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Histological Effect of Platelet-Rich Plasma on Temporomandibular Joint Osteoarthritis: Systematic Review in Animal Models

Efecto Histológico del Plasma Rico en Plaquetas en Osteoartritis de la Articulación Temporomandibular: Revisión Sistemática en Modelos Animales

Veronica Iturriaga[1,2,3,4,5]; Schilin Wen[3,5,6]; Héctor Torres[7]; Javier Gonzalez[7]; Davis C. Thomas[8,9] & Thomas Bornhardt[1,2,3,4,5]

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SUMMARY: The aim of this systematic review was to assess the histological effects of platelet-rich plasma (PRP) on temporomandibular joint osteoarthritis (TMJ-OA) in animal models. A systematic search was performed using PubMed, WoS, EMBASE, Science Direct and SCOPUS databases. The inclusion criteria were experimental studies in animal models that evaluated the use of PRP as a treatment for TMJ-OA with or without arthrocentesis/arthroscopy. Comparison was made to a healthy control group or to other treatment. The variables evaluated were the histological effects of the treatments, characteristics of the primary articles, characteristics of the sample studied and the risk of bias. The systematic search identified 120 studies. Eventually 5 studies were included in the analysis. Four of the studies showed a statistically significant repair in joint tissues and improvement of cartilage thickness in animals treated with PRP. The global risk of bias was unclear. The results of this systematic review suggest that PRP treatment in TMJ-OA has benefits at the histological level in cartilage, articular disc and articular bone tissue in animal models. However, due to the low number of studies and the risk of bias, further research is needed to recommend its use.

KEY WORDS: Platelet-rich plasma; Temporomandibular disorders; Temporomandibular joint, Osteoarthritis; Growth factors; Systematic review.

INTRODUCTION

Osteoarthritis (OA) is the most common degenerative bone disease of the temporomandibular joint (TMJ). TMJ-OA manifests with facial pain, causing functional limitation and severe disability (De Rossi *et al*., 2014). The use of Platelet rich plasma (PRP) has recently gained considerable attention as a therapeutic approach in diseases such as TMJ-OA. PRP is an autologous biological material without immunogenicity which may be processed in a number of ways to obtain a concentrate rich in platelets and / or fibrin (Marx, 2001; Lana *et al*., 2017; Varshnet *et al*., 2019). PRP contains various cellular and molecular components. The cellular fraction of PRP is composed mainly of platelets, peripheral blood mononuclear cells and lymphocytes. In contrast, molecular components of PRP include growth factors (GF) and cytokines released by platelet alpha-granules. These components play an important functional role in tissue regeneration and repair, by modulating and stimulating mesenchymal cell proliferation, and differentiation mainly into fibroblasts, osteoblasts and chondrocytes (Cole *et al*., 2010; Dohan Ehrenfest *et al*., 2014; Lana *et al*., 2017).

There is a lack of consensus regarding the terminology in the literature, on the various types of PRP, and there are different classification systems (Lana *et al*., 2017). Overall, PRP and fibrin-rich plasma (PRF) are the

[1] Department of Integral Adult Care Dentistry, Universidad de La Frontera, Temuco, Chile.
[2] Temporomandibular Disorder and Orofacial Pain Program, Universidad de La Frontera, Temuco, Chile.
[3] Sleep & Pain Research Group, Universidad de La Frontera, Temuco, Chile.
[4] Center of Excellence in Morphological and Surgical Studies (CEMyQ), Universidad de La Frontera, Temuco, Chile.
[5] Doctoral Program in Morphological Sciences, Universidad de La Frontera, Temuco, Chile.
[6] Universidad Autónoma de Chile, Chile.
[7] Dental School, Universidad de La Frontera, Temuco. Chile.
[8] Rutgers School of Dental Medicine, Newark, USA.
[9] Eastman Institute of Oral Health, Rochester, USA.

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two platelet concentrates that have been identified. PRP has a low amount of fibrin and may be administered via injection or in gel form. Moreover, due to greater fibrin volume in PRF, the gel form is the preferred method, since PRF is not suitable for injection. Dohan Ehrenfest *et al*. (2014) classified these two entities into four categories, according to the presence of fibrin and the amount of cellular content. These are pure platelet-rich plasma (P-PRP), plasma rich in leukocytes and platelets (L-PRP), pure platelet rich fibrin (P-PRF), leukocyte and platelet rich fibrin (L-PRF) (Dohan Ehrenfest *et al*., 2014). Lana *et al*. (2017) recently proposed a classification system, that specifies the concentration of mononuclear cells within the leukocyte component, along with other aspects inherent to the preparation, since the differences could impact the effect of treatment.

