ESCAPING SPIN WIZARDRY IN PAIN MEDICINE

LEARNING CLASSIFICATION, QUANTIFICATION, AND SPECIFICATION (2025)

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CONFLICT OF INTEREST DISCLOSURE

No actual or potential financial conflicts of interest associated with the material presented in this lecture.

SUMMARY

A) Learning Points for the Session.

B) Types of PRP Concentrates and the Importance of Leukocytes.

C) Influence of Outside Elements in the Preparation.

D) The Importance of Interpersonal Variations in Whole Blood Samples.

SUMMARY

E) Biochemical Effects of PRP Concentrates in Different Target Tissues (Joint and Tendon).

F) The Importance of Classification, Quantification, and Specification.

G) Controversies and Future Directions of Research.

LEARNING POINTS BY THE END OF THE SESSION:

A) **DISTINGUISH** between different types of PRP Concentrates.

B) **UNDERSTAND** the potential influence of external elements in the PRP concentrate.

C) **ENUMERATE** the main biological effects of PRP in different target tissues (joint and tendon).

D) **RECOGNIZE** the clinical importance of classification, quantification, and specification.

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Daring discourse

From spin wizardry to regenerative alchemy: a philosophical inquiry into healing and standardization

Guilherme Ferreira-Dos-Santos [1,2]

product, may only observe modest improvement. These concrete examples of variability serve as poignant reminders that our current nomenclature often masks profound methodological differences.

The ancient parable of the blind men and the elephant offers a striking metaphor here. Each blind man, touching only a part of the elephant, describes it in entirely different terms—a snake, a

Ferreira-Dos-Santos G. **From Spin Wizardry to Regenerative Alchemy: A Philosophical Inquiry Into Healing and Standardization.** *Reg Anesth Pain Med.* Published Online First: 29 April 2025.

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Narrative Review

Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review

Guilherme Ferreira-Dos-Santos, MD[1], Mark Friedrich B. Hurdle, MD[2], Steven R. Clendenen, MD[3], Jason S. Eldrige, MD[2], and Wenchun Qu, MD, PhD[2]

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review**. *Pain Physician*. 2022;25(1):15-27.

Table 1. *The most important α-granule growth factors and their contributions to the process of tissue healing and repair.*

Growth Factor	Role in Tissue Healing and Repair
bFGF-1	1. May contribute to stimulate angiogenesis; 2. Mediates cell migration; 3. Stimulates proliferation of capillary endothelial cells; 4. Influences fibroblasts to produce collagenase; 5. Contributes to the production of granulation tissue.
EGF	1. Mitogenic factor; 2. Stimulates the proliferation and differentiation of fibroblasts, epidermal and epithelial cells; 3. May play an enhancer role on osteogenic differentiation of mesenchymal stem cells (by increasing ECM mineralization).
HGF	1. Mitogenic factor; 2. Promotes angiogenesis (particularly after ischemia); 3. Accelerates healing by promoting the dedifferentiation of epidermal cells; 4. Regulates cell growth, cell motility, and morphogenesis.
IGF-1	1. Expressed mainly in the early inflammatory phase; 2. Anabolic effects; 3. Stimulates protein synthesis, the proliferation of myoblasts and fibroblasts; 4. Enhances collagen and ECM matrix; 5. May contribute to early modulation of edema.
PDGF-AB	1. Expressed in the early stages of tendon repair; 2. Facilitates the proliferation of other growth factors; 3. Attracts mesenchymal stem cells and leukocytes; 4. Stimulates angiogenesis; 5. Contributes to tissue remodeling.
TGF-β1	1. Proinflammatory type 2 cytokine (antibody response enhancer); 2. Immunosuppressant during the early inflammatory phase; 3. Aids in cell migration and fibronectin binding; 4. Augments production of tendon sheath fibroblasts; 5. Improves tendon mechanics during the healing process; 6. Controls angiogenesis and fibrosis.
VEGF	1. Expression peaks in the late inflammatory and proliferative phases; 2. Promotes angiogenesis (neovascularization).

Legend: bFGF-1, Basic fibroblast growth factor one; ECM, Extracellular matrix; EGF, Epidermal growth factor; HGF, Hepatocyte growth factor; IGF-1, Insulin-like growth factor 1; PDGF-Aβ, Platelet-derived growth factor AB; TGF-β1, Transforming growth factor β1; VEGF, Vascular endothelial growth factor.

