ОБЗОРЫ / REVIEWS

Prospects for use of platelet-rich plasma in the treatment of rheumatoid arthritis

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The paper reviews the data available in the literature on the mechanisms of action of platelet-rich plasma (PRP) and the experience of its use in patients with rheumatoid arthritis (RA). It defines the place of PRP in the systemic and local therapy of RA. The chemical composition of PRP and the structure of the platelet organelles included in it are described. An estimate is made for procedures to prepare platelet-rich plasma containing different concentrations of key growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor α (TGFα), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), and epidermal growth factor (EGF). The variants of PRP classifications, which take into account differences in the composition and levels of the growth factors, are considered. The experience with intra-articular injections of autologous plasma products in patients with RA and synovitis is analyzed.

These findings lead to the conclusion that PRP therapy can be an effective tool to relieve inflammation and to stimulate local reparative processes in damaged joint tissues in patients with RA. Further study of the possibilities of using this method of therapy and the formation of a PRP-therapy protocol for patients with rheumatoid arthritis will provide effective personalized care to these patients.

Keywords: *rheumatoid arthritis; synovitis; platelet-rich plasma; platelets; growth factors; inflammation.*
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For reference: *Maglevaniy SV, Naryshkin EA, Chetina EV, Makarov MA. Prospects for use of platelet-rich plasma in the treatment of rheumatoid arthritis. Sovremennaya Revmatologiya=Modern Rheumatology Journal. 2021;15(1):87–93.* ***DOI:*** *10.14412/1996-7012-2021-1-87-93*

Rheumatoid arthritis (RA) is a chronic autoimmune rheumatic disease (RD) of unknown etiology, characterized by chronic erosive arthritis (synovitis) and systemic inflammatory damage to internal organs [1]. Small joints of the wrists and feet are most often involved, although inflammation of large joints is also often observed in RA [2]. Synovia is one of the main targets of a pathological process, which is characterized by hyperplasia of synovial membrane and formation of pannus [3]. Angiogenesis in RA is one of the factors contributing to transition of inflammation to the chronic proliferative phase, as well as persistence of chronic synovitis [4]. In this case, macrophage-like (MLS) and fibroblast-like (FLS) synoviocytes proliferate, forming a pannus that covers and damages the cartilage tissue. Synovial tissue dysfunction in RA disrupts the exchange of metabolites between blood vessels and intra-articular space, because synovial fluid with subchondral bone provides nutrition for the articular cartilage [2]. The adhesion of FLS to the extracellular matrix (ECM), their migration, invasion and formation of pannus lead to erosion and destruction of articular cartilage in RA patients due to the secretion of degrading enzymes, mainly matrix metalloproteinases and cytokines [5]. In addition, macrophages, fibroblasts, and activated peripheral blood lymphocytes enter the synovial tissue in RA patients. T-lymphocytes are involved in production of many pro-inflammatory cytokines, mainly from the tumor necrosis factor α (TNFα) and interleukin (IL) superfamilies, as well as growth factors. The role of B-lymphocytes is associated with the production of autoantibodies, such as antibodies to cyclic citrullinated peptide and rheumatoid factor [5].

RA therapy

Currently, nonsteroidal anti-inflammatory drugs, simple analgesics, glucocorticoids (GC), synthetic basic anti-inflammatory drugs (sDMARDs) and genetically engineered biological drugs (bDMARDs) are used in the RA treatment differentiated into five classes: TNFα inhibitors; anti-B-cell drugs; interleukin 1 and -6 inhibitors, T-cell costimulation. bDMARDs differ in their mechanisms of systemic action. Thus, TNFα inhibitors with high affinity and specificity bind to the soluble and membrane-bound part of TNFα, thereby reducing its concentration and preventing interaction with receptors [6]. Anti-B-cell monoclonal antibodies bind to CD20, thus causing depletion of B cells [7]. The effect of T-cell costimulation inhibitors is based on binding of the programmed cell death protein L1 (PD-L1) localized on the surface of the antigen-presenting cell, to the protein CTLA4 (cytotoxic T-lymphocyte glycoprotein 4), which is expressed on the surface of T-lymphocytes [8]. It is known that IL1 blocks the biological activity of IL1 by competitive binding to the IL1Ra receptor [9]. The mechanism of IL6 action consists in their binding to both soluble (sIL-6R) and membrane (mIL-6R) receptors and in the inhibition of their mediated signals [10].

