Myths and Facts of In-Office Regenerative Procedures for Tendinopathy

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Abstract: Tendinopathy carries a large burden of musculoskeletal disorders seen in both athletes and aging population. Treatment is often challenging, and progression to chronic tendinopathy is common. Physical therapy, nonsteroidal anti-inflammatory drugs, and corticosteroid injections have been the mainstay of treatment but are not optimal given that most tendon disorders seem to involve degenerative changes in addition to inflammation. The field of regenerative medicine has taken the forefront, and various treatments have been developed and explored including prolotherapy, platelet rich plasma, stem cells, and percutaneous ultrasonic tenotomy. However, high-quality research with standardized protocols and consistent controls for proper evaluation of treatment efficacy is currently needed. This will make it possible to provide recommendations on appropriate treatment options for tendinopathy.

Key Words: Tendinopathy, Prolotherapy, PRP, Cell Therapy

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Tendinopathies are common conditions seen in both athletic and aging population. Sustained pain and functional impairment due to tendon impairment significantly impede sports-related activities and ability to work. Repetitive microtrauma leads to failure of tendon cells to regenerate normal tendon tissue and angiofibroblastic hyperplasia ensues.[1] Histological findings demonstrate necrotic tenocytes, collagen disarray, and neovascularization in injured tendons. Without a rich blood supply, tendon tissue has an intrinsic low healing potential, which makes tendinopathies extremely difficult to treat, especially once they reach the chronic stage and fibrotic scarring has occurred. Current standard treatments in clinical practice include various rehabilitation programs, nonsteroidal anti-inflammatory drugs, extracorporeal shockwave therapy (ESWT), corticosteroids, and operative options. Diagnosis of tendinopathy is traditionally clinical. However, diagnostic ultrasound (US) has gained popularity because it allows point-of-care tissue characterization of tendon, muscle, and nerve with ease of access.[2] Ultrasound may reveal tendon thickening, loss of fibrillar continuity, and neovascularization via Doppler mode indicating tendon injury. Clinical regenerative therapies for tendinopathy can be divided into the following three large categories: (1) chemical procedures, (2) orthobiologic procedures, and (3) mechanical procedures.[3,4] In contrast to conventional steroid injections, which are used to modulate pain, these emerging options are being explored to eliminate/minimize degenerative tissues and to encourage regeneration.[5] The most common chemical procedure is called prolotherapy where an irritant such as dextrose or other chemicals are used to initiate an inflammatory cascade, which is considered to enable a healing process.[6] Orthobiologic procedures refer to the use of biological agents for improving orthopedically related disease processes. Most commonly used orthobiologic agents include autologous agents such as platelet-rich plasma (PRP), various types of cells (mainly stem cells from bone marrow and adipose), or allogenic agents derived from placental tissue.[7] Mechanical procedures use physical force to primarily remove degenerated tendon tissues and thereby help improve tendon structures. Such procedures include traditional percutaneous needle tenotomy (PNT) and more recently percutaneous ultrasonic tenotomy (PUT). Research in this field has been progressing rapidly, although there is still much controversy surrounding the efficacy of these therapies, as few large randomized controlled trials (RCTs) exist. In this article, we will appraise available evidences and suggest the areas of necessary researches that relate to regenerative tendon procedures.

METHODS

A literature review was performed on the use of regenerative medicine therapies as treatment for chronic tendinopathies focusing on the following procedures: prolotherapy, PRP, cell treatments (stem cells and skin-derived tenocyte like cells), and PUT. The following terms were included: patellar tendon, Achilles tendon, common extensor tendon, rotator cuff tendon, gluteal tendon, and hamstring tendon. The search was conducted on the PubMed database in October 2017 using the following key words:

1. For prolotherapy: (prolotherapy OR hyperosmolar dextrose OR hyperosmolar glucose)
2. For PRP: (PRP OR platelet rich plasma OR platelet derived growth factors)
3. For stem cells: (stem cells OR mesenchymal stem cells OR bone marrow stem cells OR adipose stem cells)
4. For skin-derived tenocyte-like cells: (skin-derived tenocyte-like cells OR SD-TLC OR skin derived cells)
5. For PUT: (PUT OR PUT or ultrasonic tenotomy)

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6. For tendinopathy: (patellar tendon OR patellar tendinopathy OR jumper's knee) OR (Achilles tendon OR Achilles tendinopathy) OR (common extensor tendon OR common extensor tendinopathy OR lateral elbow OR tennis elbow OR lateral epicondylitis) OR (rotator cuff tendon OR rotator cuff tendinopathy) OR (gluteal tendon OR gluteal tendinopathy OR gluteus medius tendon OR gluteus medius tendinopathy) OR (hamstring tendon OR hamstring tendinopathy).

Titles and abstracts were screened, and the following inclusion criteria were used: human studies, RCTs, case series, and use of previously mentioned therapies in chronic tendinopathy. Exclusion criteria were articles analyzing other applications of the previously mentioned regenerative therapies, other preparations of cell therapies (stromal vascular fraction (SVF), bone marrow aspirate concentrate), case reports, or animal studies. Reference lists from the selected articles were also screened. The full texts were read and relevant data were extracted for use in this review. This is not an all-inclusive systemic review of the previous literature.

RESULT/DISCUSSION

Prolotherapy: Mechanism of Action

Prolotherapy has been in practice for more than 80 yrs dating back to the 1937 when it was used on the thumb ulnar collateral ligament of a surgeon to treat both pain and ligamentous laxity.[8] The most common injected solution in prolotherapy is hyperosmolar dextrose. This solution is supposed to work by creating a hypertonic environment, causing cell rupture and upregulation of platelet-derived growth factors (PDGF). Sodium morrhuate is another agent used for its properties that are theorized to attract inflammatory mediators (e.g., $CD43^+$ leukocytes, $ED1^+$, and $ED2^+$ macrophages)[9] and act as a vascular sclerosant to reduce neovascularization. Cellular irritants such as phenol, glycerin, and glucose are no longer used in practice.[10]

Prolotherapy for Patellar Tendinopathy

Prolotherapy studies in patellar tendinopathy and Osgood-Schlatter disease generally report good outcomes with reduction in pain. In the study by Ryan et al.,[11] 47 subjects with patellar tendinopathy refractory to conservative treatment received US-guided injections of 25% dextrose with lidocaine. Subjects received injections at 6-wk intervals based on symptom improvement with a mean ± SD of 4 ± 3.4 injections required. At 45-wk follow-up, there was a significant reduction in pain at rest and with activity, which were accompanied with sonographic improvement in both vascularity and echogenicity. Another RCT by Topol et al.[12] demonstrated the efficacy of unguided prolotherapy in Osgood-Schlatter disease, which is a traction apophysitis of patellar tendons (a patellar tendinopathy spectrum disease). This study randomized 65 knees in 54 subjects aged 9–17 yrs with recalcitrant Osgood-Schlatter disease to three treatment groups: 12.5% dextrose injection, lidocaine injection, or a therapeutic exercise group. The injection treatment groups received three injections at 4-wk intervals. Greater rates of returning asymptomatic patients to sports were observed in the prolotherapy group (84%) versus the lidocaine (46%) and exercise (14%) groups at 1 yr.

