Comparative Effects Of Platelet-Rich Plasma And Platelet-Rich Fibrin On Achilles Tendon Healing In Wistar Rats: A Randomized Experimental Study

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ABSTRACT

Background:
Achilles tendon healing is a complex and relatively slow biological process due to limited vascularization and the predominance of type I collagen, often resulting in suboptimal biomechanical recovery. Autologous platelet-based therapies such as platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have been proposed to enhance tendon healing; however, comparative evidence remains limited.

Objective:
To compare the effects of PRP and PRF on Achilles tendon healing in a Wistar rat model using histopathological and biomechanical assessments after a one-month observation period.

Methods:
An experimental study was conducted using male Wistar rats divided into three groups: control (n = 10), PRP (n = 9), and PRF (n = 10). Tendon healing was evaluated by histopathological parameters, including cellular response (hypertrophy), inflammation and matrix quality, vascularization, cellular/collagen orientation, and vacuolization. Biomechanical properties were assessed using tensile strength testing and tendon length change during loading. Statistical analysis was performed using chi-square tests for categorical variables and independent t-tests or Mann–Whitney tests for numerical variables, with $p < 0.05$ considered statistically significant.

Results:
A total of 29 Achilles tendon specimens were analyzed. Histopathological evaluation showed no statistically significant differences among groups in cellular response ($p = 0.386$), inflammation and matrix quality ($p = 0.104$), or vascularization ($p = 0.149$). In contrast, significant differences were observed in cellular/collagen orientation ($p < 0.001$) and vacuolization ($p < 0.001$), with the PRF group demonstrating more favorable tissue organization. Biomechanical testing revealed no significant difference in tensile strength between the control and PRP groups ($p = 0.619$). The PRF group demonstrated significantly higher tensile strength compared with the control group ($p < 0.001$), while the difference between PRP and PRF did not reach statistical significance ($p = 0.051$). Tendon length change during tensile testing differed significantly between the control and PRF groups ($p = 0.011$), whereas no significant differences were observed between control and PRP ($p = 0.211$) or

between PRP and PRF (p = 0.278).
Conclusion:
In this Wistar rat model, PRF was associated with superior collagen organization and improved biomechanical performance compared with PRP and control, particularly during the remodeling phase of Achilles tendon healing. These findings suggest that PRF may represent a more effective biological adjunct than PRP for enhancing tendon repair.

Introduction

Achilles tendon injury represents a common musculoskeletal problem that can lead to prolonged pain, functional limitation, reduced physical activity, and decreased quality of life.[1] As the strongest and largest tendon in the human body, the Achilles tendon plays a critical role in lower limb biomechanics by transmitting forces generated by the gastrocnemius–soleus complex during walking, running, and jumping. Despite its mechanical importance, the Achilles tendon has limited intrinsic healing capacity due to relatively poor vascularization and low cellularity, which often results in delayed or incomplete tissue regeneration following injury. [2,3]

Tendon healing is a complex biological process that occurs through overlapping phases of inflammation, proliferation, and remodeling.[1],2 In the early inflammatory phase, hematoma formation and inflammatory cell infiltration initiate the release of cytokines and growth factors required for tissue repair. This is followed by the proliferative phase, characterized by increased tenocyte activity and deposition of a provisional extracellular matrix. Ultimately, the remodeling phase determines the final quality of the healed tendon, during which collagen fibers reorganize from a disorganized pattern into parallel, longitudinal alignment along the direction of mechanical loading. Failure of this remodeling process may result in inferior mechanical strength, increased risk of re-injury, and chronic tendon dysfunction.[2,3]

Conventional management of Achilles tendon injury, whether surgical or non-surgical, primarily aims to restore continuity and alignment of the tendon structure. However, these approaches do not directly address the biological limitations of tendon healing. Consequently, interest has grown in biological augmentation strategies designed to enhance the intrinsic repair process and improve the structural and functional outcomes of tendon healing. Among these strategies, autologous platelet-based therapies have attracted considerable attention due to their relative safety, accessibility, and potential to deliver a high concentration of growth factors directly to the injury site. [1,3]

