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The Use of Platelet-Rich Plasma (PRP) in the Treatment of Achilles Tendinopathy in Athletes: a Review of Current Guidelines

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ABSTRACT

Objective: This review provides a comprehensive evaluation of platelet-rich plasma (PRP) injections for the treatment of Achilles tendinopathy in athletes. The evaluation is based on a systematic review. The review covers studies published between 2017 and 2026.

Methods: A systematic search of the PubMed database was conducted. The search identified 20 high-quality studies. These included meta-analyses, systematic reviews, and randomized controlled trials. The analysis focused on clinical outcomes. It focused primarily on VISA-A scores. The review also evaluated technical factors. These included cellular composition, injection frequency, and anatomical location of the tendon injury.
Results: The analysis evaluated data from 697 patients. PRP demonstrates biological potential. However, meta-analyses reveal no significant benefit over placebo for midportion tendinopathy ($p = 0.085$). Multiple injections (e.g., four) result in superior tendon remodeling. This approach is more effective than a single dose. PRP displays increased efficacy for insertional tendinopathy. It is also beneficial for patients unresponsive to standard treatments. However, the supporting evidence is statistically fragile (median Fragility Index = 5) and subject to publication bias.
In clinical practice, the results indicate that PRP should not be considered a first-line treatment. This limitation applies to midportion Achilles tendinopathy. PRP may be considered for patients with insertional lesions. It is also an option for those who have not improved. This applies after at least six months of standard conservative management. Repeated, carefully structured injection procedures may be necessary to achieve positive results. However, each case requires individualized assessment given the current weakness and fluctuation of the evidence. Routine use of PRP in general practice is not supported by strong evidence. Therefore, the treatment should be reserved for select, refractory cases.
Conclusions: PRP is not recommended as a first-line treatment. It should instead be considered as an auxiliary option reserved for chronic, recalcitrant cases. Currently, there are no uniform protocols. There is also significant statistical instability within the current evidence base. Therefore, clinicians should exercise considerable caution before routinely implementing PRP in sports medicine practice.
Keywords: PRP, platelet-rich plasma, Achilles tendinopathy, sports medicine, orthobiologics.

1. Introduction

1.1. Clinical Context and Epidemiology

Achilles tendinopathy (AT) is still a significant clinical challenge in contemporary sports medicine. It affects both elite athletes and recreationally active individuals. The condition is characterized by chronic pain, localized swelling, and functional impairment. These symptoms arise from a pathological tissue response to repetitive mechanical overload. Inflammation was historically considered the primary cause. However, recent molecular research shows a failed healing response. It also reveals degenerative changes within the extracellular matrix [1]. Epidemiological data highlight advances in rehabilitation protocols. Approximately 30-40% of patients do not achieve satisfactory outcomes. This failure occurs following standard conservative treatments such as eccentric

loading exercises or extracorporeal shock wave therapy (ESWT). This therapeutic gap stresses the imperative need for more effective biological strategies to modulate the degenerative tendon environment [2].

1.2. The Role of Platelet-Rich Plasma (PRP) in Tendon Therapy

Interest in orthobiologics has increased substantially in recent years. This is notably true for the clinical application of Platelet-Rich Plasma (PRP). PRP is an autologous concentrate of blood platelets. It contains a varied array of growth factors, including Transforming Growth Factor-beta (TGF-β), Platelet-Derived Growth Factor (PDGF), and Vascular Endothelial Growth Factor (VEGF). These proteins are believed to stimulate tenocyte proliferation. They additionally enhance collagen synthesis and promote neoangiogenesis [2]. The biological rationale for PRP use is well established, intending to transform a chronic, degenerative environment into an active, regenerative state. This translational potential has led to the extensive adoption of PRP injections in prominent sports medicine clinics worldwide. In these settings, PRP is frequently referred to as a "gold standard" in regenerative orthopedics [3].

1.3. Controversies and the "Clinical-Scientific Gap".

There is considerable clinical interest in PRP. Despite this, its in vivo efficacy is still a matter of debate among the scientific community. Early optimistic results have been increasingly contested. This challenge comes from exhaustive randomized controlled trials (RCTs) conducted between 2017 and 2026. These trials often report no significant superiority of PRP over saline injections (placebo) [4]. This variation in clinical outcomes is likely because of substantial methodological heterogeneity across studies. This includes differences in cellular composition. For instance, studies compare leukocyte-rich [LR-PRP] versus leukocyte-poor [LP-PRP] formulations. The heterogeneity also involves variable dosage regimens. Additionally, the anatomical lesion location varies between midportion and insertional tendinopathy [5]. The current evidence base requires a critical synthesis. This review must move beyond a simple "PRP versus control" comparison. Advanced statistical metrics, including the Fragility Index, and sub-analyses of clinical "non-responders", provide a more subtle understanding of which patient subgroups may benefit from biological injections [6].