Some studies which have evaluated the clinical effects of PRP in TMJ-OA treatment in humans, have mainly analyzed pain relief and improvement in range of motion (Hegab *et al*., 2015; Hancı *et al*., 2015; Cömert Kiliç & Güngörmüs, 2016; Fernández Sanromán *et al*., 2016). Although, in those studies, the effect on cartilage, disc and articular bone were not considered. In this context, studies in animal models have been carried out to clarify the histological effects of PRP on joint structures. Consequently, the aim of this systematic review was to assess the histological effects of PRP on TMJ-OA in animal models.

MATERIAL AND METHOD

Design and protocol. A systematic review was carried out to answer the research question: What are the histological effects of PRP on TMJ-OA in animal models? The systematic review protocol was registered in the international prospective register of systematic reviews (PROSPERO) from the National Institute for Health Research database (www.crd.york.ac.uk/prospero), code reference number CRD42018112914. The systematic review was reported according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Page *et al*., 2021).

Eligibility criteria and outcomes. Inclusion criteria were: 1) Experimental studies in animal models; 2) Articles that evaluated the use of PRP (in any of its versions) as a treatment for TMJ-OA accompanied or not, by arthrocentesis / arthroscopy; 3) Studies that presented a healthy control group or comparison with other treatments. Exclusion criteria were: Studies that contained animal models that analyzed other pathologies. The main outcome was the histological effects of PRP on TMJ-OA in animal models. Other outcomes of interest were: scientific characteristics of the primary studies (language, year of publication and journal), characteristics of the studied sample (animal model, sample size, method of induction of TMJ-OA, type of PRP, centrifugation program, use of anticoagulant, activator type, experimental protocol and complications of the experiment), as well as risk of bias assessment of the studies. For the purposes of this review, the nomenclature used by the authors of each article regarding the type of PRP used, was maintained.

Databases and search strategy. WoS, EMBASE, PubMed, ScienceDirect, SCOPUS databases were searched. In the initial phase, the search terms were identified. Subsequently, a sensitive search was carried out, adding the Boolean operator "OR" and "AND", and the limits "experimental studies" in "animal models". The search was performed in April 2020, and was adapted to each database and its corresponding language. The strategies for each database searched are detailed in Table I.

Study Selection and Data Extraction. All references identified were extracted through Mendeley® reference manager. Duplicate articles were eliminated. The articles were screened independently by two researchers (JG - HT); they were first evaluated by title, then abstract and finally the full article. For this process, Cochrane Collaboration Covidence® tool was used. The same two authors independently extracted the following information from each article using a standardized and predefined spreadsheet: publication data, animal model, sample size, induction method of TMJ-OA, type of PRP, centrifugation program, use of anticoagulant, activator type, experimental protocol, experiment complications and results obtained. A third reviewer (VI) resolved discrepancies throughout the entire process.

Risk of Bias of Individual Studies. Two researchers (JG - HT) independently assessed the risk of bias of the articles finally included. A third reviewer (SW) resolved discrepancies. The Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) was used to assess the risk of bias (Hooijmans *et al*., 2014). This tool evaluates 6 items: selection bias, performance bias, detection bias, attrition bias, reporting bias and other sources of bias. Additionally, specific questions were included to strengthen the analysis, based on the evaluation used by Cafferata *et al*. (2019) in their methodology. Possible responses to signaling questions were: yes - when bias parameters were explicitly noted in the article; no - when it was noted that risk bias parameters were not performed; unclear - when it was not mentioned whether it was carried out or not. Based on the responses, the domains concerning risk of bias were classified as low, high, or unclear. Review Manager software version 5.3 was used for analysis.

Table I. Search strategies and search results for each database consulted.