Prolotherapy for Achilles Tendinopathy

An early case series showed reduced pain at 6 wks after US-guided, intratendinous 25% dextrose injections in 33 cases of both insertional and midportion Achilles tendinosis.[13] The subjects required an average of four injections at 1.5-mo interval, and although statistical significance was defined as $P = 0.10$, the improvement was seen with pain at rest and pain with tendon-loading activities, with improvement on sonographic hyperemia in 55% of the treated tendons. Yelland et al.[14] randomized 43 subjects with midportion Achilles tendinopathy (AT) into a 12-wk therapy program of eccentric loading, weekly unguided 20% glucose prolotherapy injection with local anesthetics, or combined 20% prolotherapy/eccentric load exercise groups. Prolotherapy alone or in combination with eccentric exercise showed greater reduction in pain at 6 mos, although longer-term results at 12 mos showed no significant difference. A potential attention bias should be noted as injection protocol included performance of injection until minimum clinically important change, resulting in three times more visits in injection groups. Interestingly, four injections (range, 2 to 11) were required to achieve the minimum clinically important change, which was similar to Maxwell's case series.

Prolotherapy for Common Extensor Tendinopathy

Common extensor tendinopathy (CET) is one of the most heavily studied anatomic structures for prolotherapy. Scarpone et al.[15] performed a double-blind RCT involving a total of 24 subjects with CET in whom three landmark guided injections at 4-wk intervals of 10.7% dextrose and 14.7% sodium morrhuate by volume versus saline control was used without tenotomy. Tenotomy refers to insertion of the needle into the tendon with or without injection of the solution, resulting in fiber disruption and induction of bleeding to promote healing. The intervention resulted in significant reduction in elbow pain and improvement in strength in the prolotherapy group compared to the control.[15] Carayannopoulos et al.[6] randomized 24 subjects into two groups, administering various landmark-guided prolotherapy agents including phenol, glycerin, 12.5% dextrose, and sodium morrhuate, and compared the response to corticosteroid injection. Subjects were given two injections at 4-wk intervals. Improvements in pain and function, as evidenced by visual analog scale (VAS) for pain and disability/symptom (Disabilities of the Arm, Shoulder, and Hand [DASH]) scores, were noted in both groups with no significant intergroup differences or differences in subject satisfaction although an attenuation effect in VAS scores was seen in the corticosteroid group beyond 6 mos as noted by a decreased change in VAS score compared with the 3-mo follow-up. This may suggest that studies involving benefits of prolotherapy would require a longer duration of follow-up.[6] The study of 84 subjects by Shin et al.[16] demonstrated decreased VAS pain scores and improved sonographic appearances of tendon after three landmark-guided injections of 15% dextrose. Figure 1 demonstrates a sonographically guided CET prolotherapy injection.

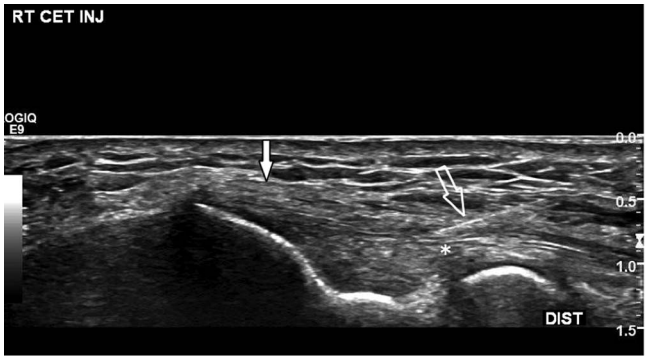

FIGURE 1. Sonographically guided CET prolotherapy injection with CET (arrow) and radial collateral ligament (asterisk) seen in anatomic long axis view with the needle (open arrow) guided in an in-plane, distal-to-proximal technique. The radius is distal, to the right, and the humerus is proximal, to the left.

Prolotherapy for Rotator Cuff Tendinopathy

A few RCTs exist that have evaluated prolotherapy in chronic rotator cuff tendinopathy, and although they do not have consistent control groups, they all did find a significant reduction in pain and disability with prolotherapy. A recent RCT by Seven et al.[17] treated 101 subjects with chronic rotator cuff lesions to either the US-guided 25% (subacromial bursa) and 15% (tendon insertion) dextrose prolotherapy injection group or a physical therapy (PT) group. The prolotherapy group required a mean of 5.23 injections (range, 2–6). This study demonstrated significant improvement in pain score, disability index, and shoulder range of motion (except external rotation) at 6-wk, 12-wk, and 1-yr follow-up in the prolotherapy group compared with the PT group, although it should be noted that there was no difference at 3 wks. There was 93% patient satisfaction in the prolotherapy group versus 57% in the control group at 1 yr. In a case series of 126 subjects, three to eight prolotherapy injections with 16.5% dextrose by volume solution without imaging guidance were given to patients unresponsive to aggressive conservative treatment.[18] At 1-yr follow-up, strength, range of motion, and pain were significantly improved in the treatment group over the control group. See Figures 2A and B demonstrating sonographically guided prolotherapy injection for rotator cuff tendinopathy.

Current View of Prolotherapy Injection for Tendinopathies

Table 1 summarizes literature discussed in this section of the review. Common extensor tendinopathy studies seem to show most robust data for success, whereas prolotherapy seems to be promising for patellar, Achilles, and rotator cuff tendinopathies. Finally, studies suggest that multiple injections are most likely required and seem to be safe. Little is known about the benefits of "prehab" and postinjection therapies. There have not been any clinical studies for the use of prolotherapy in gluteal or hamstring tendinopathies. Although high-level evidences are still few, with the low risk of adverse events given its long history in existence and efficacy, dextrose prolotherapy can be considered as an alternative to conventional treatments such as PT or corticosteroid injections in chronic refractory tendinopathies.

Improving Prolotherapy Clinical Studies

The mechanism of action by prolotherapy has not been established, and this will continue to be the area of active discussion and will likely require further preclinical investigations. Optimal procedural protocols have not been determined including frequency, concentration of dextrose, and injection location (peritendon *vs.* intratendinous). This may depend on the targeted tendon location (lower *vs.* upper extremity tendon) and on the severity and chronicity of tendon injuries. Ultrasound guidance will maximize injection accuracy and study reproducibility and allows assessment of varying degree of tendinopathy.