1.4. Objectives of the Study

The central research question guiding this review is: To what extent are platelet-rich plasma (PRP) injections clinically effective? This applies to treating Achilles tendinopathy in athletes. The assessment is based on current high-quality scientific evidence. Accordingly, this review thoroughly assesses the body of literature to address the following specific aims:

- **Clinical Efficacy:** To verify the overall clinical effectiveness of PRP. This entails assessing pain reduction (VAS) and functional improvement (VISA-A scores). These outcomes are compared to alternative or sham interventions.
- **Protocol Variables:** To examine the impact of technical parameters. This focuses on the evidence-supported number of PRP injections. It also evaluates the optimal intervals between injections. It considers the presence or absence of leukocytes in PRP formulations. These factors influence final treatment results. Recent high-quality studies indicate a particular protocol. Four ultrasound-guided PRP injections administered at 14-day intervals produce significantly better structural and functional outcomes than a single dose. Additionally, the choice of PRP formulation is key. Leukocyte-poor PRP is commonly preferred in chronic degenerative cases to minimize pro-inflammatory effects. At the same time, leukocyte-rich PRP may be considered in acute or early-phase injuries. This review integrates current evidence on these technical parameters to help clinicians select the most effective and appropriate PRP protocols for individual patients.
- **Anatomical Specificity:** To determine the significance of the anatomical lesion location. This includes comparing midportion versus insertional tendinopathy. This distinction helps predict therapeutic success.
- **Methodological Strictness:** To critically appraise the quality and statistical dependability of available research. This utilizes tools such as the Fragility Index. The ultimate goal is to formulate evidence-based guidelines for clinical practice.

2. Methods

2.1. Search Strategy and Data Sources

The research material for this in-depth critical narrative review was obtained through a systematic, structured search. The primary data source was the PubMed database. The search period was limited to peer-reviewed

publications from July 2017 to the first quarter of 2026. This restriction was implemented to capture recent studies. These articles reflect notable technological developments in PRP centrifugation kits. These progressions have caused a paradigm shift in orthobiologic therapies, rendering earlier protocols mostly obsolete.

To maximize both sensitivity and specificity in the literature retrieval process, a robust Boolean search string was developed. The primary search matrix utilized the following combination of Medical Subject Headings (MeSH) and free-text keywords: ((“PRP” OR “platelet-rich plasma” OR “orthobiologics”) AND (“Achilles” OR “Achilles tendon”) AND (“tendinopathy” OR “tendinosis” OR “tendon injury” OR “tendon rupture”)). In addition to the primary database search, a manual hand-search of the reference lists of all included full-text articles and prominent prior systematic reviews was conducted to identify any relevant gray literature or “fugitive” trials that may have eluded the primary electronic algorithmic search.

2.2. Eligibility Criteria (PICOS Framework)

Strict inclusion and exclusion criteria were established a priori. These followed the PICOS (Population, Intervention, Comparison, Outcomes, Study design) framework. This approach ensured the highest degree of methodological strictness and clinical relevance:

- **Population (P):** The study population comprised adult human subjects aged 18 to 65 years. These included both professional athletes and recreationally active individuals. Participants required a formal clinical and radiological diagnosis. The diagnosis had to specify either midportion or insertional Achilles tendinopathy. Studies involving systemic inflammatory joint diseases (e.g., rheumatoid arthritis) or patients receiving concurrent corticosteroid injections were strictly excluded to prevent confounding variables.
- **Intervention (I):** The primary intervention reviewed was targeted local injection of platelet-rich plasma (PRP). This was administered either as a standalone monotherapy or utilized as a biological adjunct to standardized conservative rehabilitation protocols (e.g., Alfredson's eccentric loading program). Both leukocyte-rich (LR-PRP) and leukocyte-poor (LP-PRP) formulations were eligible for inclusion.
- **Comparison (C):** Acceptable comparator groups included patients receiving placebo injections, such as physiological saline. Other acceptable comparators were dry needling, isolated conservative physical therapy, or extracorporeal shock wave therapy (ESWT).
- **Outcomes (O):** Included studies were required to report at least one validated objective functional measurement scale. Examples included the VISA-A score, VAS pain scale, or return-to-play timelines.
- **Study Design (S):** To maintain analytical integrity, only studies representing the highest levels of evidence-based medicine (Level 1 and Level 2) were included. This comprised randomized controlled trials (RCTs), robust systematic reviews, and meta-analyses.

Exclusion criteria were rigorously applied to filter out low-quality evidence. Consequently, case reports, retrospective case series, non-peer-reviewed expert commentaries, in vitro cellular models, and in vivo animal studies were systematically excluded. Furthermore, only publications in English were considered to secure exact data extraction and interpretation.

2.3. Selection Process and Data Extraction

The study selection process followed a systematic, multi-stage filtration protocol. This aimed to reduce selection bias. The initial phase entailed the electronic identification of relevant titles and abstracts. This was followed by the automated and manual removal of duplicates using reference management software. In the second phase, the remaining abstracts were diligently screened against the PICOS criteria. This step determined their clinical relevance to the review’s predefined objectives. The final phase entailed a critical, in-depth analysis of the full-text articles. This evaluated their methodological integrity, conformity to protocols, and statistical validity. Ultimately, 20 high-quality, peer-reviewed publications were deemed eligible. These were included in the final qualitative synthesis.
Data extraction was performed using a standardized, customized tabular matrix. The extracted key clinical indicators included: (1) study characteristics (authors, publication year, study design, and sample size); (2) participant demographics (age, sex, athletic status, and duration of symptoms before intervention); and (3) specific technical parameters of the PRP intervention (centrifugation protocols, cellular composition, presence or absence of leukocytes, activation methods, single versus serial injections, and ultrasound guidance utility).