Platelet-Rich Plasma (PRP) is a plasma fraction enriched with platelets that release bioactive molecules such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and insulin-like growth factor (IGF), all of which are involved in cell proliferation, angiogenesis, and collagen synthesis.[4-7] PRP has been widely investigated as an adjunctive therapy in tendon and ligament injuries.[8] However, clinical and experimental outcomes remain inconsistent, likely due to substantial variability in preparation protocols, platelet concentration, leukocyte content, and activation methods. This heterogeneity complicates interpretation of PRP efficacy and limits its reproducibility across studies.[9]

Platelet-Rich Fibrin (PRF) is considered a second-generation platelet concentrate that differs fundamentally from PRP in both structure and biological behavior. PRF is prepared without anticoagulants and forms a three-dimensional fibrin matrix that entraps platelets and leukocytes.[10-13] This fibrin scaffold functions as a natural extracellular matrix, providing mechanical support for cell migration while allowing sustained and gradual release of growth factors over time.[12-14] These characteristics suggest that PRF may be particularly advantageous during the remodeling phase of tendon healing, when collagen organization and matrix maturation are critical determinants of biomechanical strength.[1,2]

Experimental studies have suggested that PRF may promote more organized collagen deposition, improved tissue integration, and enhanced biomechanical properties compared with PRP.[12-15] However, direct comparative evidence between PRP and PRF in tendon healing remains limited, particularly with respect to simultaneous evaluation of histopathological remodeling and

biomechanical performance. Moreover, the biological mechanisms underlying potential differences between PRP and PRF effects on tendon healing are not yet fully understood. [15]

Animal models, particularly the Wistar rat (Rattus norvegicus), provide a controlled and reproducible platform for investigating tendon healing mechanisms and evaluating biological interventions.[19,20] Histopathological assessment allows detailed evaluation of cellular response, matrix quality, vascularization, collagen orientation, and degenerative changes such as vacuolization, while biomechanical testing offers objective measurement of functional tendon strength and viscoelastic behavior. Integration of these outcomes is essential to understand how microscopic tissue changes translate into macroscopic mechanical performance.[2,3]

Therefore, the present study aimed to compare the effects of PRP and PRF on Achilles tendon healing in a Wistar rat model using combined histopathological and biomechanical assessments after a one-month observation period. By focusing on both tissue remodeling quality and mechanical properties, this study sought to clarify whether PRF provides superior biological and functional advantages over PRP, thereby contributing evidence to support the selection of optimal platelet-based therapies for tendon healing.[15]

Methods

Study design and animals: This randomized experimental study used male Wistar rats. Animals were acclimatized for seven days and weighed within a range of 300–400 g. Thirty rats were enrolled, with six additional rats prepared as reserves. One PRP-group specimen was excluded, resulting in 29 analyzed specimens.

Preparation of PRF: Rats were anesthetized by inhalation ether. Approximately 3 cc of blood was collected from the infraorbital plexus into a non-anticoagulated tube (non-EDTA) and centrifuged at 2700 rpm for 12 minutes. Three layers formed: platelet-poor plasma (upper), PRF clot (middle), and red blood cell fraction (lower). The PRF clot was isolated using forceps, trimmed from red blood cell remnants, and placed on sterile gauze for immediate use.

Preparation of PRP: Blood (3 cc) was collected into an EDTA tube. The first centrifugation was performed at 3000 rpm for 3 minutes to separate red blood cells, buffy coat, and plasma. The plasma and buffy coat were transferred to a sterile tube and centrifuged again at 3000 rpm for 10 minutes, producing a platelet concentrate. PRP activation was performed using thrombin and/or 10% calcium chloride at a 9:1 ratio.

Surgical procedure and intervention: Animals were shaved at the operative site, disinfected with povidone-iodine, and anesthetized using ketamine–xylazine (0.15–0.20 mL/rat). A vertical incision was made on both hind limbs to expose the operative field. PRP or PRF was applied according to group allocation.

