

## Platelet-Rich Fibrin for treating temporomandibular disorders in adults: a Scoping Review protocol

### Fibrina rica em plaquetas para o tratamento de disfunções temporomandibulares em adultos: um protocolo de revisão de escopo

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**ABSTRACT | INTRODUCTION:** Different biologically active products have been applied to manage pain and mandibular functional disability in intra-articular Temporomandibular Joint Disorders (TMD) but without effectively controlling the degenerative joint disease. Platelet concentrates aim to enhance tissue healing and facilitate its regeneration. Intra-articular injections of liquid Platelet-Rich Fibrin (PRF) in patients with TMD have demonstrated effectiveness in the management of pain and dysfunction, also having a stimulatory effect on cartilage and bone tissues. **OBJECTIVE:** This review aims to examine how research has been conducted regarding the use of PRF as a treatment tool for Temporomandibular Joint Disorders (TMD). **INCLUSION CRITERIA:** This review will focus on studies that address adults with TMD without restrictions on gender or ethnicity. TMD will be classified according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) physical axis (Axis I). Also, we will include publications in any language or date of publication. **METHODS:** This protocol will follow the JBI guidance for Scoping Reviews. We shall conduct a literature search to identify published research, with no limits on the year of publication/conception, format, or language. Two independent reviewers will screen and select publications based on inclusion criteria. The review decision process will be provided in a flowchart-based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for Scoping Reviews. Finally, we shall present extracted data from each study in piloted forms in conceptual categories such as intervention type, population and sample size, duration of intervention, aims, the methodology adopted, key findings, and gaps in the research.

**KEYWORDS:** Platelet-Rich Fibrin. Research gaps. Scoping Review. Temporomandibular joint disorders.

**RESUMO | INTRODUÇÃO:** Diferentes produtos biologicamente ativos têm sido utilizados para o controle da dor e da incapacidade funcional mandibular nas Disfunções da Articulação Temporomandibular (DTM) intra-articulares, mas sem a capacidade de controlar eficazmente as doenças articulares degenerativas. Os concentrados plaquetários visam melhorar a cicatrização dos tecidos e facilitar sua regeneração. As injeções intra-articulares de Fibrina Rica em Plaquetas (PRF) líquida em pacientes com DTM têm demonstrado eficácia no manejo da dor e disfunção, tendo também um efeito estimulatório sobre a cartilagem e tecidos ósseos. **OBJETIVO:** O objetivo desta revisão é examinar como a pesquisa tem sido conduzida em relação ao uso de PRF como método de tratamento das Disfunções da Articulação Temporomandibular (DTM). **CRITÉRIOS DE INCLUSÃO:** Esta revisão se concentrará em estudos que tratem adultos com DTM sem restrições de gênero ou etnia. As DTM serão classificadas de acordo com os Critérios de Diagnóstico para Disfunções Temporomandibulares (DC/TMD) eixo físico (Eixo I). Também incluiremos publicações em qualquer idioma ou data de publicação. **MÉTODOS:** Este protocolo seguirá a orientação da JBI para revisões de escopo. Conduziremos uma pesquisa bibliográfica para identificar pesquisas publicadas, sem limites de ano de publicação/concepção, formato ou idioma. Dois revisores independentes selecionarão as publicações, com base em critérios de inclusão. O processo de decisão de revisão será descrito em um fluxograma baseado nos Itens Preferenciais de Relatórios para Revisões Sistemáticas e Recomendações de Meta-Análises (PRISMA) para revisões de escopo. Finalmente, apresentaremos dados extraídos de cada estudo em formulários divididos em categorias conceituais como tipo de intervenção, população e tamanho da amostra, duração da intervenção, objetivos, metodologia adotada, principais conclusões e lacunas na pesquisa.

**PALAVRAS-CHAVE:** Fibrina rica em plaquetas. Lacunas de pesquisa. Revisão de escopo. Disfunção da articulação temporomandibular.