Primary outcome measures extracted included pain intensity. This was quantified using the Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS), and functional musculotendinous performance, measured using the gold-standard Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire. Secondary endpoints

incorporated structural tendon parameters. These were acquired from state-of-the-art imaging modalities (such as tendon thickness and neovascularization severity visualized via Doppler ultrasonography and Magnetic Resonance Imaging) and the calculation of Return to Play (RTP) timelines for the injured athletic cohorts.

2.4. Quality Assessment and Synthesis Strategy

Due to the anticipated methodological heterogeneity in orthobiologic clinical trials, particularly the lack of standardization in PRP preparation kits and variability in post-injection rehabilitation protocols, a formal quantitative meta-analysis of all pooled data was considered inappropriate. Such an approach could generate misleading or artificially synthesized conclusions. Therefore, a critical narrative synthesis was adopted.

The methodological quality and inherent risk of bias of the included RCTs were critically evaluated. Attention was directed toward potential flaws in the randomization sequence generation, allocation concealment, blinding of participants and outcome assessors (single-masked versus double-masked), and the handling of incomplete outcome data or high patient attrition rates. Furthermore, high-level statistical metrics, notably the Fragility Index, were extracted or calculated where possible to assess the robustness of the statistically meaningful findings reported in the primary literature, ensuring that the final clinical recommendations are grounded in stable, reliable evidence rather than fragile statistical irregularities.

3. Results

3.1. Objectives of the Results Analysis

This section systematically synthesizes data. This data is extracted from selected high-tier scientific publications. These sources include comprehensive meta-analyses, rigorous systematic reviews, and well-powered randomized controlled trials (RCTs). The primary analytical objective is to identify the true clinical effectiveness of Platelet-Rich Plasma (PRP) injections in affecting the degenerative tendon environment. Effectiveness is primarily appraised through patient-reported outcomes. That is specifically pain reduction (measured using the Visual Analog Scale [VAS] or Numeric Rating Scale [NRS]) and functional musculotendinous improvement (measured using the validated Victorian Institute of Sport Assessment-Achilles [VISA-A] questionnaire). Furthermore, for athletic cohorts, Return to Play (RTP) timelines and rates are critically evaluated. Secondary objectives involve investigating the substantial effect of technical and procedural variables. These variables include cellular composition (leukocyte concentrations), dosage frequency (single versus serial regimens), anatomical lesion location, and the utility of ultrasound (US) guidance. These variables directly influence final outcomes. These thorough findings are intended to inform and refine contemporary, evidence-based clinical guidelines for the management of Achilles tendinopathy among both professional and recreational athletes.

3.2. General Therapeutic Efficacy and Return to Play

The assessment of PRP's clinical utility reveals a polarized landscape.

The most recent and comprehensive umbrella systematic review [7] incorporates 13 clinical trials and 697 patients. This review suggests considerable therapeutic potential for PRP. It is effective in easing symptoms of chronic Achilles tendinopathy. Patients demonstrated substantial reductions in VAS pain scores. There is also functional improvement on the VISA-A scale at final follow-up. Notably, 85% of patients (95% CI: 65% to 98%) returned to sports, and 72% reported satisfaction with treatment. Nonetheless, these apparent benefits are constrained by an extremely high degree of statistical heterogeneity (I^2 = 97%) among included studies. This is due to marked variability in preparation protocols, patient demographics, and symptom duration also vary significantly. Ultimately, this variation compromises the generalizability of the findings.

Conversely, a highly rigorous, tightly controlled meta-analysis [5] challenges the clinical advantage of PRP. This study compares PRP directly to a saline placebo. By isolating high-quality RCTs, the mean difference in VISA-A scores at 6 months was 5.3 points in favor of PRP (95% CI: -0.7 to 11.3; p = 0.085). That difference is well below the established Minimal Clinically Important Difference (MCID) of 12 points. This lack of clinically meaningful improvement was also seen in structural imaging outcomes. There were no significant differences in ultrasound-measured anterior-posterior tendon thickness (p = 0.663). Similarly, there were no differences in Doppler-detected neovascularization (p = 0.695). Return to Play rates differed by only 1.4% to 1.8% between groups. This narrow margin is not statistically or clinically significant.

The intensity of the dosage protocols can partially explain the differences in these outcomes. Notably, a study evaluated a four-injection PRP protocol [8]. Patients received the injections at 14-day intervals. They exhibited significantly greater improvements. These results were superior to those receiving a single injection. At 24 weeks, the serial PRP group improved by 20 points on the VISA-A scale. This gain substantially exceeded the placebo group's 9-point gain. The serial group also showed a statistically significant reduction in tendon thickness. This was confirmed on ultrasound ($p < 0.05$). This suggests that multiple, spaced injections facilitate genuine structural remodeling rather than simply masking symptoms.

In sharp contrast, a highly powered multicenter trial [4] (N = 240) effectively dismantled the clinical rationale for utilizing single-dose PRP injections in chronic, recalcitrant cases. Following a 6-month observation period, the VISA-A score for the single-dose PRP cohort (54.4 points) was nearly identical to the sham-injected control group (53.4 points; $p = 0.36$). The trial concluded that a solitary PRP dose failed to provide any biological benefit. The results did not exceed the placebo effect. This was observed in a cohort whose symptoms averaged 24 months in duration. Furthermore, the single biological injection was associated with a markedly higher incidence of transient injection-site discomfort and localized swelling (82% vs. 61% in placebo).