Platelet-Rich Plasma: Mechanism of Action

Since the first documented musculoskeletal application of PRP in the 1990s, PRP has been studied extensively for various conditions including tendinopathy. Platelet-rich plasma is obtained by centrifugation of autologous blood and collecting concentrated platelets in plasma. Platelet-rich plasma is considered to exert regenerative effect via growth factors (GFs). Platelets produce a variety of GFs such as PDGF, VEGF, bFGF, TGF, HGF, and IGF that are involved in stimulating chemotaxis, extracellular matrix synthesis, and cell migration and proliferation.[19] Along with GFs, chemokines (IL-1β, PF4), adhesive proteins (plasminogen, fibrinogen, vitamin D–binding

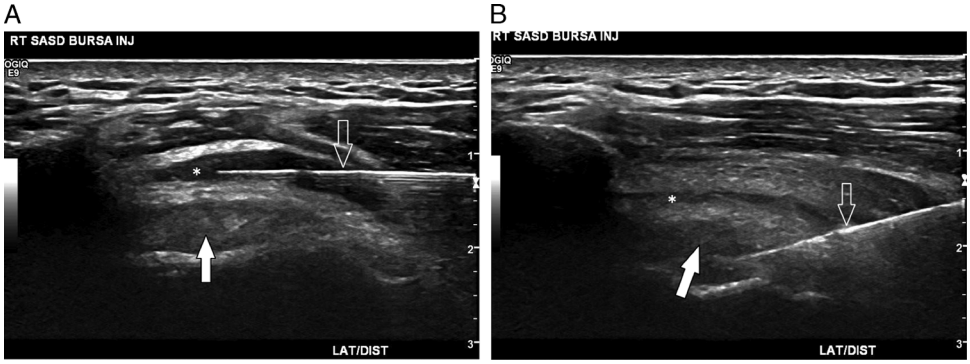

FIGURE 2. Sonographically guided prolotherapy injection for rotator cuff tendinopathy with long axis view of subacromial bursa (asterisk) and supraspinatus tendon (closed arrow). Acromion is located medially, to the left. A, Needle (open arrow) is directed in plane, lateral to medial, into the subdeltoid subacromial bursa. B, Needle is directed in plane, lateral to medial, into the tendinopathic supraspinatus tendon (closed arrow).

TABLE 1. Summary of clinical trials discussed for prolotherapy in tendinopathy

Reference	Level of Evidence	Pathology	No. Patients	Average Age	Therapeutic Protocol	US Guidance	Prolotherapy Solution	Outcome Measure	Follow-up	Main Findings
Ryan et al.[11]	Level IV case series	Patellar tendinopathy	45 subjects (47 knees)	38.3 ± 14.3 yrs	Dextrose injections (mean, 4 ± 3.4)[a]	Yes	25% dextrose	VAS, US examination	Mean, 45 wks	Significant reduction in pain at rest, with ADLs, and during sport. Improved neovascularity and hypoechoic lesion appearance on US.
Topol et al.[12]	Level I RCT	Osgood-Schlatter disease	54 subjects (65 knees) *n* = 17 dextrose *n* = 18 lidocaine *n* = 19 control	NA (range, 9–17 yrs)	Dextrose injection monthly × 3 Lidocaine injection monthly × 3 Therapeutic exercise	No	12.5% dextrose	NPPS	1 yr	Greater rates of asymptomatic return to sport in prolotherapy group.
Yelland et al.[14]	Level I RCT	Achilles tendinopathy	43 subjects *n* = 14 glucose *n* = 14 combo *n* = 15 exercise	46 (exercises and combination) *vs.* 48 (glucose) yrs	Hypertonic glucose (average, 9.5 injections) Hypertonic glucose + eccentric exercise (average, 8.7 injections) 12-wk eccentric exercise (mean, 3.3 formal sessions)	No	20% hypertonic glucose	VISA-A, Likert scale, PGIC, VAS	12 mos	More rapid pain improvement in prolotherapy and combo therapy groups over exercises alone. No difference in long-term functional scores.
Maxwell et al.[13]	Level IV case series	Achilles tendinopathy	36 subjects	52.6 yrs	Dextrose injections (repeat q6w until symptoms resolved)[a]	Yes	25% dextrose	VAS at rest, during ADLs, and during activity; tendon appearance on US	12 mos	Reduced pain and neovascularity on US at 6 wks after treatment. No improvement in hypoechoic lesions on US.
Scarpone et al.[15]	Level I RCT	Lateral epicondylosis	24 subjects *n* = 12 prolotherapy *n* = 12 control	48 yrs	Prolotherapy injections monthly × 3 (at supracondylar ridge, lateral epicondyle, and annular ligament) Saline injection monthly × 3 (same location)	No	10.7% dextrose, 14.7% sodium morrhuate, and local anesthetic	Likert scale, extension, and grip strength	1 yr	Significant improvement in pain and isometric strength in prolotherapy group that was maintained at 12 mos.
Carayannopoulos et al.[6]	Level I RCT	Lateral epicondylosis	24 subjects *n* = 11 prolotherapy *n* = 13 corticosteroid	49 (prolotherapy) *vs.* 46 (steroid) yrs	2 prolotherapy injections at 4-wk interval (annular ligament, lateral epicondyle, and radial collateral ligament) 2 corticosteroid injections at 4-wk interval (same locations)	No	12.5% dextrose, phenol glycerine, and sodium morrhuate	VAS, QVAS, DASH	6 mos	Improved pain and function in both groups but no significant intergroup differences.
Shin et al.[16]		Lateral epicondylosis	84 subjects	NA	3 prolotherapy injections	No	15% dextrose	VAS, US tendon appearance	6 mos	Significantly improved pain, and decreased hypervascularity and improved tendon structure on US in prolotherapy

(Continued on next page)

TABLE 1. *(Continued)*

Reference	Level of Evidence	Pathology	No. Patients	Average Age	Therapeutic Protocol	US Guidance	Prolotherapy Solution	Outcome Measure	Follow-up	Main Findings
Seven et al.[17]	Level I RCT	Rotator cuff tendinopathy	101 subjects $n = 57$ prolotherapy $n = 44$ control	57 (prolotherapy) *vs.* 44 (control) yrs	Prolotherapy to subacromial bursa and tendon insertions (mean, 5.23 injections)[c] PT 3×/wk × 12 wks	Yes	25% dextrose (subacromial bursa) 15% dextrose (tendon insertions)	VAS, SPADI, WORC, patient satisfaction, shoulder ROM	Minimum 1 yr	Significant improvements in pain, disability index, and shoulder ROM (except ER) with prolotherapy.
Lee et al.[18]	Level IV case series	Rotator cuff tendinopathy	126 subjects $n = 63$ prolotherapy $n = 63$ control	54.1 ± 7.8 (prolotherapy) *vs.* 55.8 ± 6.6 (control) yrs	3–8 prolotherapy injections (average, 4.8 ± 1.3 injections) Continued conservative treatment	No	16.5% dextrose	VAS, SPADI, AROM, maximal tear size on US, analgesic use	1 yr	Prolotherapy demonstrated significantly improved strength, ROM, and pain over control.

