Osteoarthritis (OA) is an extremely prevalent joint condition in the United States, affecting over 30 million people [1]. Its pathophysiology is linked with inflammation of the synovial tissue and degeneration of articular cartilage, resulting in pain and decreased function [2–4]. OA normally affects larger weight-bearing joints, with the number of people suffering from knee OA anticipated to reach 67 million by 2030 [1]. Normally, OA is managed with activity modification, physical therapy, pharmacological agents (such as, NSAIDs, corticosteroids, viscosupplementation, opioids, etc.), and surgery after conservative management modalities have failed [5]. These treatment options have limitations, continually trying to reduce pain as opposed to aiming on the underlying pathology [5,6].

Over the last decade, a number of molecular targets, such as interleukin-1 (IL-1), transforming growth factor-β (TGF-β), matrix metalloproteinases (MMPs), etc., have been identified as being involved in the etiopathogenesis of OA [7–9], yet many treatments may well have a negative risk-to-benefit ratio [10,11]. Thus, other safe and effective treatment options are required to address this unmet medical need.

Recently, there has been a notable growth in the use of biologics, including platelet-rich plasma (PRP), for regenerative medicine applications, particularly in musculoskeletal medicine [12]. PRP is an autologous blood-derived product containing patients’ own concentrated platelets in a small volume of plasma utilized for treatment of several conditions [13,14]. PRP exerts its effect on the adjacent tissue following release of a variety of growth factors and cytokines from the platelet concentrate [15].

Two factors—platelet count and platelet aggregation—have been indicated to affect the efficacy of PRP. No consensus exists for a standardized concentration of platelets in the PRP, and studies have demonstrated that too low or too high of a platelet count can hinder the efficacy of PRP [16]. Notably, a recent study reported that the platelet count was positively correlated with the concentration of growth factors [17]. This demonstrated that the platelet count plays a vital role in determining the capability of PRP to exert its downstream effects. Similarly, platelet aggregation is essential for platelets to secrete their growth factors via a process of intracellular protein phosphorylation [15,18].

Despite much research on preparation and activation methods of PRP [19,20], there is insufficient literature on the efficacy of PRP injections according to patient-related variables.
One study identified this gap and attempted to recognize patient-specific variables that could influence the PRP effectiveness [21]. In particular, this study identified medications, mental and physical stress levels, blood pressure, smoking status, and alcohol consumption as patient-specific variables that should be considered given their ability to affect the analgesic efficacy of PRP [21]. Nevertheless, there are limited number of studies on common medications consumed by patients and their effects on PRP. Additionally, there is a lack of detailed guidelines pertaining to which medications should be stopped prior to PRP injection. Here, the author focused on a recently published review [22] that evaluated some of the most commonly prescribed medications in the US and their effects on PRP, in order to establish guidelines for medications that need to be stopped prior to a PRP injection.

Paracetamol induced a profound diminished aggregation of platelets when compared with placebo in a dose-dependent manner [23,24]. Patients treated with non-selective NSAIDs, such as ibuprofen or indomethacin, demonstrated no change in platelet count but decreased platelet aggregation was noted. Patients who took diclofenac after recent orthopaedic procedures demonstrated substantial reduction of aggregation of platelets [25]. Decreased platelet aggregation was observed with a single dose of intravenous diclofenac with decreasing levels of TXb2 to 1.6% of baseline [26]. After a recent orthopaedic procedure, PRP samples drawn from patients who took dextroprofen or diclofenac showed a significant decrease in aggregation of platelets when compared with placebo [25]. Decreased platelet aggregation and serum TXb2 concentration were observed in healthy volunteers treated with 500 mg naproxen twice daily for 10 days [27]. A complete reversal of platelet aggregation was demonstrated within 24 h with single dose of sulindac; however, with continuous administration for 8 days, platelet aggregation remained inhibited [28]. Supratherapeutic dose of valdecoxib (40 mg BD) and therapeutic dose of naproxen (500 mg BD) and diclofenac (75 mg BD) do not interfere in the function of platelets in healthy volunteers [29]. Meloxicam decreased TXb2 production in a dose-dependent manner when compared with placebo [30]. Decreased platelet aggregation and serum TXb2 concentration were observed in healthy volunteers treated with 500 mg naproxen twice daily for 10 days [27]. A complete reversal of platelet aggregation was demonstrated within 24 h with single dose of sulindac; however, with continuous administration for 8 days, platelet aggregation remained inhibited [28]. Supratherapeutic dose of valdecoxib (40 mg BD) and therapeutic dose of naproxen (500 mg BD) and diclofenac (75 mg BD) do not interfere in the function of platelets in healthy volunteers [29]. Meloxicam decreased TXb2 production in a dose-dependent manner when compared with placebo [30]. In patients who take daily low dose aspirin, Jayaram et al. demonstrated reduced growth factors levels in freshly prepared human leucocyte rich-PRP when activated with arachidonic acid [31].