Despite conflicting overall data, a specialized systematic review examines elite athletes [9]. This review identifies a specific clinical context in professional sports, where biomechanical loading is closely managed. In this setting, PRP may promote targeted pain reduction. It can also modestly accelerate Return to Play (RTP) timelines. However, this benefit is highly conditional. PRP must be integrated into a comprehensive, multidisciplinary rehabilitation program. Additionally, the protocol requires continuous ultrasound monitoring to optimize the therapeutic window.

Table 1. Summary of key high-level clinical studies evaluating PRP success in Achilles tendinopathy.

Author (Year)	Study Design	N (Patients)	Lesion Location	Intervention Protocol	Key Clinical Findings & Statistical Significance
Boesen et al. (2017) [8]	RCT	60	Midportion	4 serial injections (14-day intervals)	Significant clinical improvement and structural remodeling ($p < 0.01$)
Kearney et al. (2021) [4]	Multicenter RCT	240	Midportion	1 single injection	No functional difference vs. placebo arm ($p = 0.36$); higher post-injection pain
Bai et al. (2023) [10]	RCT	60	Insertional	2 injections vs. ESWT	PRP clinically superior to ESWT at 6-month terminal follow-up

Kuttyadan et al. (2025) [7]	Umbrella Review	697	Mixed	Highly heterogeneous	High heterogeneity (I^2=97%); does not support routine first-line application
Nadeau-Vallée (2025) [16]	Meta-analysis	488	Mixed	Mixed protocols	Highly effective as a targeted second-line treatment for chronic non-responders
Xu et al. (2022) [6]	Systematic Review	528	Mixed	Mixed protocols	Highlights profound low evidence stability (Median Fragility Index = 5)

(Source: Own elaboration based on reviewed literature)

3.3. Impact of Technical Parameters and Lesion Location

The precise anatomical location of the tendinopathic pathology is an important yet frequently overlooked determinant of therapeutic success. Insertional Achilles tendinopathy is a condition biologically distinct from midportion tendinosis due to the involvement of the retrocalcaneal bursa and adjacent osteochondral interfaces. Emerging evidence [10] indicates that this condition responds specifically to orthobiologics. In a direct comparison, PRP provided a significantly more durable repair mechanism than Extracorporeal Shockwave Therapy (ESWT), with a pronounced clinical advantage observed at 6 months ($p < 0.05$). The mechanical mechanotransduction effects of ESWT decreased over time. The PRP cohort demonstrated sustained improvement in validated healing parameters, suggesting a fundamental alteration in the local cellular environment at the enthesis.

Procedural precision was critically examined in a dedicated systematic review and meta-analysis [11]. This specifically involved the utilization of real-time imaging. The underlying hypothesis dictates that ultrasound guidance guarantees the accurate delivery of growth factors. These are deposited directly into the hypoechoic, degenerative clefts of the tendon. Surprisingly, despite the mandated use of ultrasound guidance in the intervention arms, no statistically significant differences were observed. These outcomes were compared between PRP and blinded control groups. This lack of difference persisted at any time point for midportion tendinopathy. Furthermore, recent strong evidence [12] evaluates PRP's role as an intraoperative surgical adjuvant. In this application, it is applied directly to the tendon during open debridement or repair. The data indicate that the biological concentrate does not confer any additional statistically significant benefits. This applies to postoperative pain trajectories and long-term functional recovery ($p > 0.05$). This suggests that the surgical trauma itself may maximize the local healing response. Consequently, additional exogenous platelets become redundant.

Detailed cellular analyses [1] elegantly explain the biological mechanisms. These mechanisms underlie these profound clinical inconsistencies. The analyses focus on the specific formulation of the concentrate. They notably compare Leukocyte-Rich PRP (LR-PRP) versus Leukocyte-Poor PRP (LP-PRP). In vitro and in vivo data confirm clear biological activity. LR-PRP potently stimulates Type 1 collagen synthesis. Furthermore, it improves the ultimate load-to-failure biomechanical properties of the tissue. However, the presence of concentrated leukocytes creates a dual, highly volatile effect. This is especially true for neutrophils. In the immediate acute phases of injury, neutrophils may successfully accelerate healing. They achieve this by clearing

necrotic debris. Yet, the dynamic shifts in the context of chronic tendinopathy. These leukocytes trigger an excessive release of pro-inflammatory cytokines. They also release catabolic matrix metalloproteinases, such as MMP-8 and MMP-9. This release may unintentionally induce a hyper-catabolic response. As a result, this process actively degrades the extracellular matrix. This volatile cellular dynamic may heavily contribute to the widespread lack of efficacy. This failure is specifically observed in long-standing, fibrotic tendinopathies. This phenomenon is explicitly reported in [4].