In addition to systemic drugs, intra-articular injections are widely used in RA therapy. Thus, local administration of GC allows to quickly suppress inflammation in the joint and provide significant clinical improvement long before the effect of sDMARDs is obtained [11]. Such therapy leads to decrease in inflammatory activity because of lower cellular infiltration due to reduction in the number of T-lymphocytes and the expression of pro-inflammatory cytokines that induce the development of synovitis, such as TNFα, IL1I and vascular endothelial growth factor (VEGF) [12]. Local GC therapy is also able to suppress the expression of 5-lipoxygenase in the synovial membrane, which further increases its effectiveness in RA patients [13]. There is an evidence of effectiveness of intra-articular administration of TNFα inhibitor infliximab for the treatment of monoarthritis in RA patients, resistant to local therapy of GC and sDMARDs [14]. Local administration of TNFα inhibitors compared to subcutaneous administration resulted in a significant decrease in the proliferation of synovial tissue cells [15]. An interesting study is

devoted to intra-articular administration of methotrexate (MTX) into synovial joints, which demonstrated the effectiveness of this method in resistant synovitis, which was reduced by systemic MTX therapy [16]. In addition, a number of studies have reported on the safety and effectiveness of intra-articular injections of hyaluronic acid in RA [17]. Thus, local methods of therapy, affecting certain parts of pathogenesis of RA, can be effective in oligo- and monoarthritis.

Platelet rich plasma (PRP), its characteristics and structure

One of minimally invasive ways to improve the condition of the articular surface and restore its full functioning is the use of PRP. Platelets are small non-nuclear discoid cells that are produced by bone marrow megakaryocytes and are directly involved in the processes of inflammation, thrombosis, angiogenesis, bone remodeling, autoimmune reactions, and other physiological and pathological processes. This is due to the fact of platelet activation as a result of exocytosis, the granular structure of their cytoplasm releases a wide range of biologically active substances [18].

Platelets contain α-granules, δ-granules, lysosomes, peroxisomes, and other organelles. The α-granules contain more than 280 proteins, which belong to various functional classes [19].

In turn, δ-granules are lysosome-bound organelles that are unique to platelets [21] and play a central role in their aggregation [22]. These granules contain membrane proteins (CD63-granulophysin, LAMP2, GPIb, aIIbI3); nucleotides (ATP, GDP, ADP, GTP); biologically active amines (serotonin, histamine); carrier proteins (MRP4, VNUT, VMAT2); and ions (Ca^{2+}, Mg^{2+}, K^{+}, polyphosphate, pyrophosphate) [23].

Platelets form the basis of PRP rich of autologous platelets blood plasma, which includes various growth factors released during the activation of content of α-granules and involved in the cascade of regeneration processes [24]. Numerous studies show that platelet growth factor (PDGF), transforming growth factor β (TGFβ), VEGF, insulin-like growth factor (IGF), and epidermal growth factor (EGF) are the most significant factors for reparative processes [25, 26]. Growth factors are involved in tissue repair and counteract the catabolic effects of cytokines such as TNF and IL1. They are also involved in the stimulation of angiogenesis and protect endothelial cells from apoptosis, which ensures sufficient blood flow to the damaged tissue to initiate repair processes.

Ways to get PRP

There are several ways to synthesize PRP with target levels of the required growth factors. At the same time, methods described in the literature for obtaining PRP have common features: collection of peripheral blood samples in the presence of an anticoagulant and their subsequent centrifugation. The PRP composition is influenced by changes of individual dynamic parameters: centrifugation time, magnitude of the centrifugal force, methods of extraction of platelet concentrate (platelet plasma aspiration, which differ in speed of sedimentation during centrifugation), and activation using different doses of calcium chloride or thrombin. Combination of these parameters leads to differences in the PRP composition [27].

Classification of PRP products

In order to standardize PRP preparations, several ways of classifying them have been proposed. In 2009, classification of the platelet products was developed to divide them into four groups depending on the content of leukocytes and fibrinogen: pure platelet-rich plasma (P-PRP); platelet-rich plasma with leukocytes (L-PRP); pure platelet-rich fibrin (P-PRF) and platelet-rich fibrin with leukocytes (L-PRF) [28].

Later the DEPA classification was created by J. Magalon et al. [29] (Dose of injected platelets, Product efficiency, PRP Purity, and PRP Activation). In this classification new parameters were introduced – dose of platelets in injection and relative composition of PRP. This classification can be used to evaluate the clinical efficacy of a certain composition of PRP.

Recently, the MARSPILL classification has appeared (M: Method; A: Activation, R: Red blood cells, S: spin, P: platelets, I: image guidance, L: leukocytes, L: light activation), which is based on the ratio of platelets and mononuclear cells of peripheral blood [30]. This classification takes into account the method of obtaining plasma, presence and method of its activation, concentration of red blood cells and white blood cells, methods of cell deposition, number of platelets and presence of visual control.