Anitua et al. confirmed the reduced angiogenic potential and the capacity to induce hyaluronic acid and fibronectin of PRP in patients taking anticoagulants. The biological potential of platelet-rich growth factors is maintained in patients taking acetylsalicylic acid, acenocoumarol, glucosamine sulfate and chondroitin sulfate [32]. Cellular proliferation was not affected, whereas cellular migration was enhanced by acetylsalicylic acid, acenocoumarol, glucosamine sulfate and chondroitin sulfate. No effect on extracellular matrix proteins secreted by gingival fibroblasts was noted [33]. Ketorolac and PRP increases chondrocyte and tenocyte viability than methylprednisolone [34]. COX-2 inhibitors do not inhibit platelet activation or growth factor release from PRP [35]. Leucocyte rich PRP samples from patients using naproxen demonstrated a diminished PDGF and IL-6 levels without affecting TNF-α, IL-1β, IL-8, VEGF, and FGF-2. All factors were normalized after a 1-week washout period [36]. There was no reduction in the release of anabolic growth factors when patients used acetylsalicylic acid or acetylsalicylic acid with clopidogrel [37]. NSAIDs such diclofenac and meloxicam did not alter the release of VEGF and PDGF-AB levels of PRP [38]. There was no difference in thrombin production and platelet activation in response to TRAP-6, but there was significantly decreased ADP-induced platelet activation [39].

When administering PRP as a therapeutic agent for musculoskeletal disorders, the treating physician/surgeon must be aware of the quality of PRP being delivered at the target site, the factors responsible for procuring quality PRP, and the medications interfering with the homeostasis of PRP.

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**References**

1. Gupta, A.; Maffulli, N. Allogenic umbilical cord tissue treatment of knee osteoarthritis. *Sports Med. Arthrosc. Rev.* **2022**, *30*, 162–165. [CrossRef] [PubMed]

2. Gupta, A.; Rodriguez, H.C.; Potty, A.G.; Levy, A.H.J.; El-Amin, S.F., III. Treatment of Knee Osteoarthritis with Intraarticular Umbilical Cord-Derived Wharton’s Jelly: A Case Report. *Pharmaceuticals* **2021**, *14*, 883. [CrossRef] [PubMed]

3. Harrison-Brown, M.; Scholes, C.; Hafsi, K.; Marenah, M.; Li, J.; Hassan, F.; Maffulli, N.; Murrell, W.D. Efficacy and safety of culture-expanded, mesenchymal stem/stromal cells for the treatment of knee osteoarthritis: A systematic review protocol. *J. Orthop. Surg. Res.* **2019**, *14*, 34. [CrossRef] [PubMed]

4. Goldberg, A.; Mitchell, K.; Soans, J.; Kim, L.; Zaidi, R. The use of mesenchymal stem cells for cartilage repair and regeneration: A systematic review. *J. Orthop. Surg. Res.* **2017**, *12*, 39. [CrossRef]

5. Main, B.J.; Maffulli, N.; Valk, J.A.; Rodriguez, H.C.; Gupta, M.; El-Amin, S.F., III; Gupta, A. Umbilical Cord-Derived Wharton’s Jelly for Regenerative Medicine Applications: A Systematic Review. *Pharmaceuticals* **2021**, *14*, 1090. [CrossRef]

6. Gupta, A. Allogenic Amniotic Tissue for Treatment of Knee and Hip Osteoarthritis. *Pharmaceuticals* **2022**, *15*, 404. [CrossRef]

7. Sokolove, J.; Lepus, C.M. Role of inflammation in the pathogenesis of osteoarthritis: Latest findings and interpretations. *Ther. Adv. Musculoskelet. Dis.* **2013**, *5*, 77–94. [CrossRef]

8. Little, C.B.; Hunter, D.J. Post-traumatic osteoarthritis: From mouse models to clinical trials. *Nat. Rev. Rheumatol.* **2013**, *9*, 485–497. [CrossRef]

9. Loeser, R.F.; Goldring, S.R.; Scanzello, C.R.; Goldring, M.B. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum.* **2012**, *64*, 1697–1707. [CrossRef]

10. Bush, J.R.; Beier, F. TGF-β and osteoarthritis—The good and the bad. *Nat. Med.* **2013**, *19*, 667–669. [CrossRef]

11. Aoki, C.A.; Borchers, A.T.; Li, M.; Flavell, R.A.; Bowhus, C.I.; Ansari, A.A.; Gershwin, M.E. Transforming growth factor beta (TGF-beta) and autoimmunity. *Autoimmun. Rev.* **2005**, *4*, 450–459. [CrossRef] [PubMed]