3.4. Efficacy of PRP Compared to Alternative Conservative Methods

Evidence synthesized across multiple musculoskeletal pathologies suggests an extraordinarily high degree of tissue specificity. This specificity relates to the physiologic response to PRP injections [13]. This biological modality has consistently been shown to be highly effective for fascial pathologies. A prime example is recalcitrant plantar fasciitis. However, its application to the Achilles tendon yields mixed results. Notably, only two of eight comprehensively analyzed studies focusing on Achilles tendinopathy reported unequivocally positive outcomes. These outcomes were evaluated compared with a placebo. Similarly, an in-depth investigation into the combined effect of PRP revealed no “added value” when combined with the gold-standard conservative treatment, heavy-load eccentric training (the Alfredson protocol) [14]. When compared with a cohort receiving identical eccentric loading and a placebo injection, the differences in final VISA-A score were clinically insignificant, ranging from 0.23 to 0.83 points.

A highly clinically relevant comparison concerns the use of intratendinous corticosteroids (CS) [15]. Data show that CS injections provide a massive, immediate advantage only within the first 4 weeks post-injection (the so-called “honeymoon phenomenon”). This advantage drastically reduces acute pain via profound immunosuppression. However, this effect rapidly vanishes and becomes physically detrimental. CS actively causes localized collagen necrosis and inhibits tenocyte proliferation. By the critical 6-month mark, the dynamic entirely shifts. PRP statistically and clinically outperforms CS in both sustained pain reduction ($p < 0.00001$) and long-term functional improvement ($p = 0.003$). Consequently, PRP provides a vastly safer, biologically sound alternative. It does not undermine the structural strength of the collagen matrix or increase the risk of spontaneous tendon rupture.

Additionally, convincing evidence from [16] establishes a specific, highly successful clinical niche: PRP is an exceptionally effective second-line treatment for patients who are "non-responders". In these defined cohorts, “non-responders” are patients who have undergone a minimum of 6 months of standardized conservative rehabilitation and progressive mechanical loading (including structured physiotherapy, eccentric calf training and shock wave therapy) without achieving meaningful improvement in pain (such as less than a 30% reduction on VAS or NRS scales), function (failure to improve VISA-A by at least 12 points), or ability to resume prior activity levels. These patients also commonly present with persistent tenderness and functional limitation at follow-up assessment. That happens despite documented compliance with therapy and absence of significant comorbidities or confounding joint pathology. When this clinical definition is met, targeted PRP administration has been shown to successfully break the biological stalemate, providing significant, durable pain relief and functional restoration lasting up to 24 months post-injection ($p < 0.05$).

3.5. Time Process and Durability of the Biological Effect

The physiological timeline of tendon remodeling directly influences the interpretation of clinical trial endpoints. A comprehensive Level 1 meta-analysis [17] confirms the frustrating absence of statistically significant differences in both functionally relevant (VISA-A) and structural (ultrasound-measured tendon thickness) outcomes at the standard 3, 6 and 12-month evaluation milestones ($p > 0.05$) when comparing single-dose PRP to placebo in general tendinopathy populations. Similar underwhelming findings were reported across a spectrum of pathologies. Those pathologies range from chronic tendinosis to surgically repaired acute Achilles tendon ruptures (ATR) [2]. In the context of ATRs, while PRP application demonstrated a minor capacity to improve long-term terminal ankle mobility, it completely failed to affect critical performance measures. That includes performance measures such as isolated triceps surae muscle strength or symmetrical calf circumferences recovery.

In contrast to these delayed evaluations, some protocols isolating the early phases of tissue repair observed an acute therapeutic effect of PRP at precisely week 6. That resulted in significant reductions in pathological tendon thickness by week 12 [18]. This suggests the existence of a very narrow, highly sensitive “therapeutic window” In that period of time the explosive release of platelet-derived growth factors optimally coincides with the tissue’s endogenous proliferative phase. That requires highly synchronized rehabilitation loading to maximize the biological response.

3.6. Critical Assessment of Statistical Dependability and Quality of Evidence

Beyond the raw clinical data, the ultimate value of any systematic review rests in its appraisal of evidence quality. A definitive umbrella review [7] mapping the entire current literature concludes unequivocally that the cumulative scientific evidence does not support the routine use of PRP as a ubiquitous, first-line treatment for Achilles tendinopathy. The deep lack of long-term durability and the staggering heterogeneity in formulation protocols effectively preclude the creation of standardized, universal clinical guidelines.

Furthermore, the reliability of the current positive evidence is severely undermined by the statistically proven presence of strong publication bias [19]. Detailed evaluations of funnel plot asymmetry suggest that trials reporting negative or neutral results for PRP are systematically underrepresented. That leads to the likely artificial overestimation of the documented benefits of PRP in the wider literature. This critical observation aligns precisely with findings from advanced sensitivity analyses [20]. That analyses mathematically demonstrate that, regardless of whether researchers manipulate leukocyte concentration (LR-PRP vs. LP-PRP) or injection frequency, the overarching statistical conclusion remains unaltered: PRP, in broad application, fails to outperform a well-administered placebo.

However, the most devastating statistical concern in the PRP literature is highlighted by the Fragility Index (FI) [6]. The FI measures exactly how many patients in a trial would need to change their outcome status (from a "success" to a “failure”) to completely erase the statistical significance ($p < 0.05$) of the entire study. Alarmingly, the median FI for the landmark PRP studies was calculated at only 5. This indicates an extreme level of statistical vulnerability. That vulnerability displays in a statement that a status change in just five individual patients across an entire trial could reverse the study’s conclusions from “statistically significant” to “insignificant”. The number of patients permanently “lost to follow-up” in these long-term sports medicine trials frequently exceeds the FI of 5. This results in the fact that the current evidence base supporting PRP efficacy is considered profoundly fragile. That warrants extreme caution and scientific doubt about its routine implementation in clinical practice.