Outcome assessment: After one month, tendons were harvested. Histopathology was assessed using hematoxylin-eosin staining after fixation, dehydration, embedding, and sectioning. Semi-quantitative assessments included cellular response, inflammation/matrix quality, vascularization, cellular orientation, and vacuolization. Biomechanical testing included tensile strength measurement and post-test tendon length measurement.

Statistical analysis: Normality was tested using Shapiro–Wilk and homogeneity of variances using Levene's test. Numerical variables were presented as median (min–max) for non-normal distributions or mean±SD for normal distributions. Between-group comparisons for numerical variables used Mann–Whitney tests when non-normal and independent samples t-tests when normal with homogeneous variances. Categorical comparisons used the chi-square test. A p-value <0.05 was considered statistically significant.

Ethics statement: The study was conducted in accordance with institutional guidelines for animal care and use. Authors should insert the approval committee name and protocol number here if required by the journal.

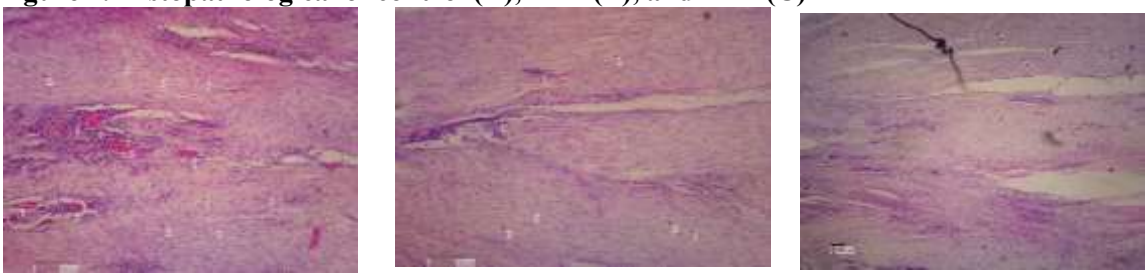
Results

A total of 29 specimens were analyzed (control n=10, PRP n=9, PRF n=10). Table 1 summarizes sample distribution and overall histopathology categories.

Histopathology: Across groups, cellular orientation differed significantly ($p<0.001$) and vacuolization also differed significantly ($p<0.001$). Cellular response ($p=0.386$), inflammation/matrix quality ($p=0.104$), and vascularization ($p=0.149$) were not significantly different.

Histological findings are summarized in Table 1 and Figure 1. These findings were consistent with the quantitative assessment presented in the table, in which the majority of samples were categorized as having good inflammation–matrix quality and vascularization.

Figure 1. Histopathological of control (A), PRP (B), and PRF (C)



(A) (B) (C)

Table 1. Sample distribution and overall histopathology categories (N=29)

Variable	n	%
Study group		
Control	10	34.5
PRP	9	31.0
PRF	10	34.5
Cellular response (chondrocyte hypertrophy)		
Good	27	93.1
Poor	2	6.9
Inflammation and matrix quality		
Good	23	79.3
Poor	6	20.7
Vascularization		
Good	26	89.7
Poor	3	10.3
Cellular orientation		
Regular	17	58.6
Irregular	12	41.4
Vacuolization		
Yes	19	65.5
No	10	34.5

However, in several microscopic fields, morphological cellular changes were observed, including cellular hypertrophy and irregular cellular orientation. These findings corresponded with the quantitative data showing a predominance of poor cellular response.

Overall, the histological specimens demonstrated relatively preserved matrix quality accompanied by suboptimal cellular morphology, reflecting ongoing tissue regeneration, as observed in both the histopathological images and the tabulated results.

Comparison of Cellular Response between Control, PRF, and PRP Groups

Cellular response assessed after one month of observation demonstrated the presence of ligament cell hypertrophy in all study groups. Clinically, a higher proportion of cellular hypertrophy was observed in the PRF group compared with the PRP and control groups. However, statistical analysis using the chi-square test showed that the difference in cellular response among the three groups was not statistically significant ($p = 0.386$).