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

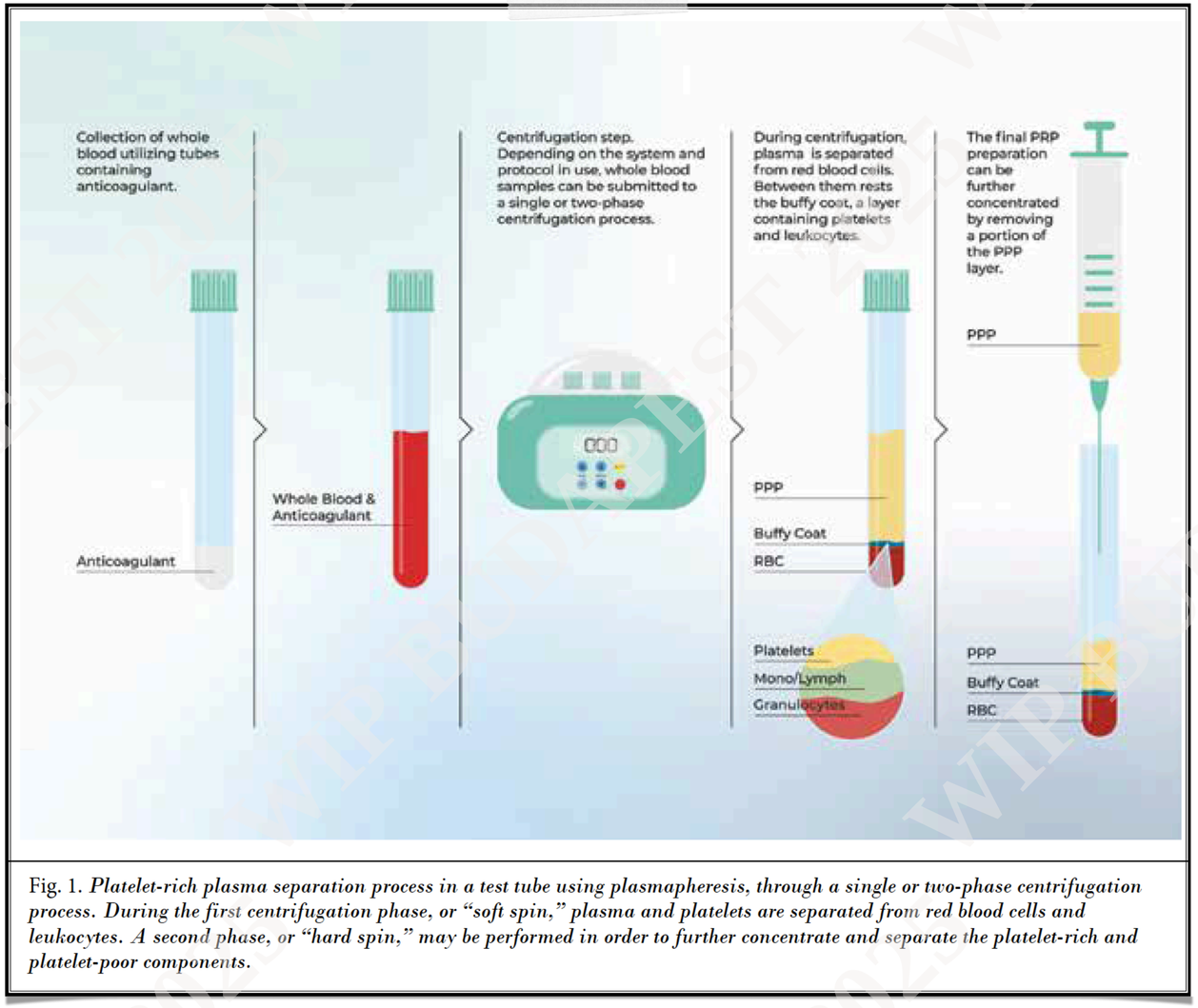
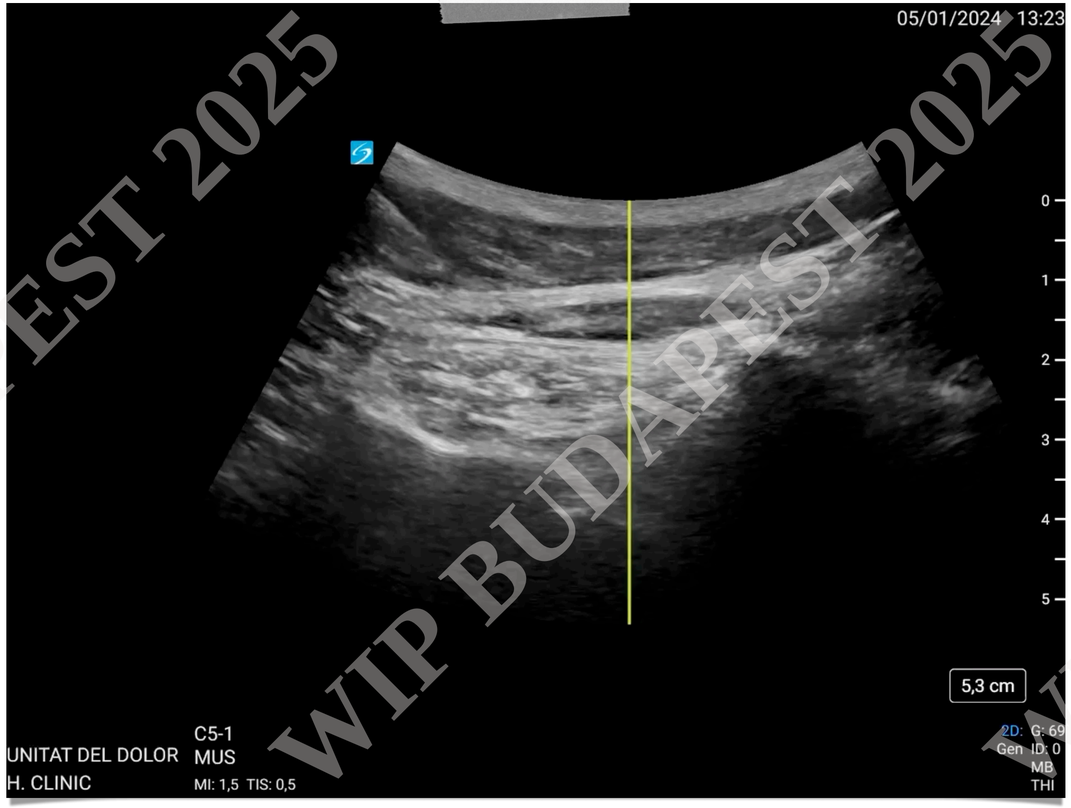