[a]Intratendinous.
[b]Peritendinous.
[c]Intratendinous and peritendinous.
AROM, active range of motion; NA, not applicable; NPPS, Nirschl Pain Phase Scale; PGIC, Patient Global Impression of Change Scale; q6w, every 6 weeks; QVAS, quadruple visual analog scale; ROM, range of motion; SPADI, Shoulder Pain and Disability Index; WORC, Western Ontario Rotator Cuff Index.

protein), proteases (MMPs, ADAMTs), and smaller molecules (serotonin, histamine) are released from platelets providing a rich environment with tendon healing capability.[20] The clotting cascade leads to a fibrin clot at the site of injury allowing for cessation of bleeding and a scaffold for cell migration and proliferation. The regenerative capacity of PRP has allowed it to be used as a conservative treatment option as well as in surgical augmentation in tendon injuries. Whereas the safety of such injections is well established, recent debate has focused on optimization of PRP formula for improved results. Depending on the preparation protocols used, PRP varies in its contents and several variables such as numbers of white blood cells, their differentials, and presence or absence of platelet-activating agents are believed to affect overall treatment outcome. Results of PRP for tendinopathy treatment have been largely variable, as discussed hereinafter with regard to patellar, Achilles, rotator cuff, and common extensor tendons; however, these are the four clinical tendinopathies that have the most robust evidences.

Platelet-Rich Plasma for Patellar Tendinopathy

All patellar tendon RCTs treated subjects who are in their 20s. Two RCTs have investigated the effect of one versus two injections of PRP at 1- to 2-wk intervals and found varying results.[21,22] Kaux et al.[21] randomized 20 surgical candidates to one versus two US-guided PRP injections. Although both groups showed improvements including approximately 40%–50% pain improvement at 12 mos, the study did not document any superior benefit of two PRP injections over one. Zayni et al.[22] randomized 40 subjects to one vs two injections and demonstrated that two US-guided PRP injections resulted in improved pain and function as evidenced by better VAS, Tegner, and Victorian Institute of Sport Assessment-Patellar (VISA-P) scores. This difference may be partly explained by the variability in PRP preparations in the previous studies in which Kaux et al.[21] formulated a solution with a higher concentration of platelets than Zayni et al.[22] (4–5 times *vs.* 2 times of whole blood) and started the rehabilitation stage sooner (5–7 days after first injection vs 2 wks after last injection). The other two RCTs investigated PRP versus ESWT and dry needling.[23,24] Vetrano et al.[23] compared two weekly US-guided PRP injections ($n = 23$) to three weekly ESWT sessions ($n = 23$) and found that 2× PRP was superior to 3× ESWT in terms of functional recovery at 6 and 12 mos. In investigations by Zayni et al.[22] and Vetrano et al.,[23] approximately 20% of subjects ended up receiving surgical interventions because of nonresponsiveness to PRP injections. Dragoo et al.[24] randomized 23 subjects to a single leukocyte-rich US-guided PRP injection with dry needling or dry needling alone groups and concluded that PRP plus dry needling provided greater reduction in pain and improvement in function scores at 12-wk follow-up although such difference was not seen at 26 wks. Dragoo et al.[24] concluded that PRP may be a viable option in managing patellar tendinopathies and may provide faster recovery.

There have been a total of 317 indexed patellar tendinopathy cases treated using various PRP formulations in case series. Most common formula reported consisted of a platelet concentration of 2–3 times of whole blood without reference to white cell counts, treating chronic patellar tendinosis with an average duration of 22.5 mos, with an average follow-up of 6–24 mos, resulting in

an average of 66% reduction in pain. The average age of indexed case series patients was 34.6 yrs old, and most common activity level represented was recreational athletics. There was a predominance of male subjects. In addition, 63% of studies performed cell counts or other forms of PRP characterization, and US guidance was implemented in 45% of these studies.[25–34]

A closer look at some of these case series reveal that pain relief can last up to 2 yrs after injections even in individuals who are at professional/semiprofessional levels of athletic competitions.[25] An investigation by Ferrero et al.[28] demonstrated that US-guided PRP injection can result in improved tendon echo texture and decreased hypervascularity. The investigation by Filardo et al.[30] showed both increased chronicity and bilateral nature of the presentation carried negative prognostication.

Platelet-Rich Plasma for Achilles Tendinopathy

There have been four published RCTs on AT. Three RCTs ($n = 98$ patients at follow-up duration of 6–12 mos) reported no benefit of a single PRP injection when compared with saline injections[35,36] or PT.[37] All three studies treated chronic midportion Achilles tendinosis without a tear. It should be noted that when comparing three negative RCTs to more than 200 indexed cases in case series, subjects in case series tended to be slightly younger (average age, 49 yrs for RCTs *vs.* 45 yrs for case series subjects) and 37% of the case series required 2–3 PRP injections for improvement. Age is known to affect activity of tendon-specific stem/progenitor cells and platelet function, which may explain the discrepancy.[38,39] Furthermore, Salini et al.[40] divided 44 subjects with recalcitrant noninsertional AT based on age (29 subjects with a mean age of 39.5 yrs and 15 subjects with a mean age of 61.5 yrs) and showed that US-guided PRP treatment was less effective in the elderly population. The most recent RCT by Boesen et al.[41] ($n = 60$; average age, 42 yrs) has been the only positive RCT investigation where four US-guided PRP injections at 2-wk intervals were found to be superior to control saline injection for midportion Achilles tendinosis at 6, 12, and 24 wks in terms of pain control and functional outcome.[41] In addition, the PRP groups demonstrated a significant reduction in tendon thickness and vascularity on US examination, most evident at 6 wks. The inconsistency of these results compared with earlier RCTs may be related to the higher PRP doses or injection numbers and due to younger age of included subjects (42 in this RCT *vs.* 49 in previous 3 RCTs for chronic midportion AT studies). The inclusion of an eccentric training regimen likely potentiated PRP benefits also.[42] See Figure 3 demonstrating a short axis view of a sonographically guided PRP injection for AT.