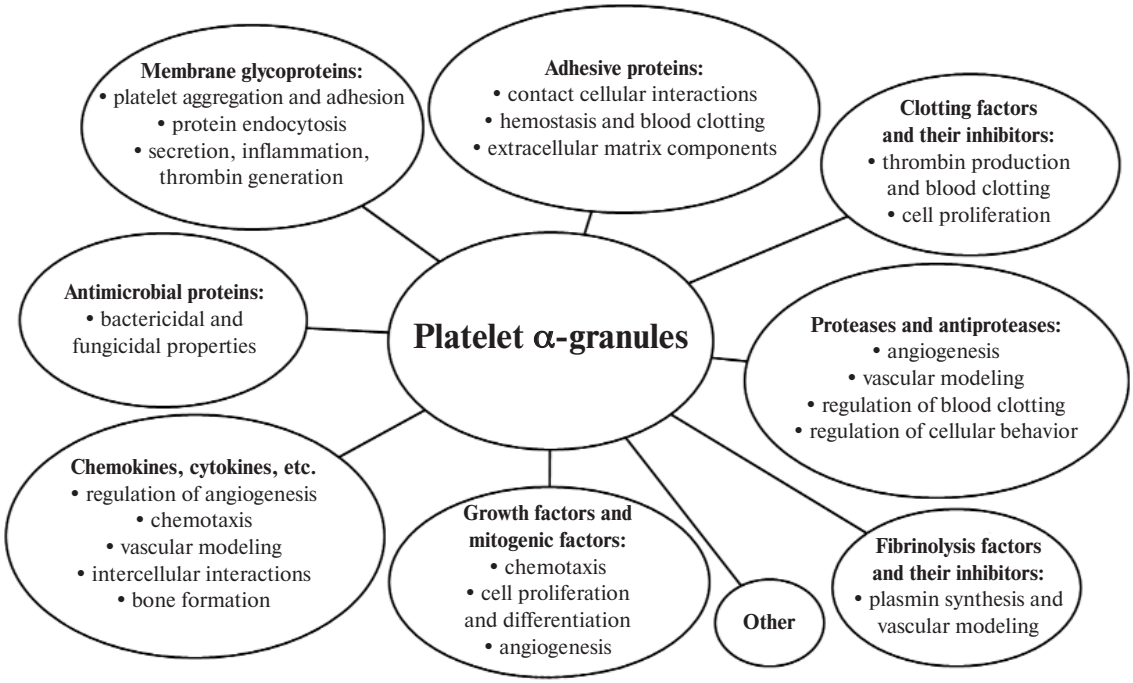
In order to predict the rate of recovery of platelets and white blood cells during centrifugal separation of whole blood in a test tube to obtain PRP, L. Piao et al. [31] proposed a theoretical model of multiphase flow. This model assumes that optimal number of intact platelets is formed when 9 ml of whole blood is centrifuged for 5, 10, and 15 minutes at an acceleration of 1000, 500, and 350 g, respectively.

Suggested PRP mechanisms

It is known that platelet products obtained by different methods contain different concentrations of growth factors and cytokines [32]. Therefore, therapy of a particular patient should be based on obtaining PRP with the specified properties. Thus, standard method for producing PRP, which includes two precipitation by centrifugation at a low speed (6 min – 1000 rpm and 8 min – 800 rpm), allows release of a large number of growth factors such as PDGF and RANTES (a cytokine that is a selective T-lymphocyte attractant belonging to the IL8 superfamily) [33], probably due to the maximum platelet content in preparation and activation of PRP by thrombin and calcium, which increases degranulation platelets. This method of obtaining PRP can be useful if the main goal of therapy is to restore ligaments, menisci at the injection site.

For angiogenesis activation and wound healing improvement, injections of platelet-rich fibrin (PRF, which is obtained by single centrifugation of blood at an acceleration of 400 g for 10–12 minutes) are used, which increases the yield of several growth factors (the main fibroblast growth factor – bFGF, -VEGF, TGFI1) and cytokines, which are localized in white blood cells and, possibly, in circulating progenitor cells located in fibrin clot.

A number of studies have shown that in case of synovitis, the content of endogenous TNF and IL6 in the intra-articular fluid increases with a decrease in the levels of VEGF and IL10. In these cases, local administration of PRGF (Plasma Rich in Growth Factors – blood plasma rich in growth factors) and PRF reduces the concentration of TNFα and IL1β, since PRGF and PRF are able to inhibit the release of pro-inflammatory cytokines [34]. Moreover, the use of different platelet products, such as PRF and PRP, helps to achieve a higher concentration of cytokines involved in tissue regeneration processes (for example, a 20-fold increase in the concentration of VEGF can be obtained in PRF) [35].