Search source	Search strategy	Search results
PubMed	(((((("Platelet-Rich Plasma"[Mesh]) OR "Platelet-Rich Fibrin"[Mesh])) OR ((((((((((Platelet-Rich Plasma [Title/Abstract]) OR Platelet-Rich Fibrin [Title/Abstract]) OR P latelet concentrates [Title/Abstract]) OR Plasma rich in growth factors[Title/Abstract]) OR thrombocyte rich plasma[Title/Abstract]) OR PRP [Title/Abs tract]) OR PRF[Title/Abstract]) OR PRGF[Title/Abstract]) OR L-PRP [Title/Abstract]) OR L-PRF[Title/Abstract]))) AND ((((((("Temporomandibular Joint "[Mesh]) OR "Temporomandibular Joint Disc" [Mesh]) OR "Temporomandibular Joint Dysfunction Syndrome"[Mesh]) OR "Temporomandibular J oint Disorders "[Mesh]) OR " Craniomandibular Disorders"[Mesh]) OR "Jaw Diseases"[Mesh])) OR (((((Temporomandibular Joint[Title/Abstract]) OR Temporomandibular Joint Disorders [Title/Abstract]) OR Temporomandibular Joint Dysfunction Syndrome [Title/Abstract]) OR Craniomandibular D isorders [Title/Abstract]) OR jaw disease [Title/Abstract])) Filters: Other Animals	41
WoS	TS=("platelet-rich plasma" OR "platelet-rich fibrin" OR "platelet concentrates" OR "plasma rich in growth factors" OR "thrombocyte rich plasma" OR "PRP" OR "PRF" OR "PRGF" OR "L-PRP" OR "L-PRF") AND TS=("Temporomandibular Joint" OR "Temporomandibular Joint Disc" OR "Temporomandibular Joint Dysfunction Syndrome" OR "Temporomandibular Joint Disorders" OR "Craniomandibular Disorders" OR "Jaw Diseases") Refined by: DOCUMENT TYPES: (ARTICLE)	33
EMBASE	('platelet-rich plasma' OR 'platelet-rich fibrin' OR 'platelet concentrates' OR 'plasma rich in growth factors' OR 'thrombocyte rich plasma'):ti,ab,kw AND ('temporomandibular joint' OR 'temporomandibular joint disc' OR 'temporomandibular joint dysfunction syndrome' OR 'temporomandibular joint disorders' OR 'craniomandibular disorders' OR 'jaw diseases'):ti,ab,kw AND 'article'/it	22
Science Direct	("platelet-rich plasma" OR "platelet-rich fibrin" OR "platelet concentrates" OR "plasma rich in growth factors") AND ("Temporomandibular Joint" OR "Temporomandibular Joint Disorders" OR "Craniomandibular Disorders" OR "Jaw Diseases") AND Research articles	9
SCOPUS	TITLE-ABS-KEY ("platelet-rich plasma" OR "platelet-rich fibrin" OR "platelet concentrates" OR "plasma rich in growth factors" OR "thrombocyte rich plasma" OR "PRP" OR "PRF" OR "PRGF" OR "L-PRP" OR "L-PRF") AND TITLE-ABS-KEY ("Temporomandibular Joint" OR "Temporomandibular Joint Disc" OR "Temporomandibular Joint Dysfunction Syndrome" OR "Temporomandibular Joint Disorders" OR "Craniomandibular Disorders" OR "Jaw Diseases") AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SRCTYPE , "j"))	83

RESULTS

Study selection. The systematic search identified 120 studies, once duplicates were eliminated. After reviewing titles and abstracts, 5 studies were evaluated in full text. No study was identified from the reference section of the studies selected for full text review or in gray literature search. Finally, five studies were included for qualitative analysis (Baek *et al*., 2011; Kütük *et al*., 2014; Wang *et al*., 2017; Coskun *et al*., 2019). In light of heterogeneity of the studies and the results which were mostly descriptive, it was not possible to perform a quantitative analysis. The flow diagram of the selection process is detailed in Figure 1.

Characteristics of the primary articles. All selected articles were written in English and published between 2011 and 2019. One article was published in the Tissue Engineering and Regenerative Medicine Journal (Beak *et al*.), two articles were published in the Journal of Oral and Maxillofacial Surgery (Kütük *et al*., 2014; Wang *et al*., 2017), one article in the Journal of Cranio-Maxillo-Facial Surgery (Coskun *et al*., 2019).

