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Review

# Peri-tendinous injections. An overview of agents and their efficacy

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## Abstract

Tendinopathy is the clinical entity representing chronic tendon injury, and it is relatively common, affecting about one-fourth of adults during their lifetime. Non-invasive management of tendon disorders includes various peri-tendinous injections. Ultrasound-guided peri-tendinous injections is a non-invasive technique with potentially therapeutic effect for tendinopathy. Commonly used drugs and agents include topical corticosteroids, PRP, autologous whole blood, hyaluronic acid, hyperosmolar dextrose, and needle tenotomy. The routine use of NSAIDs and peri-tendinous corticosteroid injections are being re-evaluated since histologic examination of pathologic tendinous tissue has shown no signs of inflammation. New non-invasive tools such as PRP, autologous whole blood, and hyaluronic acid are being investigated. These agents have been proven effective in alleviating pain and histologically improving tendon injuries. Prolotherapy is a rapidly spreading approach, but its effectiveness is currently vastly studied compared to other interventions. The simple needle fenestration of the injured tendon has also shown promising results and can be used alone or in combination with tested drugs and agents. The literature lacks extensive high-quality double-blinded clinical trials that will test the efficacy of different peri-tendinous injections and conclude which method leads to the best results. This mini-review aims to discuss the above options as far as their indications and their use are concerned.

**Keywords**

Tendinopathy; PRP; hyaluronic acid; prolotherapy

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## Introduction

Tendons are fibroelastic structures of tenocytes and tenoblasts in a rich extracellular matrix network. Tendon injuries are widespread and can be either acute or chronic [1]. Acute injuries usually include partial or complete ruptures due to extrinsic forces exceeding the tendon's resistance capacity. A combination of extrinsic and intrinsic factors causes chronic injuries. Repetitive overloading of tendons can cause trauma or accumulative microtrauma, leading to a pathological healing response [2]. Histologically, healing seems impaired, with collagen fibre disorientation and thinning, hypercellularity, absence of inflammatory cells, neovascularity, and increased glycosaminoglycan deposition [3].

Tendinopathy is a clinical entity representing chronic tendon injury. This is relatively common, affecting about one-fourth of adults during their lifetime [4]. Athletes' increasing performance demands and the wide spread of sports as hobbies in more mature age groups have augmented the risk of primary tendon lesions over the last decades [5]. The tendons most usually affected are Achilles, patella, rotator cuff tendons, wrist extensors and flexors, posterior tibial, and biceps femoris [6], but every tendon can be affected.

Treatment options are abundant for tendon disorders. However, there is no consensus on tendinopathy management[7]; treatment choice usually depends on empirical observations. Physical therapy, rest, training modification, NSAIDs and various peri-tendinous injections are a few of the available preservative options, but the results are almost always temporary and inconsistent. Surgical treatment should be preserved for cases that do not improve with less invasive approaches [8].

## Peri-tendinous injections: agents and techniques

Ultrasound-guided intra and peri-tendinous injections is a non-invasive technique with potentially therapeutic effect for tendinopathy, and it is being extensively investigated [9] in contemporary literature. Many different agents and drugs are being tested in experimental and cohort studies, with the effectiveness results awaiting proof. The authors conducted a thorough literature overview to introduce the most usual drugs used in peri-tendinous injection and their potential effectiveness.

### *Corticosteroid injections*

Peri-tendinous corticosteroid injections are the most popular and widely used [10] in chronic tendinopathies, despite the sheer lack of benefit presented in current literature [11].

Local steroids are used to decrease pain via topical inflammatory process restriction. Histologically, tendinopathy does not include signs of inflammation but is merely a pathologic healing reaction. In the rare situation with an inflammatory response, it is an indispensable part of the healing course against injury or continuous microtrauma, and its disruption can lead to adverse effects. Steroids can harm tendons' biomechanics, degrading collagen, decreasing fibroblast proliferation, and increasing inflammation and cytotoxicity [12].

The biochemical effects of steroids on tendon structures have been proven harmful in animal models [13, 14], but evidence has not yet been established in human tendons. However, there have been case reports of tendon rupture after peri-tendinous steroid administration [15, 16] and studies showing a positive correlation between local steroid usage and tendon tears [17].

Subsequently, peri-tendinous steroid injections can transiently alleviate pain and partially restore range of motion but seem to cause more damage than good at cell and tissue level, with possible long-term tendon atrophy, rupture and other adverse effects.