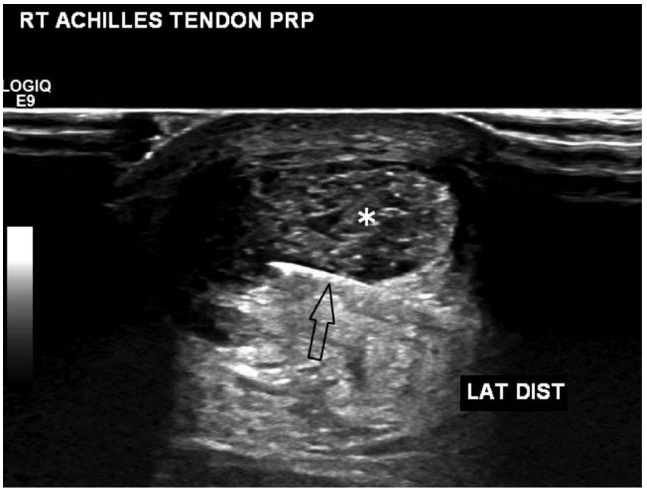

FIGURE 3. Sonographically guided PRP injection for Achilles tendinopathy with transducer in anatomic short axis view using an in-plane, lateral to medial, injection technique. Achilles tendon (asterisk), needle (open arrow).

Platelet-Rich Plasma for Common Extensor Tendinopathy

Common extensor tendinopathy is the most extensively studied tendinopathy with PRP. Most studies have used a single-injection protocol and compared it with autologous whole blood, local anesthetic, saline injection, laser therapy, or corticosteroid injection. Compared with corticosteroids, PRP has shown a longer lasting benefit in pain and function up to 2 yrs after injection.[43,44] There are two RCTs that did not show improved clinical outcome over corticosteroid. This may, however, be due to a shorter follow-up period (3–6 mos for negative studies *vs.* 6 to 24 mos for positive studies).[45,46] In four other RCTs, there was no statistically significant advantage of PRP compared with whole blood beyond the 8-wk follow-up.[47] Based on additional data, PNT seems to be complementary and should be considered as an adjunct when performing PRP injections.[48]

Platelet-Rich Plasma for Rotator Cuff Tendinopathy

In contrast to the other types of tendinopathies, rotator cuff tendinopathy research has been more geared toward surgical augmentation rather than injection monotherapy. In surgical context, there are a total of 16 RCTs combining for a total of 929 cases with no clear benefit of PRP in surgical augmentation during or after the procedure.[49–51]

For PRP monotherapy, the injection protocols have been variable among studies. Rha et al.[52] used 40–50 PNT using 25-gauge needle with two US-guided PRP injections compared with PNT alone for supraspinatus partial tear or tendinosis and discovered a greater decrease in pain and disability in the PNT + PRP group. Alternatively, Kesikburun et al.[53] injected PRP versus saline with US guidance into the subacromial space but not into the tendon and did not observe any intergroup differences.

Platelet-Rich Plasma for Gluteal Tendinopathy

There have not been any RCTs for the use of PRP in gluteal tendinopathy, but clinical case series advocate for safety and possible benefits. A case series of 21 subjects with refractory gluteus medius tendinosis or partial tear assessed US-guided intratendinous leukocyte-rich PRP injection with needle tenotomy and found that at a mean follow-up of 19.7 mos (range, 12.1–32.3 mos), there was a statistically significant improvement in all functional scores.[54] Conversely, Jacobson et al.[55] included 30 subjects (24 female) whom either received needle tenotomy alone or with US-guided leukocyte-rich PRP injection and found improvement in pain for both groups. The early advantage of tenotomy alone may be explained by the

early inflammatory effect of leukocytes in the PRP group because there was no differences between groups at 3-mo follow-up.

Platelet-Rich Plasma for Proximal Hamstring Tendinopathy

Davenport et al[56] performed a double-blind RCT comparing US-guided leukocyte-rich PRP to autologous whole blood injections with tenotomy for the 15 treatment cases of proximal hamstring tendinopathy. There were greater improvements in pain and function in the whole blood group at 12 wks, but the PRP group showed greater improvement at 6 mos. Case series have indexed a total of 28 subjects with hamstring tendinopathy treated with PRP with improvement in pain at 2- to 6-mo time frame.[57,58]

Current View of PRP Injection for Tendinopathy

Based on literature (Table 2), the strongest evidence for the beneficial effect of PRP remains as treatment for both common extensor tendinopathy and patellar tendinopathy, although there is limited evidence to show the benefit for Achilles, rotator cuff, gluteal, and proximal hamstring tendinopathies. Younger and active individuals seem to benefit from this procedure, although this needs to be further studied. In case of chronic rotator cuff tendinopathy, it seems that prolotherapy might be an appropriate consideration given current minimum evidence to recommend costly PRP over prolotherapy. Platelet-rich plasma as a surgical augmentation has shown marginal benefits. Likewise, PRP in gluteal and hamstring tendinopathies are common occurrences in clinics, without robust RCTs.

Improving PRP Clinical Studies

A strict subject and disease demographic selection combined with larger sample size, improved PRP characterization, and long-term follow-ups will be some of the key factors to better define PRP efficacy on tendinopathies. Although cell counts have become a popular method to objectify dose–response nature of this intervention, the quantification of GFs, chemokines, cytokines, and other micro particles might be necessary to elucidate dose–response relationship. Several animal studies have focused on leukocyte rich versus leukocyte poor PRP in tendinopathy, and this should be further studied in human models as well.[59] Although percutaneous needle tenotomy has been shown to be beneficial in treatment of tendinopathy, the combination with PRP should be further studied.[60] Finally, in recent years, tissue conditioning or "prehab" is seen as a way to optimize ultimate outcome in PRP treatments for tendons, and this can be another area of active research.[42]

Mesenchymal Stem Cells: Mechanism of Action

The use of stem cells in tendon injury treatment was inspired by discoveries that mesenchymal stem cells (MSCs) have the ability to differentiate into tenocytes in vitro. In vivo, however, such differentiation ability is inconsistent. Recent studies showed that stem cells are believed to benefit damaged tendons by exerting a paracrine effect from various secretomal molecules.[61] In previous animal experiments, MSCs were found to promote early tendon healing and lower reinjury risk.[62] Clinical investigations using stem cells have focused on joint diseases, and this treatment is relatively novel for tendinopathy. Systematic review of use of MSCs in arthritis research found that local irritation and transient fever were the most common adverse effects and the use of MSCs for musculoskeletal injuries seem to carry high safety.[63,64] Three sources of MSCs studied for tendon injuries are bone marrow via aspirate concentrate or cultured cells, adipose tissue via stromal vascular fracture or cultured cells, and skin.

