Regenerative Therapies in Tendinopathies and Partial Rotator Cuff Tears

Terapias Regenerativas em Tendinopatias e Roturas Parciais da Coifa dos Rotadores

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https://doi.org/10.82189/spot.75

ABSTRACT

Rotator cuff tendinopathies and partial-thickness tears are common causes of shoulder pain, particularly in adults over 40, with a significant impact on quality of life and work capacity. While conservative treatment remains the first-line approach, a substantial proportion of patients experience suboptimal outcomes. In recent years, regenerative therapies have emerged as promising alternatives or adjuncts to traditional treatment, aiming to promote tendon healing, reduce pain, and delay or avoid surgical intervention.

This review critically evaluates the current evidence on regenerative interventions, including corticosteroid injections, hyaluronic acid, prolotherapy, platelet-rich plasma (PRP), and cell-based therapies such as bone marrow aspirate (BMA) and adipose-derived mesenchymal stem cells (AD-MSCs). Among these, leukocyte-poor PRP (LP-PRP) demonstrates the most consistent results in pain relief and functional improvement, with sustained effects observed for up to 12 months. Prolotherapy and hyaluronic acid, particularly in high-molecular-weight formulations, also show favorable short-term results. Conversely, corticosteroids provide only transient analgesia and may negatively affect tendon healing if administered postoperatively.

Cell-based therapies have shown encouraging preliminary findings, including structural tendon improvement and reduction in lesion size. However, current studies are limited by methodological heterogeneity, small sample sizes, and short follow-up periods, precluding definitive conclusions.

This article emphasizes the need for individualized treatment selection based on patient profile, clinical severity, and access to therapy. Although some regenerative strategies are becoming more accessible, many remain experimental and should be restricted to research protocols until further high-quality evidence becomes available. Therapeutic decisions should involve shared decision-making, clearly addressing benefits, limitations, costs, and safety profiles of each modality.

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Recebido/Received: 2025/04/17 **Aceite/Accepted:** 2025/06/26 **Publicado online/Published online:** 2025/09/26 **Publicado / Published:** -

Keywords: Mesenchymal Stem Cells; Platelet-Rich Plasma; Regenerative Medicine; Rotator Cuff Injuries/therapy; Tendinopathy

RESUMO

As tendinopatias e as roturas parciais da coifa dos rotadores constituem causas frequentes de dor no ombro, sobretudo em adultos com mais de 40 anos, com impacto significativo na qualidade de vida e na capacidade laboral. Embora o tratamento conservador continue a ser a abordagem de primeira linha, uma proporção substancial de doentes apresenta desfechos insatisfatórios. Nos últimos anos, as terapias regenerativas têm surgido como alternativas ou adjuvantes promissores ao tratamento tradicional, com o objetivo de promover a cicatrização tendinosa, reduzir a dor e adiar ou evitar a intervenção cirúrgica.

Esta revisão avalia criticamente a evidência atual sobre intervenções regenerativas, incluindo infiltrações de corticosteroides, ácido hialurónico, proloterapia, plasma rico em plaquetas (PRP) e terapias celulares, como aspirado de medula óssea (BMA) e células estaminais mesenquimais derivadas do tecido adiposo (AD-MSCs). Entre estas modalidades, o PRP pobre em leucócitos (LP-PRP) demonstra os resultados mais consistentes em termos de alívio da dor e melhoria funcional, com efeitos sustentados até 12 meses. A proloterapia e o ácido hialurónico, particularmente em formulações de alto peso molecular, também evidenciam resultados favoráveis a curto prazo. Em contrapartida, os corticosteroides proporcionam apenas analgesia transitória e podem comprometer a cicatrização tendinosa quando administrados no pós-operatório.

As terapias celulares têm revelado achados preliminares encorajadores, incluindo melhoria estrutural do tendão e redução da dimensão das lesões. Contudo, os estudos disponíveis são limitados pela heterogeneidade metodológica, pelo reduzido tamanho amostral e por períodos curtos de seguimento, o que inviabiliza conclusões definitivas.

Este artigo sublinha a necessidade de seleção individualizada do tratamento, baseada no perfil do doente, na gravidade clínica e no acesso às terapias. Embora algumas estratégias regenerativas estejam progressivamente mais acessíveis, muitas permanecem ainda em fase experimental devendo ser restringidas a protocolos de investigação até que esteja disponível evidência de maior qualidade. As decisões terapêuticas devem assentar na tomada de decisão partilhada, abordando de forma clara os benefícios, limitações, custos e perfis de segurança de cada modalidade.