Composition and functional categories of platelet α-granules [20]

The study by A. Mishra et al. [36] established that inactivated 10% PRP significantly increases proliferation of fibroblasts and mesenchymal stem cells (MSC) in vitro. In addition, PRP, depending on the pH level at its preparation, can selectively stimulate chondrogenic differentiation of MSC, which affects the production of various cytokines. J.P. KrЯger et al. [37] discovered that PRP, via stimulating the migration and chondrogenic differentiation of subchondral MSC progenitors, effectively induces formation of a cartilage matrix rich in proteoglycans and type II collagen, thereby promoting repair of the damaged cartilage tissue. The results of the above studies can be used to create PRP with specified properties.

Thus, the method of obtaining a platelet product has great importance for achieving a specific therapeutic result when using PRP.

Multidirectional nature of PRP action in RA

PRP products can not only participate in processes of tissue regeneration, but also specifically affect the clinical manifestations of certain diseases. Since RA is characterized by an inflammatory process in joints associated with synovial hyperplasia and its invasion into adjacent bone and cartilage structures, it is assumed that PRP can contribute to the weakening of the inflammatory process in a joint and slow down the further destruction of cartilage and bone tissue by changing the rate of proliferation and differentiation of synovial cells, as well as inhibiting catabolic processes in articular cartilage. It should be noted that PRP is an autologous product, so functional disorders of platelets associated with their systemic activation in RD can have both positive and negative effects on the processes regulated by PRP. For example, a number of studies have observed both damaging and protective effects of platelets, which are associated with their simultaneous participation in the processes of hemostasis, inflammation, innate and adaptive immunity, tissue regeneration, etc. [38–40].

The multidirectional nature of action of PRP products is explained by the fact that the reactivity of platelets with a short life span (8–10 days) is determined by megakaryopoiesis, which is quantitatively regulated by thrombopoietin. At the same time, any chemical compound aimed at the maturation of platelet precursors in bone marrow can directly or indirectly change the thrombotic, immune and inflammatory potential of circulating platelets. A.Y. Gasparyan et al. [41] showed that in most systemic disorders, platelets circulate in an activated state and tend to form complexes with other inflammatory and immune cells. Thus, in RA patients with an increased number of platelets in the blood ($>400\times10^9$/l), there was a more significant decrease in the activity of the disease in response to the administration of tocilizumab compared to those who had a normal platelet level ($<400\times10^9$/l) [42]. Interacting with T-lymphocytes, mediated through P-selectin, platelets inhibit the proliferation of lymphocytes and thereby reduce the level of proinflammatory cytokines in the blood [43]. A number of studies have shown that the use of bDMARDs, in particular TNFα inhibitors, limits the ability of platelets to bind to white blood cells and activate them in patients with RA, which leads to a weakening of immune inflammation [44]. Thrombotic and inflammatory agents released by platelets can cause specific complications. At the same time, it is known that some widely used antirheumatic drugs inhibit thrombopoiesis and platelet activity [45]. Currently, there are no known ways to prevent the damaging effect of platelets or endow them with protective and regenerating functions, but research in this direction is being conducted.

Experience in the use of PRP in RA therapy

To date, PRP therapy has shown good effectiveness in treatment of osteoarthritis, as well as other diseases of musculoskele-

tal system, such as synovitis, epicondylitis, skeletal muscle injuries and tendinopathy [46–50]. Its use in RA patients has been studied insufficiently.

The ability of PRP to suppress the action of pro-inflammatory factors and reduce clinical manifestations of RA is associated by some researchers with the regulation of the phosphoinositide-3-kinase (PI3K) signaling pathway)/protein kinase B (AKT) [51]. There is also evidence that the TRAIL protein (TNF-related apoptosis-inducing ligand) contained in platelet α-granules is involved in the regulation of inflammation in RA patients by stimulating apoptosis in synoviocytes and infiltrating lymphocytes [52–54]. The results of a number of studies have demonstrated the ability of TRAIL to suppress joint inflammation and inhibit the activation of T-lymphocytes by regulating the signaling pathway independent of apoptosis [55].

The studies on the RA model in pigs indicated a significant decrease in synovial hypertrophy and its leukocyte infiltration in synovial tissue samples after PRP administration compared to the untreated samples. The decrease in the content of VEGF, IL6, IL1β, and IGF1 in synovial and cartilaginous tissues, as well as TNFα in cartilaginous tissue after intra-articular PRP administration, indicates the effectiveness of this treatment method for cartilage repair [56]. Administration of PRP to rats with adjuvant-induced RA significantly reduced the levels of MDA (malondialdehyde), a marker of oxidative stress, IL1β and TNFα, and also increased the concentrations of GSH (glutathione) and GPx (glutathione peroxidase) in the blood serum of animals, which confirms the antioxidant effect of PRP [57].