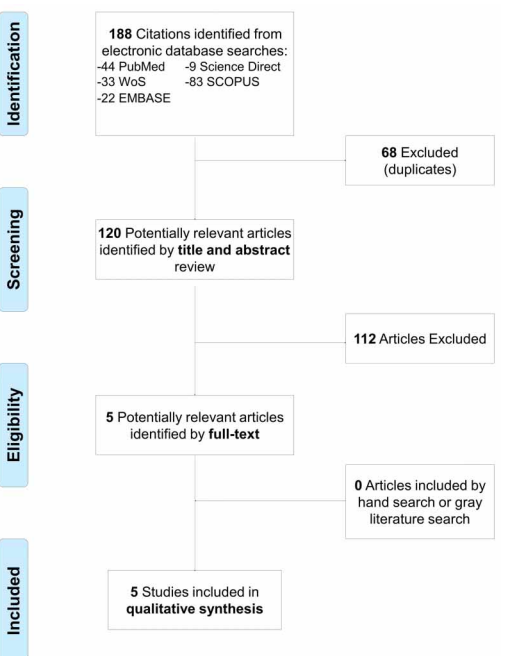

Fig. 1. Selection of the primary articles according to the framework proposed by the PRISMA statement (Page *et al*., 2021).

Characteristics of the studied sample. The selected articles comprised of a total sample of 70 animals, of which 40 were New Zealand rabbits (32 male and 8 female) (Kütük *et al*., 2014; Coskun *et al*., 2019), and 6 goats (Wang *et al*., 2017). All animals were healthy prior to testing procedures. TMJ-OA was induced by sodium mono-iodoacetate (MIA) in two of the studies (Coskun *et al*., 2019); a surgical defect was created in cartilage and subchondral bone in two studies (Kütük *et al*., 2014; Wang *et al*., 2017), and surgical defect was created in the articular disc in the remaining study (Baek *et al*., 2011). In two studies, treatment administered for TMJ-OA, was PRP intra-articular infiltration after TMJ-OA was induced (Coskun *et al*., 2019). The other three studies induced the surgical defect and inserted PRF (Baek *et al*., 2011), PRP gel intra-operatively (Kütük *et al*., 2014), and a growth factor concentrate (CGF) intra-articular membrane, this was characterized by the authors as fibrin-rich gel with platelet aggregation and CGF (Wang *et al*., 2017). No studies reported adverse effects or TMJ ankylosis. Additional features of the studied samples are summarized in Table II.

Histological effect of platelet concentrates on TMJ-OA. The histological effects of PRP on TMJ-OA were varied between studies. Coskun *et al*. (2019) compared three experimental groups. The first group was treated with a single PRP intra-articular infiltration, the second with 3 PRP infiltrations, and the third with saline solution (SS) infiltration. Even though the group with multiple PRP infiltrations showed improvement when compared to the SS group, no statistically significant differences were reported between groups, with regard to cartilage regeneration, osteochondral attachment, the

Table II. Characteristics of the analyzed samples in each of the studies.

Study	Animal model	Induction Method TMJ-OA	Type of PRP	Centrifugation program	AC Use	Activator type	Experimental protocol
Coskun*et al*., 2019	16 male New Zealand rabbits	MIA 50 _L (3 mg/mL), 4-week waiting period.	Intra-articular injection of 0.8-1 mL PRP.	Single, 3200 rpm for12 min.	Sodium citrate.	10% calcium chloride.	Group 1:Single dose of SS into L-TMJ (8 TMJ). Group 2: Single dose of PRP into R-TMJ (8 TMJ). Group 3:One weekly dose for three weeks of SS into L-TMJ (8 TMJ). Group 4: One weekly dose for three weeks of PRP into R-TMJ (8 TMJ).
Oksan*et al*., 2018	24 male Wistar rats	0.5 mg MIA, 4-week waiting period.	Intra-articular injection of 1 mL PRP($1.5x10^2$ platelets/L).	Double, 1: 200g 20 min. 220℃, 2: 480rpm 20 min.	Citrate phosphat edextrose .	Calcium chloride + bovine thrombine.	Group 1: SS into R-TMJ(8 TMJ). Group 2: MIA into R-TMJ (8 TMJ). Group3: MIA and PRP into R-TMJ (8 TMJ). L-TMJs were not included in the analysis.
Wang *et al*., 2017	6 goats	Surgical defect in cartilage and subchondral bone of mandibular condile, without waiting period.	Intra-articular implantation of CGF membrane.	Single.	Not used.	Not used.	Group 1: without intervention (2 TMJ). Group 2: SS into L-TMJ (10 TMJ). Group 3: CGF into R-TMJ (10 TMJ)
Kutuk*et al*., 2014	16 male New Zealand rabbits	Surgical defect in cartilage and subchondral bone of mandibular condile, without waiting period.	Intra-articular implantation of 1 mL PRP Gel.	Single, 14 min.	Citrate dextrose.	10% calcium chloride.	Group1: SS into L-TMJ (10 TMJ). Group 2: PRP into R-TMJ (10 TMJ).
Baek*et al*., 2011	8 female New Zealand rabbits	Surgical defect in joint disc, without waiting period.	Intra-disc implantation of 3 mm diameter of PRF.	Single, 3000 rpm for 10 min.	Not used.	Not used.	Group 1: without intervention on L-TMJ (8 TMJ). Grupo 2: PRF into R-TMJ (8 TMJ).