Bone Marrow MSCs

One French study that explored the efficacy of BM-MSCs harvested from bone marrow aspirate as orthobiologic augmentation during rotator cuff repair found that 100% of the subjects who underwent MSCs treatment with repair ($n = 45$) had healed based on US and magnetic resonance imaging versus 67% in the control repair only group at 6-mo follow-up.[65] In addition, a lower re-tear rate (13% in MSCs group vs 66% in control group) and improved tendon integrity via MRI imaging in the MSCs group was seen at 10-yr follow-up.[65] The subjects that were found to have a re-tear in the MSCs group had received fewer cells as compared with those that maintained successful repair (mean ± SD cells, 14000 ± 9000 in re-tear vs 54000 ± 23000 in successful repair group) indicating that cell concentration may play a significant role. Because 14 ml of concentrate was injected in this study, they determined that there was a risk of absence of healing when the MSCs concentration was lower than 1500 per milliliter. The size of the tear at the time of surgery, age, and time between diagnosis and repair were not found to affect healing in the MSCs group but were predictive in the control group. Both groups underwent a rehabilitation program emphasizing early range of motion, which might have had a synergistic effect to the intervention.[65] Another study by Kim et al.[66] suggests that bone marrow aspirate concentrates combined with PRP enhances proliferation and migration of tendon derived stem cells, aids in rotator cuff tendon tear healing seen on US, and improves pain as evidenced by decreased VAS scores at 3-mo follow-up. Although the effects of PRP and bone marrow aspirate concentrates cannot be delineated, the study suggests that PRP plays a role in providing a scaffold for the bone marrow aspirate concentrates to allow for regeneration and prevention of abnormal differentiation of tendon derived stem cells. Limitations of the study included small sample size, lack of control group, and inability to perform tendon biopsy from a patient with rotator cuff tendinopathy.[66]

Adipose Stem Cells

A small pilot case series of 12 subjects with chronic refractory lateral epicondylosis investigated the effects of US-guided injection of various concentrations of ASC, discovering 79% improved pain scores, improved functional performance (Mayo Elbow Performance Index), and reduced structural tendon defects on US examination up to 1-yr posttreatment.[67] There were no significant differences in degree of pain reduction or performance but the higher concentration (10^7 vs 10^6 cells in 1 ml) group experienced more rapid pain improvement with earlier performance plateau. Mild local swelling in the first 48 hrs in 50% of patients was reported with spontaneous resolution in 2 wks and no long-term adverse effects for 1 yr.

There is one level 1 RCT by Usuelli et al.[68] who studied the effects of PRP versus SVF for the treatment of midportion

TABLE 2. Summary of clinical trials discussed for PRP in tendinopathy treatment

Reference	Level of Evidence	Pathology	No. Patients	Average Age	Therapeutic Protocol	US Guidance	Platelet Count and Leukocytes	Outcome Measure	Follow-up	Main Findings
Kaux et al.[21]	Level I RCT	Patellar tendinopathy	20 subjects: $n = 10$ one PRP $n = 10$ two PRP	NA	1 *vs.* 2 PRP injections at 1-wk interval[a]	Yes	Platelet count: 8.5–9 × 10^3 per mm^3 Leukocytes: no	VAS, IKDC, VISA-P, isokinetic strength	12 mos	No benefit of 2 injections over 1 in pain relief, function, or strength.
Zayni et al.[22]	Level I RCT	Patellar tendinopathy	40 subjects: $n = 20$ one PRP $n = 20$ two PRP	24.6 (1 injection) *vs.* 24.1 (2 injections) yrs	1 *vs.* 2 PRP injections at 2-wk intervals[b]	Yes	Platelet count: 2× basal value Leukocytes: no	VISA-P, VAS, Tegner	2 yrs (minimum)	Significantly better outcome in terms of pain relief and function with 2 injections *vs.* 1 injection.
Vetrano et al.[23]	Level I RCT	Patellar tendinopathy	46 subjects: $n = 23$ PRP $n = 23$ ESWT	26.85 yrs	2 injections of PRP at 1-wk interval[a] 3 focused extracorporeal shock wave therapies	Yes	Platelet count: 0.89–1.1 × 10^6 per mm^3 Leukocytes: NA	VAS, VISA-P, modified Blazina scale	12 mos	PRP was superior to ESWT in functional recovery and pain reduction at 6 and 12 mos.
Dragoo et al.[24]	Level I RCT	Patellar tendinopathy	23 subjects: $n = 10$ PRP $n = 12$ guided dry needling	35 ± 13 yrs	1 PRP injection + PNT[b] 1 PNT[b]	Yes	Platelet count: NA Leukocytes: yes	VISA-P, Lysholm	6 mos	PRP resulted in faster recovery at 12 wks but no difference at 26 wks.
Charousset et al.[25]	Level IV case series	Patellar tendinopathy	28 subjects	27 yrs	3 PRP injections[a]	Yes	Platelet count: 2× basal value Leukocytes: no	VISA-P, VAS, Lysholm	24 mos	Improved pain, function, and tendon healing on MRI with 75% return to sport at prelevel injury within 3 mos.
Ferrero et al.[28]	Level IV case series	Patellar tendinopathy	28 subjects	37.4 yrs	3 PRP injections at a mean of 3-wk intervals[b]	Yes	Platelet count: NA Leukocytes: NA	VISA-P, US examination	6 mos	Statistically improved pain and US tendon appearance at 6 mos but not at 20 days.
Filardo et al.[30]	Level IV case series	Patellar tendinopathy	43 subjects	30.6 yrs	3 PRP injections at 2-wk intervals	No	Platelet count: NA Leukocytes: NA	Blanzina, VISA-P, EQ-VAS, Tegner	Mean ± SD, 48.6 ± 8.1 mos	Improved function up to 4-yr follow-up. Bilateral pathology or longer chronicity resulted in poorer outcome.
de Vos et al.[35]	Level I RCT	Achilles tendinopathy (midportion)	54 subjects: $n = 27$ PRP $n = 27$ saline	49.5 yrs	1 PRP injection[b] 1 saline injection[b]	Yes	Platelet count: NA Leukocytes: NA	VISA-A, patient satisfaction, return to sport	12 mos	No significant difference between groups in pain or activity level.
Krogh et al.[36]	Level I RCT	Achilles tendinopathy (midportion)	24 subjects: $n = 12$ PRP $n = 12$ saline	49.2 ± 9.4 yrs	1 PRP injection[b] 1 saline injection[b]	Yes	Platelet count: 8× basal value Leukocytes: NA	VISA-A, pain at rest, pain at activity, tendon thickness on US, color Doppler activity	12 mos	No significant differences in pain or function at 3 mos but PRP did show an increased tendon thickness on US. Dropout rate high after 3 mos.
Kearney et al.[37]	Level I RCT	Achilles tendinopathy (midportion)	20 subjects: $n = 10$ PRP $n = 10$ eccentric exercises	49 yrs	1 injection of PRP Eccentric training program 2×/d, 7 d/wk × 12 wks	No	Platelet count: NA Leukocytes: NA	VISA-A	6 mos	No significant intergroup differences.
Salini et al.[40]	Level IV case series	Achilles tendinopathy	44 subjects: $n = 29$ young $n = 15$ elderly	Young group: 39.5 ± 6.9 yrs Elderly group: 61.5 ± 5.3 yrs	3 PRP injections at 1-wk intervals[b]	Yes	Platelet count: 1.6× basal value Leukocytes: NA	VISA-A	12 mos	PRP less effective in elderly population.