Data on the usage of PRP in RA patients are few and contradictory. In a study by H. Badsha et al. [58], based on the experience of using PRP therapy in four RA patients with an inadequate response and persistent inflammation after intra-articular administration of GC: 4 and 8 weeks after PRP administration, all patients showed a decrease in pain on the visual analog scale, disease activity according to the DAS28 index, and decrease in inflammation according to ultrasound of the joints. At the same time, no adverse events were registered in any patient.

In another study, the administration of PRP to a RA patient was accompanied by the development of an allergic reaction, which could be caused by calcium citrate used for PRP activation [59].

It should be noted that PRP can promote the migration and invasion of FLS in RA patients, so regulation of these processes should be taken into account when using PRP products for treatment in order to prevent the structural progression of the disease [60].

Conclusion

Thus, PRP therapy is an effective method of relieving inflammation and stimulating local reparative processes, and convenience and safety due to the usage of autologous material expand the possibilities of its use in RD. However, the role of PRP therapy in RA patients is currently understudied. At the same time, the accumulated theoretical knowledge and a small but successful experience in practical application provide basis for further evaluation of this method and the formation of a protocol for PRP therapy in such patients.

ЛИТЕРАТУРА/REFERENCES

1. Насонов ЕЛ, Каратеев ДЕ, Балабанова РМ. Ревматоидный артрит. В кн.: Насонов ЕЛ, Насонова ВА, редакторы. Ревматология. Национальное руководство. Москва: ГЭОТАР-Медиа; 2008. С. 290-331. [Nasonov EL, Karateev DE, Balabanova RM. Rheumatoid arthritis. In: NasonovEL, Nasonova VA, editors. *Revmatologiya. Natsional'noe rukovodstvo* [Rheumatology. National guidelines]. Moscow: GEOTAR-Media; 2008. P. 290-331].

2. Bartok B, Firestein GS. Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunol Rev.* 2010 Jan;233(1):233-55. doi: 10.1111/j.0105-2896.2009.00859.x.

3. Orr C, Vieira-Sousa E, Boyle DL, et al. Synovial tissue research: a state-of-the-art review. *Nat Rev Rheumatol.* 2017 Aug;13(8): 463-75. doi:10.1038/nrrheum.2017.115. Epub 2017 Jul 13.

4. Elshabrawy HA, Chen Z, Volin MV, et al. The pathogenic role of angiogenesis in rheumatoid arthritis. *Angiogenesis*. 2015 Oct; 18(4):433-48. doi: 10.1007/s10456-015-9477-2. Epub 2015 Jul 22.

5. Fang Q, Ou J, Nandakumar KS. Autoantibodies as Diagnostic Markers and Mediator of Joint Inflammation in Arthritis. *Mediators Inflamm*. 2019 Oct 27;2019: 6363086. doi: 10.1155/2019/6363086. eCollection 2019.

6. Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. *Int Immunol.* 2015 Jan; 27(1):55-62. doi: 10.1093/intimm/dxu102. Epub 2014 Nov 19.

7. Насонов ЕЛ. Фармакотерапия ревматоидного артрита: новая стратегия, новые мишени. Научно-практическая ревматология. 2017;55(4):409-19. [Nasonov EL. Pharmacotherapy for rheumatoid arthritis: New strategy, new targets. *Nauchno-prakticheskaya revmatologiya*. 2017;55(4):409-19. (In Russ.)].

8. Korhonen R, Moilanen E. Abatacept, a novel CD80/86-CD28 T cell co-stimulation modulator, in the treatment of rheumatoid arthritis. *Basic Clin Pharmacol Toxicol.* 2009 Apr;104(4):276-84. doi: 10.1111/j.1742-7843. 2009.00375.x. Epub 2009 Feb 18.

9. Dayer JM, Feige U, Edwards CK 3rd, et al. Anti-interleukin-1 therapy in rheumatic diseases. *Curr Opin Rheumatol.* 2001 May;13(3): 170-6. doi: 10.1097/00002281-200105000-00004.

10. Насонов ЕЛ. Новые направления фармакотерапии ревматических заболеваний – ингибиция интерлейкина 6 и интерлейкина 17. Современная ревматология. 2013; 7(3):5-14. [Nasonov EL. New areas of the pharmacotherapy of rheumatic diseases are inhibition of interleukin-6 and interleukin-17. *Sovremennaya revmatologiya = Modern Rheumatology Journal.* 2013;7(3):5-14. (In Russ.)]. doi: 10.14412/1996-7012-2013-04

11. Олюнин ЮА. Внутрисуставные инъекции лекарственных препаратов в комплексном лечении ревматических заболеваний. Современная ревматология. 2015;9(1):78–83. [Olyunin YuA. Intra-articular drug injections in the combination treatment of rheumatic diseases. *Sovremennaya revmatologiya = Modern Rheumatology Journal.* 2015;9(1): 78-83. (In Russ.)]. doi: 10.14412/1996-7012-2015-1-78-83