OA: osteoarthritis; TMJ: temporomandibular joint; PRP: platelet-rich plasma; AC: anticoagulant; MIA: sodium mono-iodoacetate; rpm: revolutions per minute; R-TMJ: right temporomandibular joint; L-TMJ: left temporomandibular joint; CGF: concentrated growth factor, SS: saline solution.

appearance of chondrocytes, or histological changes in subchondral bone structure.

In the experimental group, Kütük *et al*. (2014) observed greater bone regeneration versus the control group treated with SS ($p < 0.011$). Similarly, in the group treated with PRP, the regeneration of articular cartilage was greater, although these results were not statistically significant. Unlike the SS treated group, where the mandibular condyle surface was found to be irregular and collagen fibers were disarranged, forming thick and dense bundles, the group treated with PRP presented a thicker cartilage with thin, homogeneous and well-organized collagen fibers.

Wang *et al*. (2017) observed that TMJs treated with a CGF membrane presented greater regeneration of the middle areas of cartilage and articular bone, when compared to TMJs treated with SS ($p = 0.008$ and $p = 0.002$, respectively). Although, there was less regenerated connective tissue in the group treated with CGF than in the group treated with SS ($p = 0.009$).

Finally, the effect of PRF in a surgical defect repair of the articular disc, was evaluated by Baek *et al*. (2011). In their study, greater proliferation of chondroblasts / chondrocytes and cell differentiation were reported in the treated versus the untreated group. Figure 2 shows a summary of the review process and main results.

Bias Risk Assessment. The overall risk of bias of the studies was unclear. The risk of bias graph and summary are presented in Figures 3 and 4, respectively.

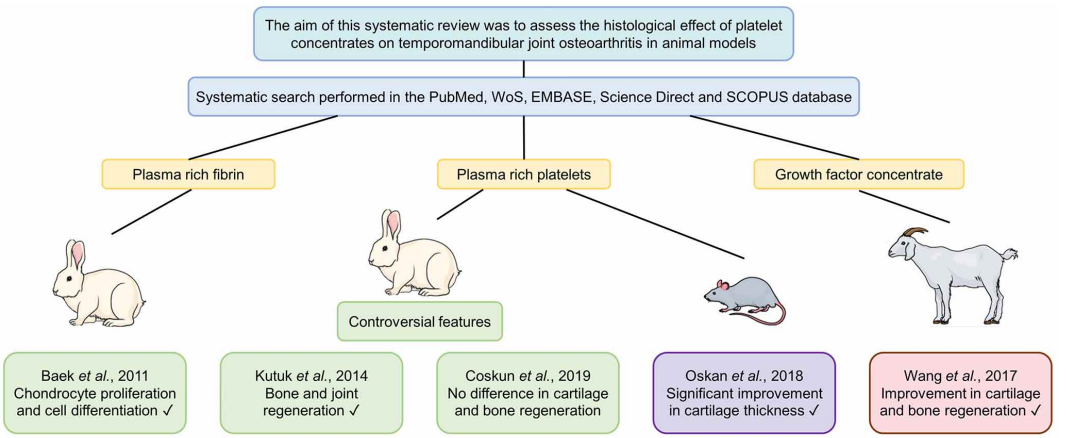

Fig. 2. Summary of the review process and main results.

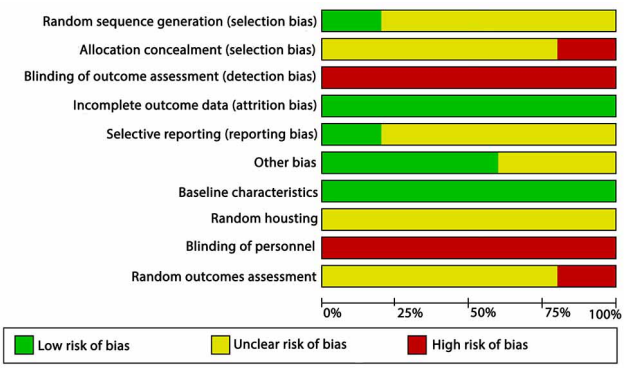

Fig. 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages in all studies included, according to Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) (Hooijmans *et al*., 2014). Red color shows high risk of bias, yellow corresponds to unclear risk and green to low risk of bias.