## Introduction

Temporomandibular Disorders (TMDs) are painful and/or dysfunctional conditions that affect the masticatory muscles and/or temporomandibular joints (TMJ).<sup>1</sup> These conditions are considered a heterogeneous group of health problems. Characteristic symptoms such as muscle and/or joint pain, limited mandibular function, and joint noises may be prevalent, alone or in association, in up to 75% of the adult population.<sup>2</sup> Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) physical axis (Axis I) divides TMD into two major groups: (a) painful TMD; (b) intra-articular TMD. Masticatory myalgia and temporomandibular arthralgia are painful TMDs. Intra-articular TMD involves articular disc displacement and degenerative joint diseases. Thus, according to this classification system, one can have temporomandibular arthralgia in the absence of TMJ degenerative; conversely, joint cartilage and bone degeneration are not necessarily accompanied by painful symptoms.<sup>3</sup>

Different conservative and invasive protocols have been extensively tested in an attempt to manage intra-articular TMD. Arthrocentesis, followed by intra-articular injection of different biologically active products, has been demonstrated to be safe and effective in controlling pain and restoring mandibular opening, but not necessarily for degenerative disease control. Viscosupplementation with Hyaluronic Acid (HA) by direct joint infiltration is considered a standard treatment for patients with temporomandibular osteoarthritis.<sup>4</sup> The therapeutic properties of HA are based on its mechanical and metabolic action. Mechanical action is associated with lubrication and, consequently, less joint wear, with reduced friction within the intra-articular space, while its metabolic action involves facilitating nutrition in avascular areas of the articular cartilage. Clinical trials have evaluated the therapeutic efficacy of HA infiltration procedures in the TMJ. A Systematic Review<sup>5</sup> showed immediate and long-term pain improvement (15 days to 24 months) superior to placebo (saline injection) and equal to that obtained by corticosteroid infiltration, but without side effects. However, this therapeutic protocol does not seem to significantly affect the regeneration of damaged joint tissues in patients with advanced degenerative diseases. Therefore, treatment protocols based on injections of growth factors to induce or facilitate tissue regeneration

seem to be the next step for both intermediate and late stages of degenerative joint disease.

Platelet-Rich Plasma (PRP) is the first generation of platelet concentrates. It is obtained after blood has been collected in tubes with anticoagulant, centrifuged and platelets and coagulation cascade are activated by thrombin and/or calcium, providing a weak fibrin network.<sup>6,7</sup> Platelet-Rich Fibrin (PRF) is considered a second-generation platelet concentrate, obtained without anticoagulant or clotting activators.<sup>8,9</sup> In this way, a more organized and dense fibrin matrix in which the anchored growth factors can be slowly released is structured.<sup>10</sup> In addition, as it is not necessary to use anticoagulants and exogenous activators such as thrombin, the use of PRF also provides a simplified method of use. Clinical trials have demonstrated intra-articular injections of liquid PRF effectiveness in patients with temporomandibular joint (TMJ) pain and dysfunction.<sup>11-15</sup> Platelet concentrates anchored in a fibrin matrix may enhance the tissue healing process, having a stimulatory effect on the cartilage and bone joint structures, as well as an inhibitory effect on some cytokines that may induce tissue degeneration.<sup>11-13</sup>

A preliminary search of PROSPERO, MEDLINE, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted and no current or in-progress Scoping Reviews or Systematic Reviews addressing the use of PRF in TMD were identified.

Thus, this Scoping Review aims to identify how research has been conducted regarding the use of Platelet-Rich Fibrin (PRF) for temporomandibular joint disorders, as well as to identify and analyze gaps in knowledge in the field. If feasible, we will use the results of this Scoping Review as a precursor for a Systematic Review of this topic.

### Review question

i) How has the research regarding the use of Platelet-Rich Fibrin for temporomandibular joint disorders been conducted?"

### Inclusion criteria

#### Participants

This review will consider studies that have include adults with temporomandibular joint disorders.

We will not place any restrictions on gender or ethnicity. We will include publications in any language or date of publication. For this Scoping Review, we define temporomandibular joint disorders according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) physical axis (Axis I), which divides the TMD into two major groups: the painful TMD and the intra-articular and not necessarily painful TMD.