12. Andia, I.; Maffulli, N. Mesenchymal stromal cell products for intra-articular knee injections for conservative management of osteoarthritis. *Ther. Adv. Musculoskelet. Dis.* **2021**, *13*, 1759720X21996953. [CrossRef] [PubMed]

13. Carr, A.J.; Murphy, R.R.; Dakin, S.G.; Rombach, I.N.E.S.; Wheway, K.I.M.; Watkins, B.; Franklin, S.L. Platelet-rich plasma injection with arthroscopic acromioplasty for chronic rotator cuff tendinopathy: A randomized controlled trial. *Am. J. Sports Med.* **2017**, *45*, 2891–2897. [CrossRef] [PubMed]

14. De Almeida, A.M.; Demange, M.K.; Sobrado, M.F.; Rodrigues, M.B.; Pedrinelli, A.; Hernandez, A.J. Patellar tendon healing with arthroscopic acromioplasty for chronic rotator cuff tendinopathy: A randomized controlled trial. *Am. J. Sports Med.* **2012**, *40*, 1282–1288. [CrossRef] [PubMed]

15. Alousouj, J.; Thompson, M.; Hulley, P.; Noble, A.; Willett, K. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery. *J. Bone Joint Surg. Br.* **2009**, *91*, 987–996. [CrossRef]

16. Weibrich, G.; Hansen, T.; Kleis, W.; Buch, R.; Hitzler, W.E. Effect of platelet concentration in platelet-rich plasma on peri-implant bone regeneration. *Bone* **2004**, *34*, 665–671. [CrossRef] [PubMed]

17. Taniguchi, Y.; Yoshioka, T.; Sugaya, H.; Gosho, M.; Aoto, K.; Kanamori, A.; Yamazaki, A. Growth factor levels in leukocyte-poor platelet-rich plasma and correlations with donor age, gender, and platelets in the Japanese population. *J. Exp. Orthop.* **2019**, *6*, 4. [CrossRef]

18. Zhou, L.; Schmaier, A.H. Platelet aggregation testing in platelet-rich plasma: Description of procedures with the aim to develop standards in the field. *Am. J. Clin. Pathol.* **2005**, *123*, 172–183. [CrossRef]

19. Cavallo, C.; Roffi, A.; Grigolo, B.; Mariani, E.; Pratelli, L.; Merli, G.; Kon, E.; Marcacci, M.; Filardo, G. Platelet-rich plasma: The choice of activation method affects the release of bioactive molecules. *Biomed. Res. Int.* **2016**, *2016*, 6591717. [CrossRef]

20. Mazzocca, A.D.; McCarthy, M.B.R.; Chowaniec, D.M.; Cote, M.P.; Romeo, A.A.; Bradley, J.P.; Arciero, R.A.; Beitzel, K. Platelet-rich plasma differs according to preparation method and human variability. *J. Bone Joint Surg. Am.* **2012**, *94*, 308–316. [CrossRef]

21. Kuffler, D.P. Variables affecting the potential efficacy of PRP in providing chronic pain relief. *J. Pain Res.* **2018**, *12*, 109–116. [CrossRef]

22. Kao, D.S.; Zhang, S.W.; Vap, A.R. A Systematic Review on the Effect of Common Medications on Platelet Count and Function: Which Medications Should Be Stopped before Getting a Platelet-Rich Plasma Injection? *Orthop. J. Sports Med.* **2022**, *10*, 23259671221088820. [CrossRef]

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23. Munsterhjelm, E.; Niemi, T.T.; Ylikorkala, O.; Silvanto, M.; Rosenberg, P.H. Characterization of Inhibition of Platelet Function by Paracetamol and Its Interaction with Diclofenac in Vitro. *Acta Anaesthesiol. Scand.* **2005**, *49*, 840–846. [CrossRef] [PubMed]

24. Munsterhjelm, E.; Munsterhjelm, N.M.; Niemi, T.T.; Ylikorkala, O.; Neuvonen, P.J.; Rosenberg, P.H. Dose-Dependent Inhibition of Platelet Function by Acetaminophen in Healthy Volunteers. *Anesthesiology* **2005**, *103*, 712–717. [CrossRef] [PubMed]

25. Schippinger, G.; Prüller, F.; Divjak, M.; Mahla, E.; Fankhauser, F.; Rackemann, S.; Raggam, R.B. Autologous Platelet-Rich Plasma Preparations: Influence of Nonsteroidal Anti-Inflammatory Drugs on Platelet Function. *Orthop. J. Sports Med.* **2015**, *3*, 232596715588896. [CrossRef] [PubMed]

26. Munsterhjelm, E.; Niemi, T.T.; Syrjälä, M.T.; Ylikorkala, O.; Rosenberg, P.H. Propacetamol Augments Inhibition of Platelet Function by Diclofenac in Volunteers. *Br. J. Anaesth.* **2003**, *91*, 357–362. [CrossRef]