### *Platelet-Rich-Plasma injections (PRP)*

PRP is autologous patient plasma with a higher concentration of platelets [18] (three to eight times higher than whole blood). Platelets are derived from megakaryocytes and, except for being essential to blood clot formation, they release many active biomolecules containing growth factors. Platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β) and vascular endothelial growth factor (VEGF) are the most important agents excreted by platelets, which actively assist in the healing process. According to the literature, platelets might

**Table 1:** Pros and cons of the different types of peri- tendinous injections

| Type of peri-tendinous injection | **Pros** | **Cons** |
|---|---|---|
| **- Corticosteroid injections** | - Pain relief<br>- Inflammation reduction | - Cell and tissue damage<br>- Tendon atrophy - rupture |
| **- PRP injections** | - Pain relief<br>- May offer definite treatment | - Effectiveness still under investigation |
| **- Hyaluronic acid** | - Enhancing collagen production<br>- Enhancing proliferation of mesenchymal cells<br>- Accelerate tendon recovery | - Unknown mechanism of action<br>- Not effective on inflammation |
| **- Whole blood** | - Low cost<br>- Ease of use and preparation | - Little literature comparing its effectiveness |
| **- Dextrose prolotherapy** | - Pain relief<br>- Amelioration of ROM | - Variable results |
| **- Percutaneous tendon fenestration** | - Reactivates healing process<br>- Microtrauma liberates growth factors | - Usually, needs to be combined with other injection therapy, like PRP |

even promote stem cell recruitment and collagen production from fibroblasts [19].

Peri-tendinous PRP injections have shown promising results in chronic tendinopathy management [20, 21, 22, 23, 24, 25]. Platelets are activated after they are injected into the tendon via their interaction with free collagen and release growth factors that promote and augment the healing course of actions. The generative effect of PRP has been proven histologically, and PRP injections have shown clinical improvement in pain and range of motion in cases with different kinds of tendinopathy. The rapidly increasing interest in PRP injections is unveiled in the numerous currently registered studies investigating its effectiveness.

The reactivation of the healing process seems connected to the resumption of an inflammatory state, and leukocytes play a tremendous role in inflammation. PRP can currently be divided into leukocyte-rich (LR-PRP) and leukocyte-poor (LP-PRP). The interaction between leukocytes and platelets can be pro or anti-inflammatory with regenerative potential. This combination of autologous cells may offer the definitive therapeutic effect that is pursued but is still being studied with promising future results [26].

*Hyaluronic acid*

Hyaluronic acid (HA) is a high–molecular-weight glycosaminoglycan and the primary component of synovial fluid, providing lubrication and shock absorption [27]. It is also one of the fundamental components of tendon tissue, contributing to its biomechanical properties. It has been tested in several clinical trials as a therapeutic means for managing tendinopathy. It has been proven effective in patients with rotator cuff tendinopathy [28, 29, 30], tennis elbow [31], patellar [32] and Achilles [33] tendinopathy.

Although the exact mechanism of action is not yet thoroughly investigated, peri-tendinous HA injections accelerate tendon recovery by enhancing collagen production and proliferation of specific mesenchymal cells, such as chondrocytes and hematopoietic cells [34]. The viscoelastic effects of HA on connective tissue have been suggested to warrant its use for tendinopathy management. Hyaluronic acid

has been proven to improve function and reduce pain without the complications of corticosteroids. Further research needs to be conducted to determine the stages of tendinopathy that can benefit the most from HA injections [35].

*Whole blood*

Compared to PRP, autologous whole blood injections present decreased cost and ease of preparation and use. In addition, clinical benefit has been shown concerning pain and mobility improvement. Thus, the effects of autologous whole blood versus PRP injections are worth investigating. According to the literature, whole blood is equally effective to PRP in managing lateral elbow tendinopathy [36] and hamstring tendinopathy [37]. However, certain reviews suggest the superiority of PRP for specific tendon disorders. Further investigation needs to be conducted to assess the cost-effectiveness of this debuting non-invasive approach meticulously.

*Dextrose prolotherapy*

Prolotherapy with hypertonic dextrose has been used for years for chronic musculoskeletal pain with variable results in literature [38]. Prolotherapy has also been introduced as a non-invasive treatment option in tendinopathy management.

The suggested mechanism of action includes the initiation of the inflammatory response cascade and enhancing the tendon healing process. Peri-tendinous hypertonic dextrose infusion can induce mesenchymal cell proliferation and collagen production [39], significantly improving range of motion (ROM) and pain.