Fig. 1. *Platelet-rich plasma separation process in a test tube using plasmapheresis, through a single or two-phase centrifugation process. During the first centrifugation phase, or "soft spin," plasma and platelets are separated from red blood cells and leukocytes. A second phase, or "hard spin," may be performed in order to further concentrate and separate the platelet-rich and platelet-poor components.*

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review. *Pain Physician*. 2022;25(1):15-27.



Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

TYPES OF PRP CONCENTRATES AND THE IMPORTANCE OF LEUKOCYTES

Because **the inclusion of leukocytes in the final preparation may affect the potency and efficacy of the final product**, the more generic term “PRP” does not distinguish between different products with different specificities.

Wasterlain AS, Braun HJ, Dragoo JL. **Contents and Formulation of Platelet-rich Plasma.** *Operative Tech Orthop*. 2012;22:33-42.

Kobayashi Y, Saita Y, Nishio H, *et al*. **Leukocyte Concentration and Composition in Platelet-rich Plasma (PRP) Influences the Growth Factor and Protease Concentrations.** *J Orthop Sci*. 2016;21:683-689.

TYPES OF PRP CONCENTRATES AND THE IMPORTANCE OF LEUKOCYTES

Leukocyte-rich PRP (LR-PRP) - PRP Preparation with leukocyte count **ABOVE** the patient's baseline. Associated with a more intense **PRO-INFLAMMATORY** local response.

Leukocyte-poor PRP (LP-PRP) - PRP preparation with leukocyte count **BELOW** the patient's baseline. Mainly associated with an **ANTI-INFLAMMATORY** local response.

Wasterlain AS, Braun HJ, Dragoo JL. **Contents and Formulation of Platelet-rich Plasma.** *Operative Tech Orthop*. 2012;22:33-42.