Palavras-chave: Células-Tronco Mesenquimais; Lesões da Roturas da Coifa/tratamento; Medicina Regenerativa; Plasma Rico em Plaquetas; Tendinopatia

INTRODUCTION

Rotator cuff injuries are among the most common causes of shoulder pain and dysfunction in adults, particularly those over the age of 40. Their estimated prevalence ranges from 20% to 30% in this age group and exceeds 60% in elderly individuals.[1] These conditions encompass a spectrum that includes tendinopathies, partial tears, and full-thickness tears, often associated with cumulative degenerative and biomechanical factors.

From a clinical and functional standpoint, these injuries significantly impact patients' quality of life and represent a substantial economic burden on healthcare systems. It is estimated that shoulder-related complaints account for up to 16% of musculoskeletal consultations in primary care, with rotator cuff tendinopathy being the leading cause of prolonged work absenteeism.[2] Furthermore, more than 50% of consultations with shoulder specialists are attributed to rotator cuff tendinopathy or tears, underscoring the high prevalence and clinical relevance of these conditions.[3]

The pathophysiology of tendinopathies involves a chronic process of extracellular matrix disorganization, reduced cellularity, vascular changes, and the presence of microtears, often occurring without a classic inflammatory response.[4] Partial tears, in turn, may represent either a progression of this degenerative process or result from acute traumatic injuries, each with distinct prognostic and therapeutic implications.

The initial treatment of these conditions is typically conservative, focusing on functional rehabilitation and pain control. However, many patients do not achieve satisfactory outcomes with conventional measures. In such cases—particularly in symptomatic and refractory partial tears—complementary or surgical approaches may become necessary.[5]

In this context, regenerative therapies have emerged as promising alternatives to traditional management. Interventions such as platelet-rich plasma (PRP) injections, prolotherapy, hyaluronic acid, modulated-action corticosteroids, and cell-based products—such as bone marrow aspirate (BMA) or adipose-derived mesenchymal cells (AD-MSCs)—have been investigated for their potential to promote tissue regeneration, shorten rehabilitation time, and avoid or delay the need for surgery.[6]

However, the results remain heterogeneous, mainly due to variability in application protocols, the type of product used, and assessment methods. Most available studies evaluate the use of these therapies as adjuncts to surgery, and there are still gaps regarding their isolated effects.[7,8] Moreover, there is a lack of evidence in specific populations such as the elderly, athletes, or manual laborers,[9] making it difficult to establish universal recommendations.

This article aims to critically review the recent literature on the use of regenerative strategies in the conservative treatment of tendinopathies and partial rotator cuff tears, emphasizing evidence of clinical efficacy, structural impact, safety, and cost-effectiveness.

CORTICOSTEROIDS

Subacromial corticosteroid injections are still frequently used to manage pain and inflammation in rotator cuff disorders. However, their effects on the biological tendon repair process have generated controversy in the specialized literature. One of the main reasons corticosteroid injections have returned to the center of the debate is their ability to suppress natural inflammatory processes essential for healing. Inflammation usually plays a key role in tendon injury repair—an effect that regenerative therapies aim to stimulate. Corticosteroids suppress these inflammatory responses, potentially impairing the healing process.[10,11]

Experimental studies have shown that corticosteroids can exert adverse effects on tenocytes and the collagen matrix, compromising the structural and biomechanical integrity of the tendon. In addition, a reduction in microvascularization at the tendon insertion site has been observed, further aggravating the already limited blood supply in this region. These findings support the arguments against the routine use of this approach.[10,11]

The reviews conducted by Wang *et al*[12] and Mohamadi *et al*[13] evaluated the clinical effects of corticosteroid injections on pain relief and functional improvement compared to PRP and placebo injections, respectively. Both studies found a reduction in pain scores within 3 to 6 weeks after corticosteroid use, with no benefits observed beyond 3 months. A recent 2024 study conducted by Wang[14] supports previous evidence, highlighting that while corticosteroid injections may offer short-term pain relief, they do not contribute to structural recovery and might even impair long-term tendon healing.

Although widely debated, a clinical study by Baverel *et al*[10] did not demonstrate an increased risk of retear when a single corticosteroid injection was administered preoperatively. However, when performed postoperatively, patients showed worse functional outcomes and a higher failure rate.