4. Discussion

4.1. The Bench-to-Bedside Discrepancy and the Placebo Conundrum

A comprehensive critical analysis of the aggregated scientific literature shows a considerable and consistent discrepancy between the theoretical, *in vitro* biological potential of platelet-rich plasma (PRP) and its objectively observed *in vivo* clinical success in the management of Achilles tendinopathy. A central axis of debate within current sports medicine literature is the glaring failure. It is because of large-scale, highly powered, multicenter randomized controlled trials, most notably the ATM (Achilles Tendinopathy Management) project [4]. They demonstrate any statistically or clinically meaningful benefits of PRP over a simple physiological saline placebo. This stands in clear contrast to the plethora of smaller single-center clinical trials that routinely demonstrate considerable, almost miraculous regenerative benefits.

This variation requires a more in-depth examination of the control groups used in these trials. The injection of physiological saline is rarely a true, inert “placebo”. The physical act of introducing fluid into the paratenon or the degenerative substance of the tendon creates a highly relevant “volume effect” or “hydrodissection”. This mechanical separation of tissue planes can actively flush out accumulated nociceptive neurotransmitters (such as Substance P and glutamate), strip away pathological neovessels, and mechanically break down micro-adhesions [5]. Furthermore, the micro-trauma induced by the needle itself (fenestration) initiates a localized acute bleeding response. That is what successfully mimics a mild autologous blood injection. Consequently, when large trials compare PRP to saline fenestration, they are not comparing an active biologic to nothing. They are comparing a highly concentrated biologic to a mechanically active intervention. Proving a statistically significant advantage over this active control is an incredibly high hurdle. That explains the underwhelming results of major trials like the ATM project.

4.2. Pharmacokinetics, Dosage, and the Need for a Cumulative Stimulus

A significant portion of the observed clinical inconsistency may be directly explained by extreme variations in dosage protocols and administration timelines. The vast majority of studies reporting negative or neutral

outcomes utilized a single-injection paradigm. However, the basic science of tendon turnover fundamentally contradicts this approach. The Achilles tendon is a classically bradytrophic tissue. It is characterized by limited primary vascularity and an exceptionally low metabolic rate, which leads to a collagen half-life measured in years rather than days. When a single dose of PRP is administered, the alpha granules within platelets degranulate rapidly and release up to 95% of the growth factors they store (TGF-β, PDGF, VEGF). All of it is happening during the first hour post-injection [1].

Findings from the landmark multi-injection trial [8] strongly suggest that effective structural regeneration of such a metabolically sluggish tissue requires a sustained, "cumulative biological stimulus". Their serial protocol of four injections spaced at 14-day intervals aligns much more closely with the natural, prolonged timeline of the physiological proliferative phase of tissue healing. This series produced lasting structural changes (documented via objective ultrasound metrics) that were absent following a single administration. This result clearly indicates that current routine clinical practices, which overwhelmingly favor a single, isolated "one-and-done" procedure due to financial and administrative constraints, may be fundamentally physiologically inadequate for triggering optimal soft-tissue healing in chronic tendinopathy.

4.3. Anatomical Specificity: Insertional vs. Midportion Biomechanics

An additional important consideration determining PRP efficacy is the highly specific anatomical location of the pathological lesions. Subgroup evidence strongly indicates that insertional Achilles tendinopathy (IAT) responds significantly more favorably to orthobiologic therapy than standard midportion tendinopathy [10]. This divergent response profile is closely linked to the biomechanical forces acting on these discrete regions.

The midportion of the Achilles tendon is subjected almost exclusively to uniaxial tensile loading during the stretch-shortening cycle. In contrast, the insertional enthesis represents a highly complex transitional organ. During dorsiflexion, the insertion is subjected not only to extreme tensile stress but also to deep compressive and shear forces against the posterosuperior prominence of the calcaneus (frequently worsened by Haglund's deformity). The enthesis relies on a specialized fibrocartilaginous transition zone to dissipate these compressive loads. It is highly plausible that the concentrated growth factors within PRP are significantly more effective for stimulating the specialized chondrocyte-like cells within this fibrocartilage transition zone than they are at altering the behaviour of the deeply senescent tenocytes residing in the avascular midsubstance. This biomechanical and cytological rationale is strongly corroborated by recent findings [10] demonstrating the clear superiority of PRP over mechanically based treatments, such as extracorporeal shockwave therapy (ESWT), particularly at this complicated anatomical site.

4.4. The Leukocyte Dilemma and the Risk of Catabolic Exacerbation

The precise cellular composition of PRP formulations, notably about the inclusion or deliberate exclusion of leukocytes, remains one of the most contentious issues in modern regenerative orthopedics. Laboratory data confirm that leukocyte-rich PRP (LR-PRP) strongly stimulates acute collagen synthesis, but a deeper translational analysis of this mechanism [1] raises a serious clinical warning about the induction of a secondary inflammatory response during the strictly chronic phase of tendinopathy.

