattus norvegicus" OR "Rats, Norway" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory" OR "Rats, Wistar" OR "Wistar Rats" OR "Rats, Sprague Dawley" OR "Sprague-Dawley Rats" OR "Rats, Sprague Dawley" OR "Sprague Dawley Rats" OR "Rats, Holtzman" OR "Holtzman Rats") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin"))
LIVIVO	("Rats" OR "Rat" OR "Rattus" OR "Rattus norvegicus" OR "Rats, Norway" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin")
Scopus **http://www.scopus.com/**	((("Rats" OR "Rat" OR "Rattus" OR "Rattus norvegicus" OR "Rats, Norway" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin")))
LILACS **http://lilacs.bvsalud.org/**	("Rats" OR "Rat" OR "Rattus") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin")
	("Rats" OR "Rat" OR "Rattus" OR "Rattus norvegicus" OR "Rats, Norway" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin")
SciELO **http://www.scielo.org/**	(("Rats" OR "Rat" OR "Rattus" OR "Rattus norvegicus" OR "Rats, Norway" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin"))
	("Rats" OR "Rat" OR "Rattus" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory") AND ("Platelet-Rich Fribrin" OR "Platelet Rich Fibrin")
Web Of Science **http://apps.webofknowledge.com/**	((("Rats" OR "Rat" OR "Rattus" OR "Rattus norvegicus" OR "Rats, Norway" OR "Rats, Laboratory" OR "Laboratory Rat" OR "Laboratory Rats" OR "Rat, Laboratory" OR "Rats, Wistar" OR "Wistar Rats" OR "Rats, Sprague Dawley" OR "Sprague-Dawley Rats" OR "Rats, Sprague Dawley" OR "Sprague Dawley Rats" OR "Rats, Holtzman" OR "Holtzman Rats") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin")))
Embase	('rats'/exp OR 'rats' OR 'rat'/exp OR 'rat' OR 'rattus'/exp OR 'rattus' OR 'rattus norvegicus'/exp OR 'rattus norvegicus' OR 'rats, norway' OR 'rats, laboratory' OR 'laboratory rat'/exp OR 'laboratory rat' OR 'laboratory rats'/exp OR 'laboratory rats' OR 'rat, laboratory') AND ('platelet-rich fribrin' OR 'fibrin, platelet-rich' OR 'platelet rich fibrin'/exp OR 'platelet rich fibrin')
OpenGrey **http://www.opengrey.eu/**	(Rats OR Rat OR Rattus) AND (Platelet-Rich Fribrin OR Fibrin, Platelet-Rich OR Platelet Rich Fibrin)
OpenThesis **http://www.openthesis.org/**	("Rats" OR "Rat" OR "Rattus") AND ("Platelet-Rich Fribrin" OR "Fibrin, Platelet-Rich" OR "Platelet Rich Fibrin")

Table 2. Main characteristics of the eligible studies

Author, year	Population Qualification				Intervention Characteristics			
	Race	*Amount*	*Average weight*	*Age of rats*	*Blood volume*	*Methods of collect and centrifugation*	*Bone repair evaluation time*	*Methodology Analysis*
Oliveira *et al*., 2015	Wistar	48	450 - 550g	+	3.5 ml to produce autogenous PRF and 10 ml for the homogeneous PRF from donor rats.	Intracardiac puncture. The blood was centrifuged immediately for 10 min at speeds of 3000 rpm.	30 and 60 days	Histomorphometric. Bone area (%)
Abdullah, 2016	Sprague – Dawley	45	350 - 450g	20-22 weeks	4mL of each rat.	Orbital sinus in a plain tube and immediately centrifuged 3000 rpm for 12 minutes.	1, 2, 3, 4 and 6 weeks	MCT. Bone Volume (mm^3)
Sindel *et al*., 2017	Wistar	40	+	+	3.5 ml	Obtained from ventral tail artery. The blood was immediately centrifuged at 3000 rpm for 10 min.	21 days	Histomorphometric. Longest trabecule (%)
Dülgeroglu & Metineren, 2017	Wistar	16	300-350g	Mature	Blood taken from 4 rats.	Centrifuged at 3000 rpm for 10 minutes	4 weeks	Histological
Akyildiz *et al*., 2018	Sprague – Dawley	23	300-380g	12 months	4mL from the donor animal.	Cardiac puncture into a plain tube and immediately centrifuged 3000 rpm for 10 minutes.	2 and 6 weeks	Histomorphometric. Bone area (%)
Raafat *et al*., 2018	Wistar	48	150-200g	Adult	Around 5 ml	Human venous blood was collected. The vacutainer tubes were centrifuged at 3000 rpm for 10 min.	One and Two-months	Histomorphometric. Bone area (%)
do Lago *et al*., 2020	Wistar	40	350-450g	9 to 11 weeks	3.5 ml to produce autogenous PRF	Intracardiac puncture. The blood was centrifuged immediately for 12 min at speeds of 2700 rpm.	4 and 8 weeks	Histomorphometric. Bone area (%) Descriptive histology
Grecu *et al*., 2019	Wistar	35	220-420g	Newer than 6 months	10 ml from a donor rat	Intracardiac puncture. The blood was centrifuged at 1300 rpm for 8 minutes	45 days	MCT and Histomorphometric
Queiroz, 2019	Wistar	128	450-500g	+	5ml	Intracardiac puncture. The blood was centrifuged at 400 G for 12 minutes	2, 7, 14 e 28 days	Histomorphometric. Bone area (%)
Pola, 2013	Wistar	90	350-450 g	5-6 months	3,5 ml	Intracardiac puncture. The blood was centrifuged at 400 G for 12 minutes	7, 15, 30 days	

Note: + Not mentioned by the author

Table 3. Main Outcomes of the eligible studies

Author	Main Outcomes
Pola, 2013	PRP resulted in accelerated bone formation when compared to control and PRF
Oliveira *et al*., 2015	The use of only PRF did not enhance bone repair. The association of PRF and Bio Oss© enhanced bone repairs.
Abdullah, 2016	At an initial time, the use of only PRF did not enhance bone repair. Although, after three weeks, the results of PRF alone was statistically like PRF with b-TCP.
Sindel *et al*., 2017	The use of PRF did not enhanced the bone repair process at the early time point.
Dülgeroglu & Metineren, 2017	The results indicate that PRF enhances the bone repair in long bones.
Akyildiz *et al*., 2018	The use of PRF showed to be effective on bone repair process at the early time point.
Raafat *et al*., 2018	To the one-month analysis, PRF was not as efficient as SIM or SIM/PRF. Although, in the two-month analysis, PRF with SIM/PRF were greater effect on induced bone defect.
do Lago *et al*., 2020	At first time of analysis, the results of PRF and Bio-Oss were similar. But at the second time, Bio-Oss with PRF showed better results the new bony area.
Grecu *et al*., 2019	New bone formations have been shown to be prevalent in the PRF augmented defect
Queiroz, 2019	The PRF was favorable from the initial to the later periods, assisting in the inflammatory response and bone neoformation

FIGURE LEGENDS

Figure 1 - *Flowchart* adapted from the PRISMA statement showing the literature search and selection processes.

Figure 2 - Summary of the types of bias risk across all included studies assessed by the SYRCLE tool.

Figure 3 - *Forest plot* of estimates reported by eligible studies that assessed the effect of PRF on bone repair Histomorphometry. The standardized mean differences of the evaluated parameters and their respective 95% confidence intervals are represented by squares for the individual studies. The diamonds at the end represent the general average differences estimated from the included studies.

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