What can be stated at this point regarding corticosteroid injections is that their use provides pain relief for less than 3 months, and their administration in the postoperative period should be avoided. Although there is no evidence to contraindicate corticosteroid injections in the preoperative period, due to the potential risk of retear, alternative pain management strategies are advisable in cases with possible surgical indications. Finally, there is no clinical evidence that a single subacromial corticosteroid injection causes structural damage or functional impairment, and it may be a valid strategy in cases where pain is a limiting factor for initiating adequate rehabilitation.

HYALURONIC ACID

To date, only one randomized clinical trial has evaluated the isolated use of hyaluronic acid in patients with partial rotator cuff tears. Conducted by Chou *et al*[15] in 2010, this study compared hyaluronic acid to placebo and demonstrated significant improvements in pain and function after six weeks of treatment, with these benefits sustained over a mean follow-up period of nearly three years.

More recent studies, such as the one by Cai *et al,*[16] have investigated the combined effect of hyaluronic acid and PRP, yielding more favorable results than the isolated use of each substance. A randomized clinical trial published in 2023 also reinforced the symptomatic efficacy of hyaluronic acid, particularly in high molecular weight formulations, which demonstrated positive effects lasting up to six months. However, the impact on function was more limited than PRP.[17]

A larger number of studies are available regarding the treatment of rotator cuff tendinopathies.[17] Both high and low-molecular-weight formulations showed better results than physiotherapy alone, particularly in short-term pain relief and improvements in quality of life. Additionally, low

molecular weight hyaluronic acid demonstrated greater tolerability among patients.[18,19]

A systematic review conducted by Lin *et al*[20] indicated a trend toward the superiority of hyaluronic acid over placebo for symptom control for up to six weeks, with functional improvement observed for up to 12 weeks. However, benefits beyond this period were not consistently demonstrated.

Overall, hyaluronic acid is a safe and potentially effective alternative, especially for pain control. Although its cost is higher, particularly in high molecular weight formulations, it may represent a viable option in cases where other therapies pose risks or are contraindicated. However, further well-designed clinical studies are still needed to determine its proper medium- and long-term effects when used in isolation.

PROLOTHERAPY

Prolotherapy, a technique involving the injection of hyperosmolar dextrose-based solutions, has attracted growing interest in regenerative medicine due to its potential to stimulate tissue repair processes. Nevertheless, there is still no consensus on a standardized protocol for its application.[21]

The review conducted by Catapano *et al*[22] highlighted the wide variation among studies regarding the concentration of glucose used (ranging from 12.5% to 25%), application techniques, injected volume, number of sessions, and intervals between them. This methodological heterogeneity hinders standardization and, consequently, the direct comparison of results.

Overall, studies show that the technique—mainly when performed with multiple serial injections at different points in the affected region—may be more effective than physiotherapy alone in relieving pain and improving function. A meta-analysis published in 2024 reinforced the efficacy of prolotherapy in reducing pain and improving function for up to 12 months, mainly when ultrasound-guided and performed in multiple serial sessions, with high safety and no serious adverse events reported.[23]

Despite the encouraging results, the variety of protocols across studies limits the ability to establish definitive clinical guidelines. Therefore, although prolotherapy appears to be a promising alternative in the conservative management of tendinopathies and partial rotator cuff tears, further standardized research is needed to clarify its mechanisms of action, ideal indications, and the durability of its effects.

PLATELET-RICH PLASMA

The different methods of obtaining and preparing PRP lead to considerable variability in clinical outcomes, making it difficult to draw definitive conclusions about its efficacy in tendinopathies and partial rotator cuff tears. Variations in centrifugation protocols, the presence of leukocytes, and platelet concentrations result in PRP preparations with diverse biological properties, which influence the observed therapeutic effects.[24] The lack of standardization hinders comparisons between studies and the development of reliable meta-analyses, thereby preventing the formulation of evidence-based clinical guidelines.