Prolotherapy is a rapidly spreading means for preservative treatment of various soft tissue disorders. The literature lacks high-quality research assessing the effectiveness of hyperosmolar dextrose injections in chronic tendon disorders. Some reviews suggest little to no benefit from prolotherapy [40], whereas other studies have presented amelioration of mobility and pain in Achilles [41] and rotator cuff [42] tendinopathy. Further well-organized double-controlled trials are necessary to conclude the debate on prolotherapy effectiveness for chronic tendon disorders.

*Percutaneous tendon fenestration or needle tenotomy (PNT)*

Ultrasound-guided tendon fenestration has also been used successfully in managing chronic tendon disorders and even tendon tears. The technique includes passing a needle several times (20-25) through the tendinous tissue. The rationale behind this technique is converting a failing chronic healing process into an acute response [43] by multiple needle microtrauma. In addition, the induced bleeding provides the tendon with autologous red blood cells and platelets, which release healing-promoting growth factors.

The improvement of tendinopathy-related symptoms via PNT has been recognized in many studies [44, 45], but has not been widely compared to other non-invasive interventions. Other peri-tendinous injections can be combined with PNT, such as PRP or autologous whole blood, to enhance the induced regenerative result and promote tendon healing. As the non-invasive clinical approach and management of tendinopathy gain ground, the need for a preservative but definitive treatment arises. Subsequently, these combinations are currently subjected to extensive investigation [46].

## Discussion

Tendon disorders represent many acute or chronic tendon pathologies, mainly caused by overuse conditions, where the tendon part of the muscle-tendon unit is imposed to excess force and stress. They represent one of the most frequent clinical diagnoses, accounting for 30% of all musculoskeletal consultations [47]. These injuries are usually encountered in athletes, presenting the highest prevalence in elite athletes, and different tendons are affected in distinct ways. Tendons of the rotator cuff, the long head of the brachial biceps, the extensors and flexors of the wrist, the thigh adductors, the posterior tibialis tendon, the patellar tendon, and the Achilles tendon are the districts most often involved [6], but every tendon can suffer damage.

Sport activity is the most recognizable risk factor for tendon injuries. However, other modifiable and not modifiable risk factors are taking part in developing tendon disorders. Age seems to be a

factor that influences the prevalence of tendinopathy since adolescents seem to be less affected compared to adults [48]. Sex is another factor influencing the presentation of specific tendinopathies in athletes [49]. Occupational exposure to intense-force repetitive movements combined with poor workplace ergonomics is a known risk factor affecting the upper extremities and predisposing to lateral epicondylitis [50].

Additionally, drugs can negatively affect tendinous tissue predisposing to injuries, such as corticosteroids, quinolone antibiotics, aromatase inhibitors, and statins [51]. Obesity is another risk factor since the increased weight puts excess force on the muscle-tendon units, leading to faster tendon wear. Lastly, numerous metabolic diseases can be presented with clinical symptoms of tendinopathy, such as chronic gouty arthritis, hypercholesterolemia, diabetes mellitus, and thyroid pathologies.

Surgery for chronic tendinopathy has presented inconsistent results and increased morbidity. Thus, it is not preferred as the go-to treatment choice [52], but it is preserved for patients that do not show improvement after six months with less invasive approaches. The routine use of NSAIDs and peri-tendinous corticosteroid injections are being re-evaluated since histologic examination of pathologic tendinous tissue has shown no signs of inflammation, which could benefit from anti-inflammatory agents. It is currently believed that these medications only offer transient pain relief with possible long-term adverse effects. Subsequently, new non-invasive tools are being investigated.

PRP, autologous whole blood and hyaluronic acid are materials proven effective in alleviating pain and histologically improving tendon injuries. Prolotherapy is a rapidly spreading approach, but its effectiveness is currently vastly studied compared to other interventions. The simple needle fenestration of the injured tendon has also shown promising results. It can be used as a standalone treatment or in combination with tested drugs and agents such as PRP and autologous whole blood.

The literature lacks extensive, high-quality double-blinded trials that will test the efficacy of different peri-tendinous injections and conclude which method leads to the best results in reconditioning the healing process, alleviating pain, and re-establishing range of motion. The treatment choice lies in the clinicians' empirically generated opinion, modified according to patients' characteristics and requirements.

**Conclusion**

Chronic tendon disorders are a frequent clinical entity encountered by the orthopaedic surgeon. Numerous non-invasive approaches exist, such as rest, training modification, NSAIDs, and abundant available drugs and agents for peri-tendinous injections. Tendinopathy is a non-inflammatory failed healing process that renders topical steroids inappropriate and harmful. New techniques have been presented, but further investigation is mandatory to show the best means available for non-invasive long-term management and even treatment of chronic tendon injuries.

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