### **Concept**

The concept under examination will be Platelet-Rich Fibrin used to treat temporomandibular disorders. Platelet-Rich Fibrin is defined as a second-generation platelet concentrate without the use of anticoagulants or activators. It consists of platelets and growth factors in a fibrin mesh structure that, during tissue remodeling, gradually releases growth factors and cytokines capable of improving wound healing.<sup>9,18,19</sup> We shall include studies that tested PRF at any dosage, regimen, and duration, with or without co-interventions.

### **Context**

We shall include evidence from research published in biomedical journals or pre-print databases, such as primary studies, Systematic or Narrative Reviews, guidelines, grey literature (thesis, government documents, etc.). We will include evidence from any study design, the format of publication (abstracts, full text, etc.), or the date of publication. We shall include evidence from any setting (inpatient or outpatient), with no restrictions on the country origin or sociocultural and economic status.

### **Types of sources**

This Scoping Review will consider quantitative, qualitative, and mixed methods study designs for inclusion.

## **Methods**

This protocol follows the guidance from the Joanna Briggs Institute Manual for the development of Scoping Reviews<sup>16</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

extension for Scoping Reviews (PRISMA-ScR) Checklist for the final reporting of this review.<sup>17</sup> We have sought stakeholder consultation throughout the development of this protocol, and we will seek their assistance throughout the review to enhance the validity of its outcomes. We intend to consider a consultation with the following stakeholders:

Clinicians and researchers (consumers) - to assist in refining the health topic, clarify definitions, review the research, and possibly provide understanding (i.e., through personal experience) to the concepts identified through the synthesis of the evidence. This will help us to ensure that this Scoping Review will be relevant and reduce the potential of research waste.

Topic experts - to assess whether the research is relevant to the field and to help find resources that may not be identified through the search of databases, grey literature, and references.

Methodology Experts - to assist in developing and conducting this Scoping Review and answer any methodological concerns that may arise during this process.

Information Specialists - to help define a relevant search strategy and to identify relevant databases for this topic.

### **Search strategy**

The search strategy will aim to locate published research, with no limits on the year of publication/conception, format (abstracts, full text, etc.), or language. We shall conduct a literature search to identify the non-English language publications will be translated and fully assessed for potential inclusion in the review as necessary. An initial search will be conducted in MEDLINE via PubMed using usual and known terms to identify and analyze the text words contained in titles and abstracts of retrieved papers and the index terms used to describe the articles. We will conduct an iterative search process, as additional keywords, sources, and potentially useful search terms may be discovered and incorporated into the search strategy. The terms and complete search strategies are described in Appendix I. Consultation with an information specialist was carried out parallel to the development and refinement of the search strategy adapted for each included information source, including all identified keywords and index terms.

## Information source

Databases to be searched include MEDLINE (from 1966 to date), Embase (from 1988 to date), Cochrane Library (from inception to date), and MedRXiv database (from inception to date). The reference lists of reports and articles will be searched for additional sources and will be screened for additional papers. We intend to check the reference lists/bibliographies of all studies included in the review and their related publications. We shall contact the authors of identified studies/publications and experts in the field to ask them to help identify other studies.

Additionally, we shall access Grey literature databases, Health Management Information Consortium (HMIC) database, National Technical Information Service (NTIS) database, and OpenGrey to access grey literature.

## Study/Source of evidence selection

Following the search, all identified records will be collated and uploaded into Rayyan online platform (Rayyan Systems Inc., MA, USA) and duplicates removed. We will pilot the screening selection in a random sample of 25 titles/abstracts. The authors will then discuss discrepancies and assess the need to refine the eligibility criteria. We will start the screening process when 75% of the agreement is achieved. Following a pilot test, titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Two review authors will independently screen titles and abstracts of all the publications retrieved and decide whether to include them for full-text assessment. We shall retrieve the full text of the included studies (if it is the case), and two review authors will independently screen them for final inclusion/exclusion. We shall identify and record the reasons for the exclusion of ineligible studies. The Scoping Review will record and report reasons for excluding full-text papers that do not meet the inclusion criteria. Disagreement will be resolved through discussion or, if required, consultation with a third reviewer. We will use the Rayyan online platform to take these steps, and we shall record the selection process in sufficient detail to complete a narrative description of the process. The search results will be reported in full in the final Scoping Review and presented in a Preferred Reporting Items for