(Continued on next page)

TABLE 2. *(Continued)*

Reference	Level of Evidence	Pathology	No. Patients	Average Age	Therapeutic Protocol	US Guidance	Platelet Count and Leukocytes	Outcome Measure	Follow-up	Main Findings
Boesen et al.[41]	Level I RCT	Achilles tendinopathy	60 subjects: *n* = 20 PRP *n* = 20 HVI *n* = 20 saline injection	43.1 (PRP) *vs.* 41.9 (HVI) *vs.* 40.9 (control) yrs	4 PRP injections at 2-wk intervals[c] HVI (steroid, saline, or local anesthetic)[c] Control: few drops of saline under skin	Yes	Platelet count: NA Leukocytes: NA	VISA-A, VAS, intratendinous vascularity and tendon thickness on US, heel-rise test	6 mos	PRP superior to control in terms of pain control and patient outcome. PRP with reduction in tendon thickness and vascularity on US, most evident at 6 wks.
Peerbooms et al.,[43] Gosens et al.[44]	Level I RCT	Lateral epicondylosis	100 subjects: *n* = 51 PRP *n* = 49 corticosteroid	47.3 (PRP) *vs.* 46.9 (steroid) yrs	1 injection of PRP Control: 1 injection of saline	No	Platelet count: NA Leukocytes: NA	VAS, DASH	2 yrs	Significantly better pain relief and functional improvement in PRP group.
Krogh et al.[45]	Level I RCT	Lateral epicondylosis	60 subjects: *n* = 20 PRP *n* = 20 glucocorticoid *n* = 20 saline control	45.4 ± 8.0 yrs	1 PRP injection[b] 1 corticosteroid injection[b] 1 saline injection[b]	Yes	Platelet count: NA Leukocytes: NA	PRTEE, Doppler signal and tendon thickness on US	3 mos	No difference in pain reduction or function at 3 mos but glucocorticoid showed a significant reduction in pain at 1 mo and decreased color Doppler and tendon thickness on US.
Palacio et al.[46]	Level I RCT	Lateral epicondylosis	60 subjects: *n* = 20 neocaine *n* = 20 dexamethasone *n* = 20 PRP	47.9 (neocaine) *vs.* 46.2 (dexamethasone) *vs.* 46.6 (PRP) yrs	1 injection of each treatment	No	Platelet count: NA Leukocytes: NA	DASH, PRTEE	6 mos	PRP did not provide improved results over saline or steroid.
Raeissadat et al.[47]	Level I RCT	Lateral epicondylosis	64 subjects: *n* = 33 PRP *n* = 31 AWB	45.3 ± 5.9 yrs	1 injection of each treatment	No	Platelet count: 1,227,000 ± 250,000 per mm^3 in PRP group (4.8× basal value) Leukocytes: 6740 ± 1396 per mm^3 in PRP group	VAS, PPT, modified Mayo clinic performance index for the elbow	12 mos	PRP and AWB were effective at reducing pain and improving function but there were no significant differences.
Mishra et al.[48]	Level II RCT	Lateral epicondylosis	225 subjects: *n* = 112 PRP *n* = 113 bupivicaine	48.4 (PRP) *vs.* 47.4 (control) yrs	1 PRP injection +NT 1 bupivacaine injection + NT	No	Platelet count: 5× basal value Leukocytes: yes	VAS, PRTEE	24 wks	PRP with statistically significant improvement in pain over control group at 24 wks but not 12 wks. NT seems to be complementary to PRP.
Rha et al.[52]	Level I RCT	Supraspinatus tendinosis or partial tear	39 subjects: *n* = 20 PRP *n* = 19 NT	52.2 (PRP) *vs.* 53.9 (dry needling) yrs	2 PRP injection with PNT at 4 wk intervals[a] 2 PNT at 4-wk intervals[b]	Yes	Platelet count: NA Leukocytes: NA	SPADI, shoulder ROM, physician global rating scale	6 mos	PRP resulted in greater decrease in pain and disability than dry needling alone.
Kesikburun et al.[53]	Level I RCT	Rotator cuff tendinopathy	40 subjects: *n* = 20 PRP *n* = 20 saline control	45.5 (PRP) *vs.* 51.4 (control) yrs	1 PRP injection into subacromial space[c] 1 saline injection into subacromial space[c]	Yes	Platelet count: NA Leukocytes: NA	WORC, SPADI, VAS	12 mos	No intergroup differences regarding QOL, pain, disability, or shoulder ROM.
Lee et al.[54]	Level IV case series	Gluteal tendinopathy or partial tear	19 subjects	48 yrs	1 PRP injection with PNT[b]	Yes	Platelet count: NA Leukocytes: yes	mHHS, HOS-ADL, HOS-Sport, iHOT-33	Mean, 19.7 mos	Statistically significant improvement in function
Jacobson et al.[55]	Level II prospective study	Gluteal tendinopathy or partial tear	30 subjects: *n* = 15 PRP *n* = 15 PNT	53 (PRP) *vs.* 60 (NT) yrs	1 PRP injection with PNT (10 passes)[b] 1 PNT (20–30 passes)[b]	Yes	Platelet count: 4–6× basal value Leukocytes: yes	VAS at rest and with activity	Mean, 3 mos	Faster improvement in pain scores (2 wks) in PNT group but no difference at 3 mos.

Davenport et al.[56]	Level I RCT	Proximal hamstring tendinopathy	15 subjects (17 hamstrings): n = 11 hamstrings PRP n = 6 hamstrings AWB	46.6 (PRP) *vs.* 45.4 (whole blood) yrs	1 PRP injection with PNT[b] 1 AWB injection with PNT[b]	Yes	Platelet count: NA Leukocytes: yes	mHHS, HOS-ADL, HOS-Sport, iHOT-33, US tendon appearance	6 mos	Greater improvement in pain and function in AWB group at 12 wks but better in PRP at 6 mos. No significant difference in US appearance
Fader et al.[57]	Level IV case series	Proximal hamstring tendinopathy	18 subjects	42.6 yrs	1 PRP injection[b]	Yes	Platelet count: NA Leukocytes: no	VAS	6 mos	Overall 63% improvement in pain
Wetzel et al.[58]	Level III retrospective study	Proximal hamstring tendinopathy	15 subjects (17 hamstrings): n = 12 hamstrings PRP n = 5 control	37.1 (PRP) *vs.* 42.8 (control) yrs	1 PRP injection Traditional conservative therapy	No	Platelet count: NA Leukocytes: NA	VAS, NPRS	Mean, 4.5 mos (PRP) Mean, 2 mos (control)	Significant reduction in VAS in PRP group and all patients returned to previous level of activity.