Comparison of Inflammation and Matrix Quality between Control, PRF, and PRP Groups

Evaluation of inflammation and basophilic matrix enhancement at one month revealed clinically favorable findings in all three groups. Quantitative analysis demonstrated that the proportion of samples categorized as having good inflammation and matrix quality was comparable among the control, PRF, and PRP groups. Statistical analysis using the chi-square test showed no significant difference between groups ($p = 0.104$).

Comparison of Vascularization between Control, PRF, and PRP Groups

Vascularization assessment at one month demonstrated a higher proportion of vascularized tissue in the PRF group compared with the PRP and control groups. Despite this clinical trend, statistical analysis using the chi-square test revealed that the difference in vascularization among the three groups was not statistically significant ($p = 0.149$).

Comparison of Collagen Orientation between Control, PRF, and PRP Groups

Assessment of collagen orientation at one month showed a higher proportion of regular and well-organized collagen fibers in the PRF group compared with the PRP and control groups. Statistical analysis using the chi-square test demonstrated a statistically significant difference in collagen orientation among the three groups ($p < 0.001$).

Comparison of Vacuolization between Control, PRF, and PRP Groups

Vacuolization assessment at one month showed statistically significant differences among the control, PRF, and PRP groups. The chi-square test demonstrated a significant difference in vacuolization distribution among the three groups ($p < 0.001$), with the PRF group showing the most favorable findings.

Comparison of Tensile Strength and Tendon Length Change between Control, PRF, and PRP Groups

Tensile Strength

Comparison between the control and PRP groups (Table 2) showed a mean tensile strength of $53.410 \pm 8.2657 \times 10^{-4}$ in the control group and $56.322 \pm 15.9991 \times 10^{-4}$ in the PRP group. Independent t-test analysis demonstrated no statistically significant difference between these groups ($p = 0.619$).

Table 2. Tensile strength comparison: Control vs PRP

Group	Min. tensile force ($x10^{-4}$)	Max. tensile force ($x10^{-4}$)	Mean ± SD	P-value
Control	35.7	62.99	53.410 ± 8.2657	0.619
PRP	37.0	90.0	56.322±15.9991	

Comparison between the control and PRF groups (Table 3) showed a mean tensile strength of $53.410 \pm 8.2657 \times 10^{-4}$ in the control group and $68.430 \pm 8.3018 \times 10^{-4}$ in the PRF group. Independent t-test analysis demonstrated a statistically significant difference, with the PRF group exhibiting higher tensile strength ($p < 0.001$).

Table 3. Tensile strength comparison: Control vs PRF

Group	Min. tensile force ($x10^{-4}$)	Max. tensile force ($x10^{-4}$)	Mean ± SD	P-value
Control	35.7	62.99	53.410 ± 8.2657	<0.001
PRF	55,5	80,5	68,430 ± 8,3018	

Comparison between the PRF and PRP groups (Table 4) showed mean tensile strength values of $68.430 \pm 8.3018 \times 10^{-4}$ and $56.322 \pm 15.9991 \times 10^{-4}$, respectively. Independent t-test analysis showed that the difference did not reach statistical significance ($p = 0.051$).

Table 4. Tensile strength comparison: PRF vs PRP

Group	Min. tensile force ($x10^{-4}$)	Max. tensile force ($x10^{-4}$)	Mean ± SD	P-value
PRF	55,5	80,5	68,430 ± 8,3018	0.051
PRP	37.0	90.0	56.322±15.9991	

Tendon Elongation

Comparison of tendon length change between the control and PRP groups (Table 5) showed a median value of 1.0 mm (0.00–4.00) in the control group and 3.0 mm (0.00–3.00) in the PRP group. Mann–Whitney test analysis demonstrated no statistically significant difference ($p = 0.211$).