Kobayashi Y, Saita Y, Nishio H, *et al*. **Leukocyte Concentration and Composition in Platelet-rich Plasma (PRP) Influences the Growth Factor and Protease Concentrations.** *J Orthop Sci*. 2016;21:683-689.

TYPES OF PRP CONCENTRATES AND THE IMPORTANCE OF LEUKOCYTES

Leukocyte-rich PRP (LR-PRP) - Induces predominantly **CATABOLIC** and **INFLAMMATORY** changes, such as increased MMP 1, MMP-13, IL-1β, IL-6, and TNF-α.

Leukocyte-poor PRP (LP-PRP) - Induces predominantly **ANABOLIC** effects such as increased gene expression of anabolic genes, alpha-smooth muscle actin, and collagen types I and III.

Zhou Y, Zhang J, Wu H, Hogan MV, Wang JHC. **The Differential Effects of Leukocyte Containing and Pure Platelet-rich Plasma (PRP) on Tendon Stem/Progenitor Cells – Implications of PRP Application for the Clinical Treatment of Tendon Injuries.** *Stem Cell Res Ther*. 2015;6:173-186.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

The initial whole blood sample is most often collected in the presence of an anticoagulant, which binds calcium and prevents the initiation of the clotting cascade through inhibition of the conversion of prothrombin to thrombin.

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

Table 2. *Anticoagulants utilized for platelet-rich plasma concentrate preparation and their effects on platelet count and recovery, morphology, platelet morphology, α-granule growth factor release, and bone marrow-derived mesenchymal stromal cell gene expression.*

Anticoagulant	Platelet Count / Recovery Rate	Platelet Morphology	Growth Factor Release	BM-MSC Gene Expression
ACD-A	Lowest average count / 45% of total	No influence on MPV	No significant differences in TGFβ-1 and VEGF concentration	30% different from control group
EDTA	Highest average count / 76% of total	MPV increase, likely indicating platelet activation		47% different from control group
Sodium Citrate	Medium average count / 81% of total	No influence on MPV		25% different from control group

Legend: ACD-A, Anticoagulant citrate dextrose solution A; BM-MSC, Bone marrow-derived mesenchymal stromal cells; EDTA, ethylenediamine-tetraacetic acid; MPV, Mean platelet volume; TGF-β1, Transforming growth factor β1; VEGF, Vascular endothelial growth factor.

Adapted from: Amaral RJ, da Silva NP, Haddad NF, *et al*. Platelet-rich Plasma Obtained with Different Anticoagulants and their Effect on Platelet Numbers and Mesenchymal Stromal Cells Behavior in Vitro. *Stem Cells Int*. 2016;2016:7414036.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

Some studies have also reported the utilization of PRP concentrates prepared in the absence of an anticoagulant. **In such circumstances, the time required between whole blood collection and injection must be substantially shortened.**

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

PRP separation protocols also vary in platelet activation method. ACTIVATION refers to 2 key processes: The **DEGRANULATION OF PLATELETS** to release growth factors from their α-granules, and the **CLEAVAGE OF FIBRINOGEN** to initiate matrix formation.

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

Several of the commercial kits available on the market already include an activation step before PRP administration, commonly by adding thrombin and/or calcium chloride. However, external activation may not be necessary, as PRP activates when in contact with fibrillar collagen.

Wasterlain AS, Braun HJ, Dragoo JL. **Contents and Formulation of Platelet-rich Plasma.** *Operative Tech Orthop*. 2012;22:33-42.

Kobayashi Y, Saita Y, Nishio H, *et al*. **Leukocyte Concentration and Composition in Platelet-rich Plasma (PRP) Influences the Growth Factor and Protease Concentrations.** *J Orthop Sci*. 2016;21:683-689.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

Table 3. *Head-to-head comparison of the protocols for platelet-rich plasma separation from 3 different commercial systems.*

Commercial Systems	Whole Blood Volume (mL)	Anticoagulant Utilized	Centrifuge Force (g) / Centrifuge Time	Final Volume of PRP (mL)
Cascade (MTF Sport Medicine, Edison, New Jersey)	18	Sodium citrate, 2 mL	1100 / 6 min	7.5
GPS III (Biomet Orthopedics Inc, Warsaw, Indiana)	55	ACD-A, 5 mL	1100 / 15 min	6.0
Magellan (Arteriocyte Inc, Cleveland, Ohio)	26	ACD-A, 5 mL	1200 / 17 min	6.0

Legend: ACD-A, Anticoagulant citrate dextrose solution A; PRP, Platelet-rich plasma.