Systematic Reviews and Meta-analyses for Scoping Reviews (PRISMA-ScR) flow diagram.<sup>17</sup>

## Data extraction

Data will be extracted from papers included in the Scoping Review by two independent reviewers using a data extraction tool developed by the reviewers. A draft charting form will be developed and piloted in at least one source to record the following source information: author(s), year of publication, language, origin/country of origin, study design, format (abstract, full, etc.) and study details: objectives, participants (demographics, number, etc.), content (interventions, outcomes, etc.) and context (setting, socioeconomic and cultural aspects, ethnicity, etc.). A draft extraction tool is provided (see Appendix II). The draft data extraction tool will be modified and revised as necessary when extracting data from each included paper if we judge that additional unforeseen data can be usefully extracted. Modifications will be detailed in the full Scoping Review. Any change made to the form will be reported and will not modify the review objective and question. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required.

## Data analysis and presentation

### Analysis of the evidence

We shall extract results from the included sources and descriptively map them. We shall use tables and diagrams when appropriate.

The tables and charts may also show the distribution of sources of evidence by year or period of publication, countries of origin, outcomes studied, and research methods. A descriptive summary will accompany the tabulated and/or charted results and describe how the results relate to the review objectives and question.

The results can also be classified under main conceptual categories: intervention type, population and sample size, duration of intervention, aims, the methodology adopted, key findings, and gaps in the research. For each category reported, a clear explanation shall be provided.

As this will be a Scoping Review, we do not intend to perform a quality assessment or judgment of the studies. Instead, we will retrieve and cite all available publications. No in-depth quantitative analysis will be performed, given the mapping nature of this review.

### **Presentation of the results**

We will present the overall results of the search categorized by each study design, presenting a numerical summary as a general overview of the available studies. We shall identify how many sources of evidence were retrieved and selected, with a narrative description of the search decision process accompanied by the source of evidence identification and inclusion decision flowchart. The flowchart will clearly detail the review decision process, indicating the results from the search, removal of duplicate citations, source selection, full retrieval, and additions from a third search, and final summary presentation. We shall present the interest data extracted from each study in piloted forms. The forms will contain conceptual categories such as intervention type, population and sample size, duration of intervention, aims, the methodology adopted, key findings, and gaps in the research. For each category, a clear explanation will be provided.

A narrative summary will describe the aims or purposes of the reviewed sources, concepts adopted, and results that relate to the review question.

Forms will be designed and presented to provide a clear and friendly picture of the study to the reader. If we do not retrieve any study for a given population or outcome, we will highlight this as a possible research gap and an opportunity for future research.

### **Authors' contribution**

Tesch R and Takamori E conceived, coordinated, designed, and wrote the protocol, Calcia T, Lobo F and Leitão E provided general advice on the protocol and final revision of the content. Fontes LE drafted methods section; methodological advice; designing search strategies

### **Conflicts of interest**

No financial, legal, or political conflicts involving third parties (government, corporations, and private foundations, etc.) have been

declared for any aspect of the submitted work (including, but not limited to grants and funding, advisory board participation, study design, preparation of the manuscript, statistical analysis, etc.).