Table 5. Tendon length comparison (difference) between Control and PRP

Group	Median (minimum – maximum)(mm)	P value
Control	1,0 (0,00 – 4,00)	0,211
PRP	3,00 (0,00 – 3,00)	

Comparison between the control and PRF groups (Table 6) showed a mean tendon length change of 1.6 ± 1.350 mm in the control group and 3.40 ± 1.505 mm in the PRF group. Independent t-test analysis demonstrated a statistically significant difference, with greater tendon elongation observed in the PRF group ($p = 0.011$).

Table 6. Tendon length comparison (difference) between Control and PRF

Group	Minimum length	Maximum length	Mean ± SD	P value
Control	0	4	1,6 ± 1,350	0,011
PRF	2	6	3,40 ± 1,505	

Comparison between the PRP and PRF groups (Table 7) showed median tendon length change values of 1.0 mm (0.00–4.00) and 3.0 mm (2.00–6.00), respectively. Mann–Whitney test analysis demonstrated no statistically significant difference between the two groups ($p = 0.278$).

Table 7. Tendon length comparison (difference) between PRP and PRF

Group	Median (minimum – maximum)(mm)	P value
PRP	1,0 (0,00 – 4,00)	0,278
PRF	3,00 (2,00 – 6,00)	

Discussion

Overview of PRP and PRF

This study compared Platelet-Rich Plasma (PRP) and Platelet-Rich Fibrin (PRF) for Achilles tendon healing in a Wistar rat model using histopathology and biomechanical evaluation after one month. Tendon healing is relatively slow due to limited vascularization and the predominance of type I collagen, often resulting in repaired tissue with inferior biomechanical properties compared with normal tendon.[1,2] PRP and PRF are autologous platelet-based biologic therapies aimed at accelerating repair through platelet-derived growth factors.[4-7] PRP is a liquid concentrate with rapid growth factor release, while PRF forms a three-dimensional fibrin scaffold with more gradual release.[10-13] In the present study, PRF showed more favorable outcomes than PRP and control, especially for collagen/cellular orientation, vacuolization, and tensile strength, suggesting a stronger effect on remodeling quality and biomechanical recovery.[1,2,15]

Histopathological Findings

Cellular Response

Cellular hypertrophy, representing the cellular response during tendon healing, showed a tendency toward better results in the PRF group; however, no statistically significant difference was observed among groups ($p = 0.386$). Cellular proliferation and tenocyte activation are most prominent during the early proliferative phase of tendon healing. By one month, cellular density generally decreases as collagen fibers mature and reorganize.[1,2]

Although PRP contains growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which stimulate cell proliferation and migration, the lack of significant difference in this study may be attributed to the timing of evaluation.[4-7] PRF, despite not significantly increasing cellular hypertrophy, provides a stable fibrin matrix that supports cell survival and function, emphasizing matrix quality rather than cellular quantity at this stage of healing.[10-13]

Inflammation and Matrix Quality

Inflammation and matrix quality showed clinically favorable trends in the PRF group but did not reach statistical significance ($p = 0.104$). Inflammation plays a crucial role in the early phase of tendon healing by initiating debris clearance and releasing cytokines that promote subsequent tissue repair.[1,2] However, prolonged or excessive inflammation may impair matrix organization and tendon strength.[17]

The absence of significant differences among groups may reflect the natural resolution of inflammation by the remodeling phase. Additionally, the qualitative nature of histopathological assessment may have limited the detection of subtle differences in matrix quality at a single time point. PRF's ability to modulate inflammation through gradual growth factor release and leukocyte entrapment within the fibrin matrix may still contribute to improved long-term tissue stability, even if not statistically evident at one month.[10-13]

Vascularization

Vascularization was higher in the PRF group compared with PRP and control; however, this difference was not statistically significant ($p = 0.149$). Angiogenesis is essential during early tendon healing to supply oxygen and nutrients required for cellular activity and matrix synthesis.[1,2] Growth factors such as vascular endothelial growth factor (VEGF), present in both PRP and PRF, promote neovascularization.[6,7]