Neutrophils are the most abundant leukocytes in LR-PRP. They are laden with highly catabolic enzymes, including matrix metalloproteinases (specifically MMP-8 and MMP-9) and reactive oxygen species (ROS). The athletes present with a prolonged, multi-year history of tendinosis, where the tissue is not actively inflamed but rather locked in a state of "failed healing" and matrix degradation. In this case the sudden introduction of millions of concentrated neutrophils may paradoxically worsen the ongoing catabolic processes. This massive, uncalibrated inflammatory surge may degrade whatever fragile collagen scaffolding remains. This paradoxically increases immediate post-injection pain and severely delays the athlete's return to play (RTP). Such event illustrates the absolute necessity for individualized therapy [9]. Clinicians must shift away from a "one-size-fits-all" approach and carefully correlate the cellular composition of the biologic (e.g., selecting leukocyte-poor variants in chronic degenerative cases) with the patient's specific pathological timeline.

Furthermore, this illustrates the essential role of high-resolution ultrasound guidance. Blind injections are no longer acceptable in contemporary sports medicine. Precise sonographic delivery ensures that the orthobiologic concentrate is accurately deposited into hypoechoic and anechoic regions of peak neovascularization and degeneration and in that way preserving the integrity of adjacent healthy, load-bearing collagen bundles.

4.5. Statistical Weakness and the Crisis of Evidence Reliability

The most crucial, overarching conclusion of this thorough review pertains to the highly questionable statistical soundness of the widely reported successes of PRP. Embedding the Fragility Index (FI) into the critical appraisal of these sports medicine trials [6] fundamentally shifts the paradigm for evaluating PRP efficacy.

The FI measures the absolute number of patients whose outcome would need to flip from "success" to "failure" to completely eradicate the statistical significance ($p < 0.05$) of a trial's findings. With a calculated median FI value of merely 5 across the highest-tier literature, the foundation of evidence supporting PRP is remarkably brittle. In the context of sports medicine RCTs, where participant attrition (lost to follow-up) due to club transfers, non-compliance with long-term rehabilitation, or seeking alternative off-study treatments routinely exceeds 10-15% of the total cohort, a Fragility Index of 5 is highly alarming. An outcome shift in a handful of individuals can entirely reverse positive conclusions. Consequently, clinicians must exercise extreme caution when prognosticating outcomes for elite athletes. This specific finding delivers strong, objective evidence of systemic overestimation. This phenomenon is predominantly driven by smaller, inadequately blinded studies. These specific trials are highly vulnerable to substantial attrition and confirmation bias.

4.6. Clinical Positioning and Cost-Benefit Synthesis

The interplay among biological potential, clinical data, and statistical fragility is highly complex. Consequently, platelet-rich plasma must never serve as a primary, first-line treatment. It cannot replace structured, progressive mechanical loading and exercise-based rehabilitation. Instead, modern sports medicine must properly contextualize PRP. It must be classified strictly as a costly, specialized biological adjunct. Its clinical utility is best reserved as a targeted, second-line intervention for specific scenarios, such as recalcitrant insertional tendinopathy or in true clinical non-responders, patients who have failed to improve after at least six months of supervised, heavy-load conservative management. Restricting PRP use to these indications maximizes its biological potential while lessening economic burden and avoiding unrealistic expectations.

4.7. Proposed Clinical Protocol

Current evidence supports a strict, stepwise clinical protocol.

- **1. Patient Selection:** Confirm chronic midportion or insertional Achilles tendinopathy. The condition must be strictly refractory. Patients must have failed at least six months of standardized conservative treatment.
- **2. PRP Preparation:** Prepare autologous platelet-rich plasma using validated centrifugation methods. Select the cellular formulation carefully. Leukocyte-poor PRP is specifically required for chronic degenerative cases.
- **3. Injection Schedule:** Plan a dedicated course of four PRP interventions. Separate each injection by a strict 14-day interval.
- **4. Imaging Guidance:** Real-time, high-resolution ultrasound is mandatory. This ensures exact orthobiologic delivery. The needle must directly target the hypoechoic clefts of tendon degeneration.
- **5. Post-Injection Protocol:** Implement a carefully synchronized rehabilitation program. Introduce progressive mechanical loading gradually. This mechanical progression must align perfectly with the biological proliferative phase of tendon healing.
- **6. Monitoring:** Track clinical improvement objectively. Utilize validated outcome measures, such as VISA-A and VAS scores. Employ follow-up imaging to evaluate actual changes in tendon structure and microvascularity.

This structured approach is clinically essential. It maximizes the regenerative potential of PRP. Furthermore, it ensures patient safety and drives consistent, reproducible outcomes.

4.8. Patient Communication and Ethical Matters

Patient Communication and Joint Decision-Making: Given these evidentiary limitations, clinicians need to communicate transparently with patients. That regards to the current uncertainties and possible limitations of PRP therapy. Clinicians should emphasize that, although some studies report promising results, the scientific foundation for PRP remains fragile and mixed. There is no consistent evidence supporting its advantage over

standard treatments for most patients. Patients should be informed that PRP is not a certain solution. Its positive effects, if achieved, may be modest and highly individualized. Engaging patients in an honest discussion about the possible benefits, the lack of long-term data, and the chance of disappointment will help support informed consent and match expectations. Promoting questions and actively involving patients in shared decision-making ensures that treatment choices reflect both the available evidence and the individual's values, goals, and preferences.