Adapted from: Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. **Comparison of Growth Factor and Platelet Concentration from Commercial Platelet-rich Plasma Separation Systems.** *Am J Sports Med*. 2011;39(2):266-271.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

Table 4. *Comparison of mean platelet concentration and platelet capture efficiency, red blood cell, white blood cell, and fibrinogen concentrations between three different platelet-rich plasma separation systems.*

Commercial Systems	Platelet Concentration (x103/µL)	Platelet Capture Efficiency Rate (%)	Red Blood Cells (x103/µL)	White Blood Cells (x103/µL)	Fibrinogen (mg/dL)
Cascade (MTF Sport Medicine, Edison, New Jersey)	443.8 ± 24.7	67.6 ± 4.1	0.1 ± 0.1	1.1 ± 0.2	283.8 ± 34.2
GPS III (Biomet Orthopedics Inc, Warsaw, Indiana)	566.2 ± 292.6	22.6 ± 11.8	1.5 ± 1.7	34.4 ± 13.6	286.0 ± 42.7
Magellan (Arteriocyte Inc, Cleveland, Ohio)	780.2 ± 246.5	65.5 ± 19.6	0.5 ± 0.3	11.0 ± 8.2	277.4 ± 30.5

Adapted from: Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. **Comparison of Growth Factor and Platelet Concentration from Commercial Platelet-rich Plasma Separation Systems.** *Am J Sports Med*. 2011;39(2):266-271.

INFLUENCE OF OUTSIDE ELEMENTS IN THE PREPARATION

Table 5. *Comparison of mean growth factor concentrations between 3 different platelet-rich plasma separation systems.*

Commercial Systems	PDGF-αβ (ng/mL)	PDGF-ββ (ng/mL)	TGF-β1 (ng/mL)	VEGF (ng/mL)
Cascade (MTF Sport Medicine, Edison, New Jersey)	9.7 ± 3.6	14.8 ± 2.5	0.1 ± 0.08	0.3 ± 0.3
GPS III (Biomet Orthopedics Inc, Warsaw, Indiana)	18.7 ± 12.8	23.1 ± 10.1	0.1 ± 0.08	2.4 ± 1.1
Magellan (Arteriocyte Inc, Cleveland, Ohio)	34.4 ± 10.7	33.0 ± 8.2	0.2 ± 0.1	1.2 ± 0.8

Legend: PDGF-αβ, Platelet-derived growth factor αβ; PDGF-ββ, Platelet-derived growth factor ββ; TGF-β1, Transforming growth factor β1; VEGF, Vascular endothelial growth factor.

Adapted from: Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. **Comparison of Growth Factor and Platelet Concentration from Commercial Platelet-rich Plasma Separation Systems.** *Am J Sports Med*. 2011;39(2):266-271.

INTERPERSONAL VARIATIONS IN WHOLE BLOOD SAMPLES

The normal range of platelets in the whole blood of a healthy individual is 150,000 to 350,000 platelets/µl. **Past consensus agreed on a working definition of platelet concentrate as a preparation with a MINIMUM of 1.0 x 10^6 platelets/µL (1.0 x 10^9 platelets/mL).**

Marx RE. **Platelet-rich Plasma (PRP): What is PRP and what is not PRP?.** *Implants Dental*. 2001;10:225-228.

Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. **Effect of Platelet Concentration in Platelet-rich Plasma on Peri-implant Bone Regeneration.** *Bone*. 2004;34:665-671.

INTERPERSONAL VARIATIONS IN WHOLE BLOOD SAMPLES

In other words, **for a preparation to be classified as PRP, the respective concentration of platelets should be INCREASED BY 3 TO 5 FOLD over the normal baseline.**

Marx RE. **Platelet-rich Plasma (PRP): What is PRP and what is not PRP?.** *Implants Dental*. 2001;10:225-228.

Weibrich G, Hansen T, Kleis W, Buch R, Hitzler WE. **Effect of Platelet Concentration in Platelet-rich Plasma on Peri-implant Bone Regeneration.** *Bone*. 2004;34:665-671.

INTERPERSONAL VARIATIONS IN WHOLE BLOOD SAMPLES

Variations in platelet concentrations among individuals, in addition to the daily variation in platelet parameters observed within individuals, can further affect the consistency, efficacy, and clinical outcomes of the final product.