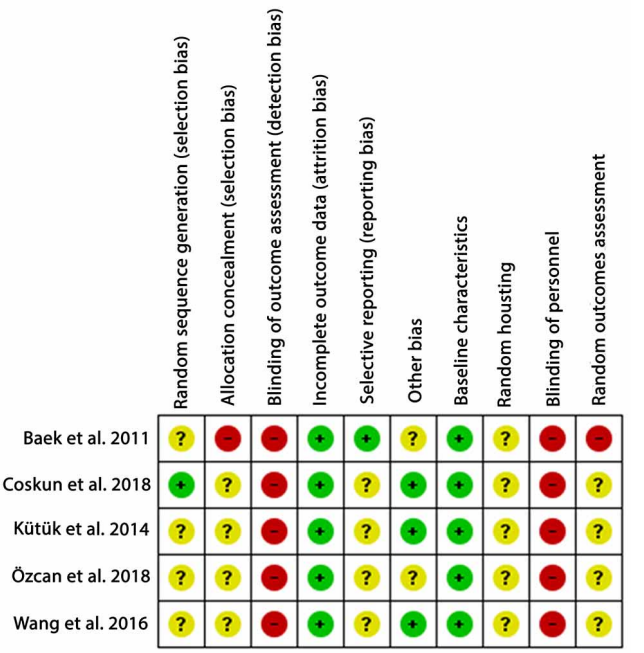

Fig. 4. Risk of bias summary according to Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) (Hooijmans *et al*., 2014). Red color shows high risk of bias, yellow corresponds to unclear risk and green to low risk of bias.

DISCUSSION

This systematic review suggests certain benefits regarding the histological effects of PRP on TMJ-OA, although the amount of evidence available is scarce.

PRP is a biological material obtained from the patient´s own blood, and once collected, is available in a liquid or gel form, depending on its content of platelets and / or fibrin (Dohan Ehrenfest *et al*., 2014). It has been proposed that PRP presents 3-8 times higher platelet concentration than normal plasma, and it is an important growth factor reservoir (Eppley *et al*., 2004; Dohan Ehrenfest *et al*., 2014; Zotti *et al*., 2019). These growth factors are biologically active polypeptides that modulate joint health recovery, and have recently been considered as adjuncts in orthobiological therapies (Zotti *et al*., 2019). Since it presents few postoperative complications and is easily obtained and processed, the benefits of PRP concerning treatment and procedures have also been noted (Bousnaki *et al*., 2018).

During the course of TMJ-OA evolution, there are changes in the subchondral bone and joint structures, starting with the focal and progressive destruction of cartilage due to the effect of inflammatory and immune response (Manfredini *et al*., 2012). In TMJ-OA the effect of PRP has mainly been attributed to its ability to stimulate the differentiation of mesenchymal stem cells and proliferation of fibroblasts, osteoblasts, and chondrocytes (Liu *et al*., 2011). Furthermore, chondrocytes would stimulate endogenously produced glycosaminoglycans, along with enhanced synovial production of hyaluronic acid. Additional effects proposed are the control of joint tissue angiogenesis and enhanced stem cell migration (Okuda *et al*., 2003; Cole *et al*., 2010; Lana *et al*., 2017; Zotti *et al*., 2019). Poor vascularization and the limited capacity of chondrocytes to synthesize collagen combined with other joint functions, make cartilage repair in synovial joints complex (Kütük *et al*., 2014). It should also be considered that TMJ joint surfaces have the particularity of being covered by fibrocartilage, as opposed to the hyaline cartilage present in most synovial joints. This could restrict tissue cell repair, as fibrocartilage has a particularly low cellular component. However, PRP stimulates the differentiation and proliferation of these cells, contributing to the regeneration and repair of joint structures (Zotti *et al*., 2019).