5. Conclusions

A comprehensive and critical synthesis of the highest-quality scientific literature from 2017 to 2026 supports the development of nuanced, evidence-based clinical recommendations for the use of platelet-rich plasma (PRP) in the management of Achilles tendinopathy. The assessment of orthobiologic interventions reveals the necessity for exacting patient selection criteria and careful protocol standardization. The following conclusions are formulated based on this critical evaluation and synthesis of current evidence:

- **Lack of Justification as a First-Line Treatment:** Aggregate scientific evidence derived from Level 1 meta-analyses and highly powered multicenter RCTs unequivocally indicates that routine PRP injections do not show a statistically or clinically significant advantage over an active placebo (saline fenestration) in the treatment of midportion Achilles tendinopathy. PRP cannot and should not replace standard progressive kinesitherapy and heavy-load eccentric training protocols. Mechanical mechanotransduction remains the absolute, irreplaceable "gold standard" of care for restoring functional tendon architecture.
- **Anatomical and Location-Dependent Efficacy:** The clinical efficacy of PRP is highly location-dependent. Evidence confirms PRP is significantly more effective for insertional Achilles tendinopathy compared to midportion lesions. The insertional enthesis is a complex anatomical zone. It is subjected to intense compressive, shear, and tensile forces. Here, biological injections effectively stimulate the fibrocartilaginous transition zone. This stimulation delivers a highly durable repair mechanism. Consequently, PRP yields superior long-term structural outcomes compared to mechanically driven modalities like extracorporeal shockwave therapy (ESWT).
- **Strategic Role as a Second-Line (Rescue) Therapy:** Platelet-rich plasma is not a routine, universal intervention. It is a targeted, second-line treatment reserved strictly for true clinical "non-responders". These patients have failed to achieve functional improvement after at least 6 months of supervised conservative management. This management includes rigorous physiotherapy and eccentric loading regimens. In these recalcitrant cases, PRP can successfully overcome persistent biological stagnation. Biological augmentation provides significant, durable pain reduction for up to 24 months. Crucially, it can substantially delay or even prevent the need for open surgical tendon reconstruction. Therefore, practitioners must explicitly reserve PRP for patients who fail exhaustive first-line measures.
- **The Critical Imperative of Protocol Intensity and Dosage:** Treatment success relies heavily on the specific injection regimen. The biological properties of PRP alone are insufficient. Current literature establishes a clear, evidence-based protocol. A series of four ultrasound-guided injections, separated by 14-day intervals, consistently improves tendon structure. This is objectively evidenced by reduced anterior-posterior thickness and decreased neovascularization on Doppler ultrasound. Conversely, single, isolated injections consistently fail to induce durable regenerative changes. Protocol intensity and cumulative dosing are absolutely essential for achieving clinically meaningful tissue remodeling.
- **Definitive Long-Term Advantage Over Corticosteroids:** Although intra-tendinous or peritendinous corticosteroids (CS) injections offer an attractive, rapid and immediate localized pain relief via profound immunosuppression (the initial 4-week "honeymoon phenomenon"), they are ultimately detrimental to tissue stability. PRP represents a vastly safer and significantly more effective biological solution over a prolonged 6 to 12 month horizon. Crucially, unlike corticosteroids, PRP does not carry the severe iatrogenic risks of catastrophic collagen fiber necrosis, focal matrix degradation, or subsequent spontaneous tendon rupture.
- **Statistical Fragility, Publication Bias, and Clinical Caution:** Clinicians must exercise extreme caution. Highly enthusiastic, early-stage reports of PRP efficacy currently permeate the literature. However, extensive statistical appraisals reveal a remarkably low Fragility Index (median FI = 5) among pivotal RCTs. The foundational evidence supporting PRP is statistically brittle. These trials show extreme vulnerability to routine patient attrition. Furthermore, publication bias is a proven, systemic phenomenon. Negative trials are systematically underreported. Consequently, the true clinical benefits of PRP are frequently inflated in the wider literature. Study outcomes remain highly sensitive to tiny fluctuations in participant numbers. Therefore, clinicians must manage athlete expectations prudently prior to any intervention.

- **Targeted Application in Competitive Sports:** Professional and elite athletics represent a unique, high-stress environment. Here, precisely timed, ultrasound-guided PRP injections can tactically support the return to play (RTP) process. The biologic can effectively modulate acute pain and accelerate localized tissue clearance. However, the injection must never function as a standalone procedure. Doing so negates any genuine biological advantage. Instead, PRP must be incorporated into a comprehensive, multidisciplinary rehabilitation program. This program must carefully calibrate progressive mechanical loading. The applied mechanical stress must perfectly match the post-injection cellular proliferative phase.

Ultimately, closing the gap between clinical expectation and biological reality necessitates not only a paradigm shift in clinical practice but also a reorientation of future research priorities. The sports medicine community must transition away from indiscriminate application of single-dose PRP, instead stress the development and rigorous evaluation of highly customized, protocol-driven orthobiologics therapies. Future research needs to prioritize prospective, high-quality studies that define optimal dosing regimens, standardized preparation protocols, and precise patient selection criteria, especially for anatomically specific and chronically recalcitrant tendinopathies. Such an approach will advance the evidence base and support the formulation of targeted, effective clinical strategies.

Disclosure

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