## **References**

1. Goldstein BH. Temporomandibular disorders: A review of current understanding. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1999;88(4):379–85. [https://doi.org/10.1016/S1079-2104\(99\)70048-X](https://doi.org/10.1016/S1079-2104(99)70048-X)
2. Solberg WK, Woo MW, Houston JB. Prevalence of mandibular dysfunction in young adults. *J Am Dent Assoc.* 1979;98(1):25–34. <https://doi.org/10.14219/jada.archive.1979.0008>
3. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet J-P, et al. Diagnostic criteria for Temporomandibular Disorders (DC/TMD) for clinical and research applications: recommendations of the International RDC/TMD Consortium Network\* and Orofacial Pain Special Interest Group. *J Oral Facial Pain Headache.* 2014;28(1):6–27. <https://doi.org/10.11607/jop.1151>
4. Escoda-Francolí J, Vázquez-Delgado E, Gay-Escoda C. Scientific evidence on the usefulness of intraarticular hyaluronic acid injection in the management of temporomandibular dysfunction. *Med Oral Patol Oral Cir Bucal.* 2010;15(4):e644-8. <https://doi.org/10.4317/medoral.15.e644>
5. Manfredini D, Piccotti F, Guarda-Nardini L. Hyaluronic acid in the treatment of TMJ disorders: A systematic review of the literature. *Cranio.* 2010;28(3):166–76. <https://doi.org/10.1179/crn.2010.023>
6. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;85(6):638–46. [https://doi.org/10.1016/S1079-2104\(98\)90029-4](https://doi.org/10.1016/S1079-2104(98)90029-4)
7. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part II: Platelet-related biologic features. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101(3):e45-50. <https://doi.org/10.1016/j.tripleo.2005.07.008>
8. Choukroun J, Diss A, Simonpieri A, Girard MO, Schoeffler C, Dohan SL, et al. Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2006;101(3):e56–60. <https://doi.org/10.1016/j.tripleo.2005.07.011>
9. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol.* 2009;27(3):158–67. <https://doi.org/10.1016/j.tibtech.2008.11.009>

10. Dohan Ehrenfest DM, de Peppo GM, Doglioli P, Sammartino G. Slow release of growth factors and thrombospondin-1 in Choukroun's platelet-rich fibrin (PRF): A gold standard to achieve for all surgical platelet concentrates technologies. *Growth Factors*. 2009;27(1):63–9. <https://doi.org/10.1080/08977190802636713>
11. Albilal JB, Vizcaíno-Herrera C, Weisleder H, Choukroun J, Ghanaati S. Liquid platelet-rich fibrin injections as a treatment adjunct for painful temporomandibular joints: preliminary results. *Cranio*. 2020;38(5):292-304. <https://doi.org/10.1080/08869634.2018.1516183>
12. Yuce E, Komerik N. Comparison of the efficiency of intra-articular injection of liquid platelet-rich fibrin and hyaluronic acid after in conjunction with arthrocentesis for the treatment of Internal Temporomandibular Joint Derangements. *J Craniofac Surg*. 2020;31(7):1870–4. <https://doi.org/10.1097/SCS.00000000000006545>
13. Torul D, Cezairli B, Kahveci K. The efficacy of intra-articular injectable Platelet-Rich Fibrin application in the management of Wilkes stage III temporomandibular joint internal derangement. *Int J Oral Maxillofac Surg*. 2021;50(11):1485-90. <https://doi.org/10.1016/j.ijom.2021.03.004>
14. Karadayi U, GURSOYTRAK B. Randomised controlled trial of arthrocentesis with or without PRF for internal derangement of the TMJ. *J Craniomaxillofac Surg*. 2021;49(5):362–7. <https://doi.org/10.1016/j.jcms.2021.01.018>
15. González LV, López JP, Díaz-Báez D, Orjuela MP, Chavez M. Clinical outcomes of operative arthroscopy and temporomandibular medical infiltration with platelet-rich fibrin in upper and lower articular space. *J Craniomaxillofac Surg*. 2021;49(12):1162-8. <https://doi.org/10.1016/j.jcms.2021.07.001>
16. Peters MDJ, Godfrey C, Mclnerney P, Munn Z, Tricco AC, Khalil H. Scoping reviews [Internet]. In: Aromataris E, Munn Z, editors. *Joanna Briggs Institute Reviewer's Manual*. Australia: Joanna Briggs Institute; 2020. Available from: <https://reviewersmanual.joannabriggs.org/>
17. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467-73. <https://doi.org/10.7326/M18-0850>
18. Miron RJ, Fujioka-Kobayashi M, Hernandez M, Kandalam U, Zhang Y, Ghanaati S, et al. Injectable platelet rich fibrin (i-PRF): opportunities in regenerative dentistry? *Clin Oral Investig*. 2017;21(8):2619–27. <https://doi.org/10.1007/s00784-017-2063-9>
19. Miron RJ, Zhang Y. Autologous liquid platelet rich fibrin: A novel drug delivery system. *Acta Biomater*. 2018;15(75):35-51. <https://doi.org/10.1016/j.actbio.2018.05.021>