12. Af Klint E, Grundtman C, Engström M, et al. Intraarticular glucocorticoid treatment reduces inflammation in synovial cell infiltrations more efficiently than in synovial blood vessels. *Arthritis Rheum.* 2005 Dec;52(12): 3880-89. doi: 10.1002/art.21488

13. Gheorghe KR, Korotkova M, Catrina AI, et al. Expression of 5-lipoxygenase and 15-lipoxygenase in rheumatoid arthritis synovium and effects of intraarticular glucocorticoids. *Arthritis Res Ther.* 2009;11(3):R83. doi: 10.1186/ar2717. Epub 2009 Jun 4.

14. Nikas SN, Temekonidis TI, Zikou AK, et al. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. *Ann Rheum Dis.* 2004 Jan;63(1):102-3. doi: 10.1136/ard.2003.006981

15. Zhang F, Ma C. Comparison of the effectiveness on intra-articular and subcutaneous TNF inhibitor in rheumatoid arthritis

patients. *Clin Rheumatol.* 2018 Jan;37(1): 199-204. doi: 10.1007/s10067-017-3806-3. Epub 2017 Sep 4.
16. Mortada MA, Abdelwhab SM, Elgawish MH. Intra-articular methotrexate versus corticosteroid injections in medium-sized joints of rheumatoid arthritis patients-an intervention study. *Clin Rheumatol.* 2018 Feb; 37(2):331-7. doi: 10.1007/s10067-017-3843-y. Epub 2017 Sep 30.
17. Saito S, Kotake S. Is there evidence in support of the use of intra-articular hyaluronate in treating rheumatoid arthritis of the knee? A meta-analysis of the published literature. *Mod Rheumatol.* 2009;19(5):493-501. doi: 10.1007/s10165-009-0189-6. Epub 2009 Jun 23.
18. Васильев СА, Берковский АЛ, Мелкумян АЛ. Пособие по изучению функции тромбоцитов. Норма и патология. Москва; 2017. С. 9-12.
[Vasil'ev SA, Berkovskii AL, Melkumyan AL. Posobie po izucheniyu funktsii trombotsitov. *Norma i patologiya* [Manual for the study of platelet function. Norm and pathology]. Moscow; 2017. P. 9-12].
19. Lippi G, Franchini M. Platelets and immunity: the interplay of mean platelet volume in health and disease. *Expert Rev Hematol.* 2015 Oct;8(5):555-7. doi: 10.1586/17474086.2015.1069703. Epub 2015 Jul 15.
20. Nurden A. Platelets, inflammation and tissue regeneration. *Thromb Haemost.* 2011 May;105 Suppl 1:S13-33. doi: 10.1160/THS10-11-0720. Epub 2011 Apr 11.
21. Raposo G, Marks MS, Cutler DF. Lysosome-related organelles: driving post-Golgi compartments into specialisation. *Curr Opin Cell Biol.* 2007 Aug;19:394-401 doi: 10.1016/j.ceb.2007.05.001. Epub 2007 Jul 12.
22. Ambrosio AL, Di Pietro SM. Storage pool diseases illuminate platelet dense granule biogenesis. *Platelets.* 2017 Mar;28(2):138-146. doi: 10.1080/09537104.2016.1243789. Epub 2016 Nov 16.
23. Flaumenhaft R, Koseoglu S. Platelet Contents. In: Schulze H, Italiano J, editors. Molecular and Cellular Biology of Platelet Formation. Cham: Springer; 2016.
24. Scully D, Naseem KM, Matsakas A. Platelet biology in regenerative medicine of skeletal muscle. *Acta Physiol (Oxf).* 2018 Jul; 223(3):e13071. doi: 10.1111/apha.13071. Epub 2018 Apr 19.
25. Akhundov K, Pietramaggiori G, Waselle L, et al. Development of a cost-effective method for platelet-rich plasma (PRP) preparation for topical wound healing. *Ann Burns Fire Disasters.* 2012 Dec 31;25(4):207-13.
26. Oudelaar BW, Peerbooms JC, Huis In't Veld R, et al. Concentrations of blood components in commercial platelet-rich plasma separation systems: a review of the literature. *Am J Sports Med.* 2019 Feb;47(2):479-87. doi: 10.1177/0363546517746112. Epub 2018 Jan 16.
27. Samra DJ, Orchard JW. Patterns of platelet-rich plasma use among Australasian sports physicians. *BMJ Open Sport Exerc Med.* 2015 Nov 9;1(1):e000054. doi: 10.1136/bmjsem-2015-000054. eCollection 2015.
28. 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 Mar; 27(3):158-67. doi: 10.1016/j.tibtech.2008.11.009. Epub 2009 Jan 31.
29. Magalon J, Chateau AL, Bertrand B, et al. DEPA classification: a proposal for standardising PRP use and a retrospective application of available devices. *BMJ Open Sport Exerc.* Med. 2016 Feb;2(1):e000060. doi: 10.1136/bmjsem-2015-000060. eCollection 2016.
30. Lana JFSD, Purita J, Paulus C, et al. Contributions for classification of platelet rich plasma - proposal of a new classification: MARSPILL. *Regen Med.* 2017 Jul;12(5): 565-74. doi: 10.2217/rme-2017-0042. Epub 2017 Jul 31.