By one month, angiogenic activity typically declines as the tendon enters the remodeling phase. Moreover, excessive or persistent neovascularization has been associated with degenerative changes in chronic tendinopathy rather than functional healing.[2] Therefore, the lack of significant differences

in vascularization at this stage may reflect appropriate physiological progression rather than insufficient biological stimulation.[2]

Collagen Orientation

Collagen orientation was the most discriminative histopathological parameter in this study. The PRF group demonstrated fully regular and parallel collagen fiber alignment, with a highly significant difference compared with PRP and control ($p = 0.000$). Proper collagen alignment is essential for effective load transmission and tensile strength in tendon tissue.[2,3]

PRP may enhance collagen synthesis but lacks a structural scaffold to guide fiber organization, potentially resulting in less orderly collagen deposition.[8,9] In contrast, PRF forms a three-dimensional fibrin network that functions as a biological scaffold, directing cell migration and collagen deposition along physiologic stress lines.[10-13] This structural guidance likely explains the superior collagen organization observed in the PRF group.[12-15]

Vacuolization

Vacuolization showed a statistically significant difference among groups ($p = 0.000$), with the PRF group exhibiting the lowest degree. Vacuolization is often associated with cellular stress, matrix immaturity, or degenerative changes within healing tendon tissue.[17] Reduced vacuolization suggests a more stable microenvironment and advanced matrix maturation.[1,2]

The sustained release of growth factors and the protective fibrin scaffold provided by PRF may help preserve cellular integrity and promote orderly matrix remodeling.[12-14] In contrast, the rapid release of growth factors in PRP may provide short-term stimulation without long-term stabilization of the healing environment.[9,12]

Biomechanical Properties

Tensile Strength

Tensile strength analysis demonstrated a significant difference between the PRF and control groups ($p < 0.001$), while no significant difference was observed between PRP and control ($p = 0.619$). The comparison between PRF and PRP approached statistical significance but did not reach the conventional threshold ($p < 0.051$). Tensile strength reflects the structural integrity of the tendon, including collagen type I content, fiber orientation, and cross-linking.[2,3]

The superior tensile strength observed in the PRF group correlates with the histopathological findings of improved collagen alignment and reduced vacuolization. These results suggest that PRF not only enhances microscopic tissue organization but also translates these improvements into meaningful mechanical strength.[2,3,15,18]

Tendon Elongation

Tendon elongation was significantly greater in the PRF group compared with the control group ($p = 0.011$), indicating improved viscoelastic properties. No significant differences were found between control and PRP ($p = 0.211$) or between PRP and PRF ($p = 0.278$). Increased elongation before failure reflects a mature collagen matrix capable of absorbing mechanical stress without premature rupture.[2,3]

The combination of increased tensile strength and improved elongation in the PRF group suggests a more physiologically balanced tendon healing response, characterized by both strength and flexibility.[2,3]

Overall Comparison Between PRF and PRP

Overall, PRF demonstrated superior effectiveness compared with PRP in enhancing Achilles tendon healing, particularly during the remodeling phase. Significant advantages of PRF were observed in collagen orientation, vacuolization, tensile strength versus control, and tendon elongation versus control. Although PRP contains biologically active growth factors, its effects were not consistently significant, likely due to variability in preparation and rapid growth factor release.[8,9] In contrast, PRF provides a stable fibrin scaffold with sustained growth factor delivery, resulting in more consistent histological organization and biomechanical improvement.[10-15] These findings support PRF as a more reliable biological modality for improving tendon healing quality and functional outcomes.[1,2,15]

Conclusion

In a Wistar rat Achilles tendon healing model, PRF demonstrated superior biomechanical recovery and was associated with more favorable tissue organization compared with PRP and control. PRF may represent a promising, low-cost biological adjunct for tendon repair that warrants further translational and clinical studies.

Conflict of interest

The authors declare no conflicts of interest related to this study.

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