Evidence suggests that the most effective formulation for these conditions is leukocyte-poor PRP with a high platelet concentration, as this composition tends to reduce the inflammatory response and promote a more favorable environment for regeneration.[24] Ultrasound-guided application is recommended for greater precision, enhancing therapeutic benefits, and minimizing risks. Multiple applications are sometimes necessary, adjusted according to the patient's response.[25]

A recent multicenter study in 2024 demonstrated that leukocyte-poor PRP (LP-PRP) provided prolonged pain relief and functional improvement for up to 12 months, superior to placebo and corticosteroids. The authors emphasized the importance of standardization and identified LP-PRP as the most effective formulation to date.[26] In 2019, Cai *et al*[16] demonstrated that combined therapy with sodium hyaluronate and PRP resulted in superior pain control and functional improvement after six months, compared to the control group—which received saline injections—and to treatments using sodium hyaluronate or PRP alone. In the systematic review by Hamid *et al*,[27] PRP injections were consistently associated with pain improvement after six months. However, functional improvement varied depending on the measurement instrument used: significant improvement was observed with the SPADI at three months, but no sustained benefits were seen at one year when assessed using the DASH score. Considering that both questionnaires have their limitations, the issue of functional improvement with PRP use remains unclear.

We highlight three recent studies on the topic. Rossi *et al*[28] investigated differences in treatment responses between cases of tendinopathy and partial rotator cuff tears. Significant improvements in pain, function, and return to sports were observed in both groups. However, these improvements were statistically and clinically more pronounced in the tendinopathy group. Additionally, 20% of patients with partial tears did not achieve satisfactory outcomes and required surgical

treatment. Vaquerizo *et al*[29] conducted a randomized clinical trial comparing the effects of corticosteroid and PRP injections. The results showed that the functional improvement achieved with PRP was similar to that reported by Rossi *et al*,[28] with both studies favoring the use of PRP. Finally, Poff *et al*[30] conducted a study comparing surgical repair to PRP injection in patients who had failed conservative treatment for partial rotator cuff tears, with a minimum follow-up of two years. Both groups showed clinically relevant improvements in pain and function. However, no statistically or clinically significant differences were observed between the two treatments, although scores were slightly higher in the surgical group.

PRP injection, when used alone or in combination with rehabilitation protocols, yields favorable outcomes in terms of pain control and functional improvement in patients with rotator cuff tendinopathy. Although outcomes are comparatively less favorable in cases where the condition has progressed to partial tears, this therapeutic modality remains an alternative option for patients who wish to avoid surgical treatment. To date, no evidence exists that PRP use leads to structural improvement of the rotator cuff tendons. Moreover, it is unknown whether PRP alters the natural course of the disease. Its indication, therefore—even within research protocols—should be approached with caution, and patients must be informed of the current limitations and evidence regarding this method.

BONE MARROW ASPIRATE / MESENCHYMAL STEM CELLS

Most studies on rotator cuff injuries involving mesenchymal stem cell therapy derived from bone marrow aspirate focus on its use as an adjuvant to surgical repair. Only two studies on this topic have been published in peer-reviewed, indexed scientific journals.

One of the relevant studies was conducted by Kim *et al*,[31] who compared physiotherapy treatment with injections using a mixture of bone marrow aspirate (BMA) and PRP without accompanying rehabilitation. Although preliminary results favored the injection approach, the conclusions are limited due to the short follow-up period of only three months. The concurrent use of PRP in a 2:1 ratio also complicates the interpretation of results. Therefore, it is impossible to draw definitive conclusions about the efficacy of BMA injection in partial rotator cuff tears.

The study conducted by Centeno *et al*[32] adopted a similar experimental design, using concentrated BMA combined with PRP and comparing the outcomes with isolated rehabilitation. Although the follow-up period was extended to 24 months, a crossover was offered to control group patients at 3 months, resulting in 10 out of 11 participants switching to the intervention group; the remaining control group patient withdrew from the study. Therefore, although the study design was robust and the results clinically promising, it is not possible to definitively conclude that injection is superior to isolated rehabilitation in the long term nor to affirm that similar outcomes would be achieved with the use of non-concentrated BMA.

To date, there are no published studies specifically evaluating the effects of bone marrow aspirate concentrate (BMAC) alone in the treatment of partial rotator cuff tears, although its higher concentration of progenitor cells could potentially yield superior outcomes.

ADIPOSE DERIVES MESENCHYMAL CELLS

The first clinical study using adipose-derived mesenchymal stem cells (AD-MSCs) for the treatment of partial rotator cuff tears was conducted by Jo *et al*.[33] Autologous fat obtained through liposuction was subjected to enzymatic processing to isolate the stromal vascular fraction. This was then expanded in culture to achieve the desired cell count according to the assigned group, low, medium, or high dose. Intralesional administration was performed under ultrasound guidance. Although there was no control group, an interesting feature of this study was the use of arthroscopic evaluation at baseline and six months after the procedure, which showed significant improvement in tendon appearance and quality and a reduction in lesion size in the medium- and high-dose groups. While all groups showed significant clinical improvement from baseline, the low-dose group demonstrated inferior outcomes in terms of pain and function compared to the higher-dose groups.