31. Piao L, Park H, Jo CH. Theoretical prediction and validation of cell recovery rates in preparing platelet-rich plasma through a centrifugation. *PLoS One.* 2017 Nov 2;12(11): e0187509. doi: 10.1371/journal.pone.0187509. eCollection 2017.
32. Kushida S, Kakudo N, Morimoto N, et al. Platelet and growth factor concentrations in activated platelet-rich plasma: a comparison of seven commercial separation systems. *J Artif Organs.* 2014 Jun;17(2):186-92. doi: 10.1007/s10047-014-0761-5. Epub 2014 Apr 20.
33. Kameyoshi Y, Dörschner A, Mallet AI, et al. Cytokine RANTES released by thrombin-stimulated platelets is a potent attractant for human eosinophils. *J Exp Med.* 1992 Aug 1;176(2):587-92. doi: 10.1084/jem.176.2.587
34. Tohidnezhad M, Bayer A, Rasuo B, et al. Platelet-Released Growth Factors Modulate the Secretion of Cytokines in Synoviocytes under Inflammatory Joint Disease. *Mediators Inflamm.* 2017;2017:1046438. doi: 10.1155/2017/1046438. Epub 2017 Nov 19.
35. Passaretti F, Tia M, D'Esposito V, et al. Growth-promoting action and growth factor release by different platelet derivatives. *Platelets.* 2014;25(4):252-6. doi: 10.3109/09537104.2013.809060. Epub 2013 Jul 15.
36. Mishra A, Tummala P, King A, et al. Buffered platelet-rich plasma enhances mesenchymal stem cell proliferation and chondrogenic differentiation. *Tissue Eng Part C Methods.* 2009 Sep;15(3):431-5 doi: 10.1089/ten.tec.2008.0534
37. Krüger JP, Hondke S, Endres M, et al. Human platelet-rich plasma stimulates migration and chondrogenic differentiation of human subchondral progenitor cells. *J Orthop Res.* 2012 Jun;30(6):845-52. doi: 10.1002/jor.22005. Epub 2011 Nov 4.
38. Cognasse F, Hamzeh-Cognasse H, Lafarge S, et al. Human platelets can activate peripheral blood B cells and increase production of immunoglobulins. *Exp Hematol.* 2007 Sep;35 (9):1376-87. doi: 10.1016/j.exphem.2007.05.021. Epub 2007 Jul 25.
39. Koupenova M, Clancy L, Corkrey HA, et al. Circulating platelets as mediators of immunity, inflammation, and thrombosis. *Circ Res.* 2018 Jan 19;122(2):337-51. doi: 10.1161/CIRCRESAHA.117.310795
40. Yeung J, Li W, Holinstat M. Platelet signaling and disease: targeted therapy for thrombosis and other related diseases. *Pharmacol Rev.* 2018 Jul;70(3):526-48. doi: 10.1124/pr.117.014530
41. Gasparyan AY, Ayvazyan L, Pretorius E. Platelets in rheumatic diseases: friend or foe? *Curr Pharm Des.* 2014;20(4):552-66. doi: 10.2174/13816128200414021314384 3.
42. Matsuno H. Remarkable efficacy of tocilizumab for treating rheumatoid arthritis in patients with high platelet counts. *Mod Rheumatol.* 2015 Jan;25(1):38-42. doi: 10.3109/14397595.2014.915073.
43. Zamora C, Canto E, Nieto JC, et al. Binding of Platelets to Lymphocytes: A Potential Anti-Inflammatory Therapy in Rheumatoid Arthritis. *J Immunol.* 2017 Apr 15;198(8):3099-108. doi: 10.4049/jimmunol.1601708. Epub 2017 Mar 1.
44. Gasparyan AY, Ayvazyan L, Mukanova U, et al. The Platelet-to-Lymphocyte Ratio as an Inflammatory Marker in Rheumatic Diseases. *Ann Lab Med.* 2019 Jul;39(4): 345-57. doi: 10.3343/alm.2019.39.4.345
45. Franck H, Rau R, Herborn G. Thrombocytopenia in patients with rheumatoid arthritis on long-term treatment with low dose methotrexate. *Clin Rheumatol.* 1996 May; 15(3):266-70. doi: 10.1007/BF02229705
46. Alsousou J, Thompson M, Harrison P, et al. Effect of platelet-rich plasma on healing tissues in acute ruptured Achilles tendon: a human immunohistochemistry study. *Lancet.* 2015 Feb 26;385 Suppl 1:S19. doi: 10.1016/S0140-6736(15)60334-8
47. Braun HJ, Wasterlain AS, Dragoo JL. The use of PRP in ligament and meniscal healing. *Sports Med Arthrosc Rev.* 2013 Dec; 21(4):206-12. doi: 10.1097/JSA.0000000000000005
48. Zhou Y, Wang JH. PRP Treatment Efficacy for Tendinopathy: A Review of Basic Science Studies. *Biomed Res Int.* 2016;2016: 9103792. doi: 10.1155/2016/9103792. Epub 2016 Aug 16.
49. Kim SJ, Yeo SM, Noh SJ, et al. Effect of platelet-rich plasma on the degenerative rotator cuff tendinopathy according to the compositions. *J Orthop Surg Res.* 2019 Dec;14(1): 408. doi: 10.1186/s13018-019-1406-4
50. Lim W, Park SH, Kim B, et al. Relationship of cytokine levels and clinical effect on platelet-rich plasma-treated lateral epicondylitis. *J Orthop Res.* 2018 Mar;36(3):913-20. doi: 10.1002/jor.23714. Epub 2017 Sep 20.
51. Shichao T, Ji L, Changqing Z. Platelet-rich plasma inhibits inflammatory factors and