[a]Intratendinous and peritendinous.
[b]Intratendinous.
[c]Peritendinous.
ASES, American Shoulder and Elbow Surgeons Score; AWB, autologous whole blood; EQ-VAS, Self-Rated Health Score; HOS-ADL, Hip Outcome Score–Activities of Daily Living subscale; HOS-Sport, Hip Outcome Score-Sport-Specific subscale; HVI, high volume injection; iHOT-33, International Hip Outcome Tool-33; IKDC, International Knee Documentation Committee; mHHS, modified Harris Hip Score; NA, not applicable; NPRS, Nirschl Phase Rating Scale; OSS, Oxford Shoulder Score; PPT, pain pressure threshold; PRTEE, Patient-Rated Tennis Elbow Evaluation; SPADI, Shoulder Pain and Disability Index; WORC, Western Ontario Rotator Cuff Index.

AT. Stromal vascular fraction can be derived from native adipose tissue or lipoaspirate and contains mature, progenitor, and stem cells. Usuelli et al.[68] randomized 23 subjects to the PRP group and 21 subjects to the SVF group to undergo a unilateral or bilateral sonographically guided Achilles tendon injection for a total of 28 tendons in each group. The SVF group demonstrated faster improvement with a significantly better outcome with regard to VAS, Victorian Institute of Sport Assessment-Achilles (VISA-A), and American Orthopedic Foot and Ankle Society Ankle-Hindfoot scores when compared with the PRP group at 15- and 30-day follow-up although both groups showed improvement. There was no statistically significant difference between the groups at follow-up beyond 30 days, although the SVF group continued to score slightly better than the PRP group on all outcome measures. Magnetic resonance imaging evaluation of the tendon lesion area did not demonstrate statistically significant improvement at 180-day follow-up, thus not correlating with pain and functional outcome measures.[68] The faster improvement in the SVF group suggests that SVF has a higher anti-inflammatory and immunomodulatory effect than PRP. The use of adipose SVF provides an advantage over purified ASCs given the native microcellular environment that may act as a scaffold for regeneration and the simplified and less costly preparatory steps.

Skin-Derived Tenocyte-Like Cells

Skin-derived tenocyte-like cells (SD-TLCs) are dermal fibroblasts that may be culturally expanded for use in regenerative therapies. There have been two RCTs for the use of SD-TLCs in tendinopathy. Clarke et al.[69] (n = 60) compared US-guided injection of SD-TLCs (17 million cells) plus PRP to PRP only for treatment of patellar tendinopathy. There was a statistically significant improvement in VISA-P scores at 6 mos for the SD-TLCs plus PRP group compared with PRP alone. Connell et al.[70] injected SD-TLCs (10 million cells) under US guidance in 12 subjects with lateral epicondylosis and demonstrated improved tendon structure on US as evidenced by decreased thickness, hypoechogenicity, vascularity, and number of tears. Functional scores (Patient Rated Tennis Elbow Evaluation) also improved at 6-wk, 3-mo, and 6-mo follow-ups. These results suggest that SD-TLCs are a relatively safe treatment option for tendinopathy although further high-level research with longer-term follow-up is needed.

Current View of Stem Cell Therapies for Tendon Injuries

The efficacy of cell therapies has been difficult to establish because of the requirement of elaborate injection preparation steps. Many preclinical questions still remain such as mechanism of action, optimum cell processing protocols (centrifugation, enzymatic digestion, and cultural expansion), or best injection/transplantation protocols (dose, procedure interval, addition of other agents such as PRP, and timing of procedure in relation to surgical intervention when applicable). To date, bone marrow aspirate concentrate as a surgical augmentation for rotator cuff tear repair and adipose SVF for AT seem to be the only indications where cell therapy should be considered although other cell therapies also seem to be safe.

Improving Clinical Stem Cell Studies

Future clinical studies can be considered to elucidate relative efficacy of cell therapies in a RCT fashion. However, clear mechanism of action and optimization of each cell therapy are still being investigated in the preclinical realm. Consorted effort between scientists and clinicians from various disciplines will be helpful in designing future trials although the high cost for cell processing may be a barrier.

Percutaneous Ultrasonic Tenotomy: Brief Discussion

Although typically not considered as a regenerative procedure, PUT is worthy of mentioning. Percutaneous ultrasonic tenotomy is performed under local anesthesia in clinics with a small incision. The probe emits ultrasonic energy that debrides tendinopathic tissue, which is then emulsified and collected for removal using saline irrigation system. Removal of tendinopathic tissue then results in subsequent regeneration of healthy tendon tissue as so believed in traditional surgical tendon debridement procedures. Clinical evidences are currently limited to case series although they are showing early successes in treating recalcitrant common extensor/flexor tendons, patellar tendons, and Achilles tendons. In a study by Seng et al.[71] for treatment of chronic lateral elbow tendinopathy, for example, 20 subjects who underwent PUT reported reduced pain (mean VAS score decreased from 5.4 to 0.4) and improved function (DASH-Compulsory score from 27.8 to 0.4) that continued to 3-yr follow-up and 100% of patients had decreased tendon thickness and reduction in hypoechoic lesion size on US. As US allows direct visualization of pathologic tendon regions, PUT in theory improves accuracy of debridement while keeping the procedure minimally invasive compared to conventional tendon debridement.

CONCLUSIONS

Tendinopathy is a prevalent condition leading to impaired sports performance in athletes and disability in the working population. Traditional measures such as PT, corticosteroid injections, or even surgical debridement are sometimes unsuccessful in relieving pain and improving function. The emerging evidences for prolotherapy, PRP, cellular injections, and, more recently, PUT have added options that seem to be safe and potentially effective, which patients can consider before contemplating a surgical option. Large variability in procedural protocol should be standardized. However, for such standardization to happen, preclinical studies need to be continued to better characterize various types of tendinopathies. Prehabilitation and postprocedural rehabilitation protocol should also be an emphasis for tendinopathy-related researches. A shift from the "point-of-care," procedure-focused treatment paradigm, to the "spectrum-of-care," prehabilitation/postprocedure rehabilitation approach may aid in optimizing the outcome of tendinopathy treatment.

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