Subsequently, in a study conducted by Hurd *et al* in 2020,[34] the outcomes of AD-MSCs were compared to those of corticosteroid injection. Twenty patients with partial tears involving more than 50% of tendon thickness and no improvement after six weeks of physiotherapy were included. The only statistically significant finding was a better functional outcome based on the ASES score from the 24th week onward. Although there was a trend toward superior results in terms of quality of life and pain, the small sample size—given that this was a pilot study—likely limited the statistical power of the findings.

A prospective study published in 2024 using adipose-derived mesenchymal stem cells demonstrated clinical improvement

and reduced lesion size for up to 12 months, with a high safety profile—even without laboratory cell culture. Despite being promising, the results are still preliminary, and these therapies should remain within research protocols.[35]

Research conducted to date shows promising results; however, due to the lack of more substantial evidence (controlled, randomized, comparative studies with larger sample sizes and long-term follow-up), this type of intervention in tendinopathies and partial rotator cuff tears should not be encouraged. Further studies are necessary before recommendations on this topic can be made.

COMPARATIVE SUMMARY OF TREATMENT MODALITIES

Effects over weeks to months:

Corticosteroids: Provide immediate pain relief lasting less than 3 months.[12,13]

Hyaluronic Acid: Improves pain and function after 6 weeks.[15,17]

Prolotherapy: Positive outcomes in pain management and functional improvement.[23]

PRP: Promising results in pain control and functional improvement, especially with leukocyte-poor PRP (LP-PRP).26

Bone and Adipose Mesenchymal Stem Cells: Preliminary positive clinical effects with stromal vascular fraction (SVF).[33,35]

Effects at ≥ 1 year:

Corticosteroids: No sustained benefit; possible deleterious effects on tendon structure.[10,14]

Hyaluronic Acid: Some studies suggest that benefits can be maintained for more than a year.[20]

Prolotherapy: Lack of studies with long-term results.[23]

PRP: LP-PRP may sustain improvements for up to 12 months.[26,30]

Bone and Adipose Mesenchymal Stem Cells: SVF has shown clinical improvement and lesion reduction for up to 1 year.[35]

Safety:

Corticosteroids: Potential risks to tendon integrity and vascularization.[10,11]

Hyaluronic Acid: Considered safe, with fewer side effects.20

Prolotherapy: Safe, with no serious adverse events reported.[23]

PRP: Safe, especially when performed under ultrasound guidance.[25]

Bone and Adipose Mesenchymal Stem Cells: Promising but lacking robust long-term studies.[33,34]

Cost-Effectiveness:

Corticosteroids: Low initial cost; indirect costs may be high due to repeated treatment failures.

Hyaluronic Acid: High cost, especially in high molecular weight formulations.[17]

Prolotherapy: Low cost and perhaps effective when performed in series.[23]

PRP: Higher cost, but with potential to reduce the need for surgery.[30]

Bone and Adipose Mesenchymal Stem Cells: High cost and limited to experimental settings.[33-35]

CONCLUSION

Treatment selection should be individualized, considering the patient's clinical profile, personal preferences, and access to available therapies. LP-PRP emerges as one of the most well-supported options in the current literature, both in terms of efficacy and safety.

Other strategies, such as high molecular weight hyaluronic acid and serial prolotherapy—mainly when image-guided—also offer practical and safe alternatives for pain management and functional improvement.

Although still associated with temporary benefits, corticosteroids play a role in specific situations. However, their use should be judicious, especially avoiding administration in the immediate postoperative period.

Therapies based on mesenchymal cells show promising early results. However, due to the limited data available, they should remain confined to research settings until solid scientific evidence confirms their long-term efficacy and safety.

Therapeutic decisions should balance expected clinical outcomes, cost, safety, and the patient's preferences regarding the type of intervention. Clear communication about the benefits and limitations of each approach is essential for informed and conscious decision-making.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse.

Apoio Financeiro: Este trabalho não recebeu qualquer subsídio, bolsa ou financiamento.

Proveniência e Revisão por Pares: Não solicitado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Declaração de Contribuição

Todos os autores contribuíram para a conceção e o desenho do estudo. Todos os autores leram e aprovaram a versão final do manuscrito.

Contributorship Statement

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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