represses rheumatoid fibroblast-like synoviocytes in rheumatoid arthritis. *Clin Exp Med.* 2017 Nov;17(4):441-9. doi: 10.1007/s10238-017-0449-2. Epub 2017 Jan 24.
52. Jin CH, Chae SY, Kim TH, et al. Effect of tumor necrosis factor-related apoptosis-inducing ligand on the reduction of joint inflammation in experimental rheumatoid arthritis. *J Pharmacol Exp Ther.* 2010 Mar; 332(3):858-65. doi: 10.1124/jpet.109.159517. Epub 2009 Nov 20.
53. Yao Q, Seol DW, Mi Z, et al. Intra-articular injection of recombinant TRAIL induces synovial apoptosis and reduces inflammation in a rabbit knee model of arthritis. *Arthritis Res Ther.* 2006;8(1):R16. doi: 10.1186/ar1867.
54. Ichikawa K, Liu W, Fleck M, et al. TRAIL-R2 (DR5) mediates apoptosis of synovial fibroblasts in rheumatoid arthritis. *J Immunol.* 2003 Jul 15;171(2):1061-9. doi: 10.4049/jimmunol.171.2.1061
55. Chyuan IT, Tsai HF, Liao HJ, et al. An apoptosis-independent role of TRAIL in suppressing joint inflammation and inhibiting T-cell activation in inflammatory arthritis. *Cell Mol Immunol.* 2018 Sep;15(9):846-57. doi: 10.1038/cmi.2017.2. Epub 2017 Apr 10.
56. Lippross S, Moeller B, Haas H, et al. Intraarticular injection of platelet-rich plasma reduces inflammation in a pig model of rheumatoid arthritis of the knee joint. *Arthritis Rheum.* 2011 Nov;63(11):3344-53. doi: 10.1002/art.30547
57. Nadia A, Asmaa M. Anti-arthritic Effects of Platelets Rich Plasma and Hyaluronic Acid on Adjuvant-induced Arthritis in Rats. I*nternational Journal of Pharmacology.* 2020;16:33-46; doi: 10.3923/ijp.2020.33.46
58. Badsha H, Harifi G, Murrell WD. Platelet Rich Plasma for Treatment of Rheumatoid Arthritis: Case Series and Review of Literature. *Case Rep Rheumatol.* 2020 Jan 31;2020:8761485. doi: 10.1155/2020/8761485. eCollection 2020.
59. Latalski M, Walczyk A, Fatyga M, et al. Allergic reaction to platelet-rich plasma (PRP): Case report. *Medicine (Baltimore).* 2019 Mar;98(10):e14702. doi: 10.1097/MD.0000000000014702
60. Shanshan Y, BinZhou Y, Chen S. Platelet-rich plasma promotes the migration and invasion of synovial fibroblasts in patients with rheumatoid arthritis. *Mol Med Rep.* 2016 Sep;14(3):2269-75. doi: 10.3892/mmr.2016.5500. Epub 2016 Jul 11.

Received/Reviewed/Accepted
11.11.2020/27.12.2020/29.12.2020

Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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