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BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

When cultured with tendon stem cells (TSC) isolated from the healthy patellar tendons of rabbits, **both LR-PRP and LP-PRP induced similar TSC differentiation into active tenocytes.**

However, **LR-PRP induced mainly CATABOLIC and INFLAMMATORY changes in differentiated tenocytes**, while **LP-PRP induced predominantly ANABOLIC effects.**

Zhou Y, Zhang J, Wu H, Hogan MV, Wang JHC. **The Differential Effects of Leukocyte Containing and Pure Platelet-rich Plasma (PRP) on Tendon Stem/Progenitor Cells – Implications of PRP Application for the Clinical Treatment of Tendon Injuries.** *Stem Cell Res Ther*. 2015;6:173-186.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

LR-PRP → **CATABOLIC and PRO-INFLAMMATORY** → **CHRONIC TENDINOPATHY**

Zhou Y, Zhang J, Wu H, Hogan MV, Wang JHC. **The Differential Effects of Leukocyte Containing and Pure Platelet-rich Plasma (PRP) on Tendon Stem/Progenitor Cells – Implications of PRP Application for the Clinical Treatment of Tendon Injuries.** *Stem Cell Res Ther*. 2015;6:173-186.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

LP-PRP → **ANABOLIC and ANTI-INFLAMMATORY** → **CHRONIC T[illegible]OPATHY** ✗

Zhou Y, Zhang J, Wu H, Hogan MV, Wang JHC. **The Differential Effects of Leukocyte Containing and Pure Platelet-rich Plasma (PRP) on Tendon Stem/Progenitor Cells – Implications of PRP Application for the Clinical Treatment of Tendon Injuries.** *Stem Cell Res Ther*. 2015;6:173-186.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

Although in the **acute phase**, **LR-PRP may exert detrimental effects** due to its **CATABOLIC** activity, the same **CATABOLIC** activity coupled with the **PRO-INFLAMMATORY changes appears vital in its role in the treatment of chronic tendinopathy**.

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BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

Conversely, the use of **LP-PRP** in soft tissue injury may result in **EXCESSIVE SCAR FORMATION** due to the **strong potential** of inducing **INORDINATE ANABOLIC EFFECTS**, **especially when administered in the acute phase.**

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

When cultured with synovial fibroblasts isolated from patients with osteoarthritis, **LR-PRP** induced a greater **INCREASE** in **PRO-INFLAMMATORY** IL-1β, IL-8, and bFGF-2, while **DECREASING ANTI-CATABOLIC** factors in chondrocytes, such as HGF and tissue inhibitor of MMP-4.

Zhou Y, Zhang J, Wu H, Hogan MV, Wang JHC. **The Differential Effects of Leukocyte Containing and Pure Platelet-rich Plasma (PRP) on Tendon Stem/Progenitor Cells – Implications of PRP Application for the Clinical Treatment of Tendon Injuries.** *Stem Cell Res Ther*. 2015;6:173-186.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

This may help explain why **LP-PRP has shown superior *in vivo* results when administered to patients exhibiting signs of mild to moderate OA**, due to its **PREDOMINANT ANTI-INFLAMMATORY** and **ANABOLIC** effects**.**

Assirelli E, Filardo G, Mariani E, *et al*. **Effect of Two Different Preparations of Platelet-rich Plasma on Synoviocytes.** *Knee Surg Sports Traumatol Arthrosc*. 2015; 23:2690-2703.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

LP-PRP → **ANABOLIC and ANTI-INFLAMMATORY** → **MILD OSTEOARTHRITIS**

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

BIOCHEMICAL EFFECTS OF PRP CONCENTRATES IN DIFFERENT TISSUES

LR-PRP → **CATABOLIC and PRO-INFLAMMATORY** → **MILD OSTEOARTHRITIS** ✗

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

EXPERT OPINION ON BIOLOGICAL THERAPY
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REVIEW

Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system

Elizaveta Kon[a,b], Berardo Di Matteo[a,b,c], Diego Delgado [d], Brian J Cole[e], Andrea Dorotei[a,b], Jason L Dragoo[f], Giuseppe Filardo[g], Lisa A Fortier[h], Alberto Giuffrida [a,b], Chris H Jo[i], Jeremy Magalon[j,k], Gerard A Malanga[l], Allan Mishra[m], Norimasa Nakamura[n], Scott A Rodeo[o], Steven Sampson[p] and Mikel Sánchez [d,q]

Kon E, Di Matteo B, Delgado D, *et al*. **Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system.** Expert Opin Biol Ther. 2020 Dec;20(12):1447-1460.