Most of the studies in this review indicated that the treatment of TMJ-OA with PRP contributed to chondrocyte proliferation; cell differentiation; bone, disc, and joint cartilage regeneration (Baek *et al*., 2011; Kütük *et al*., 2014; Wang *et al*., 2017). Nonetheless, Coskun *et al*. (2019) reported results that were different from those previously stated, which prompted some degree of controversy.

In contrast, there have been some systematic reviews evaluating the clinical effect of PRP on TMJ-OA in humans. Although the available evidence is scarce, an important effect in pain reduction and improvement in the joint movement ranges was reported, when compared to perform an arthrocentesis and / or hyaluronic acid (Haigler *et al*., 2018; Chung *et al*., 2019; Zotti *et al*., 2019; Al-Moraissi *et al*., 2020). It has been suggested that the effect of treatment could vary, depending on the PRP subtype used (Dohan Ehrenfest *et al*., 2014; Lana *et al*., 2017). On the other hand, studies carried out in other joints, such as the knee, reported favorable results (Liu *et al*., 2014; Khatab *et al*., 2018; Chouhan *et al*., 2019; Xue *et al*., 2020). However, there is no single protocol or consensus regarding the preparation of the concentrate (Kon *et al*., 2020). For this reason, in recent years, it has been proposed to unify the terminology based on a common classification of the different PRPs, in order to improve future research (Dohan Ehrenfest *et al*., 2014; Lana *et al*., 2017).

From an experimental point of view, there is currently no consensus regarding an ideal animal model for the histopathological study of TMJ-OA, with the frequent use of rabbits, rats and goats, as is evidenced in this review. On the other hand, male animals are preferred in order to circumvent hormonal influence in experimentation on articular cartilage and bone metabolism. However, this could also be a source of bias in the studies. In this regard, different methods of TMJ-OA induction have been developed in animal models, with the objective of describing the nature of this disease, and evaluating the effects of the various treatments proposed. In this review, it was noted that three of the studies used a post-traumatic TMJ-OA model (Baek *et al*., 2011; Kütük *et al*., 2014; Wang *et al*., 2017), and the remaining two studies used TMJ-OA models aimed at cellular events, specifically an MIA induction (Coskun *et al*., 2019).

Among the limitations of this review is the reduced number of studies related to the research objective, since it also presented a risk of unclear bias. It is therefore difficult to perform comparative analysis between TMJ-OA animal models used, induction methods and types of PRP associated with the therapeutic effect.

In conclusion, according to the results of this review, experimental studies in animal models of TMJ-OA suggest a positive effect of PRP on joint tissue as evidenced by histology. However, evidence is scarce regarding the histological effect of PRPs on TMJ-OA management, and further research is needed.

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RESUMEN: El objetivo de esta revisión sistemática fue evaluar los efectos histológicos del plasma rico en plaquetas (PRP) en la osteoartritis de la articulación temporomandibular (ATM-OA) en modelos animales. Se realizó una búsqueda sistemática en las bases de datos PubMed, WoS, EMBASE, Science Direct y SCOPUS. Los criterios de inclusión fueron estudios experimentales en modelos animales que evaluaran el uso de PRP como tratamiento para la ATM-OA con o sin artrocentesis/artroscopia. La comparación se realizó con un grupo de control sano o con otro tratamiento. Las variables evaluadas fueron los efectos histológicos de los tratamientos, las características de los artículos primarios, las características de la muestra estudiada y el riesgo de sesgo. La búsqueda sistemática identificó 120 estudios. Finalmente se incluyeron 5 estudios en el análisis. Cuatro de los estudios mostraron una reparación estadísticamente significativa en los tejidos articulares y una mejora del grosor del cartílago en los animales tratados con PRP. El riesgo global de sesgo fue incierto. Los resultados de esta revisión sistemática sugieren que el tratamiento con PRP en la ATM-OA tiene beneficios a nivel histológico en el cartílago, el disco articular y el tejido óseo articular en modelos animales. Sin embargo, debido al escaso número de estudios y al riesgo de sesgo, se necesitan investigaciones adicionales para recomendar su uso.

PALABRAS CLAVE: Plasma rico en plaquetas; Trastornos temporomandibulares; Articulación témporomandibular; Factores de crecimiento; Revisión sistemática.

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Corresponding author:
Prof. Veronica Iturriaga
Department of Integral Adult Care Dentistry
Universidad de La Frontera
Avenida Francisco Salazar 01145
Temuco
CHILE

E-mail: veronica.iturriaga@ufrontera.cl