27. Leese, P.T.; Hubbard, R.C.; Karim, A.; Isakson, P.C.; Yu, S.S.; Geis, G.S. Effects of Celecoxib, a Novel Cyclooxygenase-2 Inhibitor, on Platelet Function in Healthy Adults: A Randomized, Controlled Trial. *J. Clin. Pharmacol.* **2000**, *40*, 124–132. [CrossRef]

28. Green, D.; Given, K.M.; Ts’ao, C.; Whipple, J.P.; Rossi, E.C. The Effect of a New Non-Steroidal Anti-Inflammatory Agent, Sulindac, on Platelet Function. *Thromb. Res.* **1977**, *10*, 283–289. [CrossRef]

29. Leese, P.T.; Talwalker, S.; Kent, J.D.; Recker, D.P. Valdecoxib Does Not Impair Platelet Function. *Am. J. Emerg. Med.* **2002**, *20*, 275–281. [CrossRef]

30. Rinder, H.M.; Tracey, J.B.; Souhrada, M.; Wang, C.; Gagnier, R.P.; Wood, C.C. Effects of Meloxicam on Platelet Function in Healthy Adults: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Clin. Pharmacol.* **2002**, *42*, 881–886. [CrossRef]

31. Jayaram, P.; Yeh, P.; Patel, S.J.; Cela, R.; Shybut, T.B.; Grol, M.W.; Lee, B.H. Effects of Aspirin on Growth Factor Release from Freshly Isolated Leukocyte-Rich Platelet-Rich Plasma in Healthy Men: A Prospective Fixed-Sequence Controlled Laboratory Study. *Am. J. Sports Med.* **2019**, *47*, 1223–1229. [CrossRef] [PubMed]

32. Anitua, E.; Troya, M.; Zaldueguo, M.; Orive, G. Effects of Anti-Aggregant, Anti-Inflammatory and Anti-Coagulant Drug Consumption on the Preparation and Therapeutic Potential of Plasma Rich in Growth Factors (PRGF). *Growth Factors* **2015**, *33*, 57–64. [CrossRef] [PubMed]

33. Anitua, E.; Troya, M.; Zaldueguo, M.M.; Orive, G. The Effect of Different Drugs on the Preparation and Biological Outcomes of Plasma Rich in Growth Factors. *Ann. Anat.* **2014**, *196*, 423–429. [CrossRef] [PubMed]

34. Beitzel, K.; McCarthy, M.B.; Cote, M.P.; Apostolakos, J.; Russell, R.P.; Bradley, J.; ElAttrache, N.S.; Romeo, A.A.; Arciero, R.A.; Mazzocca, A.D. The Effect of Ketorolac Tromethamine, Methylprednisolone, and Platelet-Rich Plasma on Human Chondrocyte and Tenocyte Viability. *Arthroscopy* **2019**, *35*, 1164–1174. [CrossRef]

35. Hc, L.; Ke, B.; Bm, B.; Sp, F. Use of a Cyclooxygenase-2 Inhibitor Does Not Inhibit Platelet Activation or Growth Factor Release from Platelet-Rich Plasma. *Am. J. Sports Med.* **2017**, *45*, 3351–3357. [CrossRef]

36. Mannava, S.; Whitney, K.E.; Kennedy, M.I.; King, J.; Dornan, G.J.; Klett, K.; Chahla, J.; Evans, T.A.; Huard, J.; LaPrade, R.F. The Influence of Naproxen on Biological Factors in Leukocyte-Rich Platelet-Rich Plasma: A Prospective Comparative Study. *Arthroscopy* **2019**, *35*, 201–210. [CrossRef] [PubMed]

37. Smith, C.W.; Binford, R.S.; Holt, D.W.; Webb, D.P. Quality Assessment of Platelet Rich Plasma during Anti-Platelet Therapy. *Perfusion* **2007**, *22*, 41–50. [CrossRef] [PubMed]

38. Utku, B.; Dönmez, G.; Erigen, G.; Akin, Ş.; Demirel, H.A.; Korkusuz, F.; Doral, M.N. Meloxicam and Diclofenac Do Not Change VEGF and PDGF-Abserum Levels of Platelet-Rich Plasma. *Turk. J. Med. Sci.* **2017**, *47*, 570–576. [CrossRef]

39. Velier, M.; Magalon, J.; Daumas, A.; Cassar, M.; Francois, P.; Ghazouane, A.; Philandrianos, C.; Bertrand, B.; Frece, C.; Bernot, D.; et al. Production of Platelet-Rich Plasma Gel from Elderly Patients under Antithrombotic Drugs: Perspectives in Chronic Wounds Care. *Platelets* **2018**, *29*, 496–503. [CrossRef]