Table 2. Explanation of the digits of the novel PRP coding system.

Number 1 (N_1)	Basal platelet concentration in blood	0 = 0–100,000 platelets/μL 1 = 100,000–200,000 platelets/μL 2 = 200,000–300,000 platelets/μL 3 = 300,000–400,000 platelets/μL 4 = 400,000–500,000 platelets/μL 5 = 500,000–600,000 platelets/μL 6 = 600,000–700,000 platelets/μL 7 = 700,000–800,000 platelets/μL 8 = 800 … 9 = 900 … 10 = … .
Number 2 (N_2)	Platelet concentration in PRP	0 = 0–100,000 platelets/μL 1 = 100,000–200,000 platelets/μL 2 = 200,000–300,000 platelets/μL 3 = 300,000–400,000 platelets/μL 4 = 400,000–500,000 platelets/μL 5 = 500,000–600,000 platelets/μL 6 = 600,000–700,000 platelets/μL 7 = 700,000–800,000 platelets/μL 8 = 800 … 9 = 900 … 10 = … .
-		
Number 3 (N_3)	Red Blood Cells in PRP	0 = No presence/traces ($<1x10^6$/μL) 1 = Presence ($>1x10^6$/μL)
Number 4 (N_4)	White Blood Cells in PRP	0 = Less than baseline 1 = 1.01 to 2 x baseline 2 = 2.01 to 3 x baseline 3 = 3.01 to 4 x baseline 4 = 4.01 to 5x baseline 5 = > 5x baseline
-		
Number 5 (N_5)	External Activation	0 = No (endogenous) 1 = Yes
Number 6 (N_6)	Calcium Addition	0 = No 1 = Yes

3.6.2. Examples

(1) PRP obtained from blood with a mean concentration of 150,000 platelets/μL and reaching a mean concentration of 430,000 platelets/μL; presence of erythrocytes and no leukocytes; activation with thrombin: PRP code is 14–10-10.

(2) PRP obtained from blood with a mean concentration of 230,000 platelets/μL and reaching a mean concentration of 310,000 platelets/μL; no erythrocytes; double leukocyte concentration compared to blood levels and without exogenous activation: PRP code is 23–02-00.

(3) PRP obtained from blood with a mean concentration of 212,900 platelets/μL and reaching a mean concentration of 420,000 platelets/μL; with no leukocytes and no erythrocytes; and activation with calcium: PRP code is 24–00-11.

Kon E, Di Matteo B, Delgado D, *et al*. **Platelet-rich plasma for the treatment of knee osteoarthritis: an expert opinion and proposal for a novel classification and coding system.** Expert Opin Biol Ther. 2020 Dec;20(12):1447-1460.

CONTROVERSIES AND FUTURE DIRECTIONS OF RESEARCH

1) Is there a **DOSE-EFFECT RELATION** between the **PLATELET COUNT** and the **CLINICAL EFFICACY** of the preparation?
2) What is the role of platelet **ACTIVATION METHODS** on the **CLINICAL EFFICACY** of PRP concentrates?

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CONTROVERSIES AND FUTURE DIRECTIONS OF RESEARCH

3) Is there an **OPTIMAL NUMBER** of injections and **TIMEFRAME FOR APPLICATION** of multiple injection treatment cycles?
4) What is the **IMPACT** on clinical efficacy of opting for **FRESH VERSUS FREEZE-THAWED PRODUCTS**?

Ferreira-Dos-Santos G, Hurdle MFB, Clendenen SR, Eldrige JS, Qu W. **Autologous Platelet-Rich Plasma Applications in Chronic Pain Medicine: Establishing a Framework for Future Research - A Narrative Review.** *Pain Physician*. 2022;25(1):15-27.

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3) Navani A, Li G, Chrystal J. **Platelet rich Plasma in Musculoskeletal Pathology: A Necessary Rescue or a Lost Cause?** *Pain Physician*. 2017;20:E345-E356.

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QUESTIONS/COMMENTS?

THANK YOU!

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