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Type of Submission – Check all that apply:
- [ ] New Policy
- [x] Revised Policy*
- [ ] Annual Review – No Revisions

*All revisions to the policy must be highlighted using track changes throughout the document.
Please provide any clarifying information for the policy below:

CPB 0784 Blood Product Injections for Selected Indications

This CPB has been revised to state that the following are considered experimental and investigational: (i) autologous blood injection for the treatment of lateral epicondylitis and plantar fasciopathy, (ii) platelet-rich plasma injection as adjunctive material to bone graft; platelet-rich plasma injection for anterior cruciate ligament surgery, chronic wounds, osteoarthritis, and rotator cuff injuries. This CPB is revised to state that platelet-rich plasma combined with stem cells (e.g., Regenexx) is considered experimental and investigational for all indications because its effectiveness and safety have not been established.

Name of Authorized Individual (Please type or print):
Chandra A. Kee, MD

Signature of Authorized Individual:

Revised February 2015
Blood Product Injections for Selected Indications

Number: 0784

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers autologous blood injection experimental and investigational for all indications including the following (not an all-inclusive list) because its effectiveness has not been established.

- Cervical radiculopathy
- Chronic urticarial
- Lateral epicondylitis
- Plantar fasciopathy
- Temporomandibular joint (TMJ) dislocation
- Tendonopathies (e.g., elbow, heel, knee, patella, and shoulder)

Policy History

Last Review 09/08/2016
Effective: 05/08/2009
Next Review: 09/07/2017

Definitions

Additional Information

Clinical Policy Bulletin Notes
Aetna considers platelet-rich plasma injection experimental and investigational for all indications including the following (not an all-inclusive list) because its effectiveness has not been established.

- Achilles tendon ruptures
- Alopecia areata (androgenetic alopecia)
- Ankle sprain
- Anterior cruciate ligament surgery
- As adjunctive material to bone graft
- Avascular necrosis of the hip
- Cerebral palsy
- Chronic wounds
- Crohn's disease-related perianal fistula
- Gastrocnemius (calf) tear
- Hamstring injury
- Hip fractures
- Osteoarthritis (e.g., hip, knee, and temporomandibular joint (TMJ))
- Osteonecrosis of the jaw
- Plantar fasciitis
- Rotator cuff injuries
- Tendonopathies (e.g., elbow, heel, knee, and shoulder)

Aetna considers autologous platelet gel application following total knee arthroplasty experimental and investigational because its effectiveness has not been established.

Aetna considers platelet-rich plasma combined with stem cells (e.g., Regenexx) experimental and investigational for all indications because its effectiveness has not been established. (See Aetna CPB 0411 - Bone and Tendon Graft Substitutes and Adjuncts.)

Aetna considers bone marrow plasma injection experimental and investigational for the treatment of tendonopathies (e.g.,
elbow, heel, knee, and shoulder) and all other indications because its effectiveness has not been established.

Aetna considers bone marrow derived mesenchymal stromal cells administration experimental and investigational for the treatment of Crohn's disease and osteoarthritis because its effectiveness has not been established.

Aetna considers adipose-tissue-derived stem cells injection treatment for chondromalacia patellae experimental and investigational because its effectiveness has not been established.

See also CPB 0207 - Prolotherapy (../200_299/0207.html), CPB 0235 - Plantar Fasciitis Treatments (../200_299/0235.html), and CPB 0649 - Extracorporal Shock-Wave Therapy for Musculoskeletal Indications and Soft Tissue Injuries (../600_699/0649.html).

Background

Autologous Blood Injection:

Tendonopathy (tendinopathy), also known as tendonitis and tendonosis, refers to painful conditions occurring in and around tendons in response to overuse. Commonly involved tendons are those in the elbow (lateral epicondyle), heel (Achilles), knee (patella), and shoulder (rotator cuff). Conservative therapies for patients with tendonopathies include rest, eccentric exercise, physiotherapy, analgesic therapy (e.g. non-steroidal anti-inflammatory drugs), use of orthotic devices, as well as local injection of steroids. Autologous blood injection has been employed when conservative therapies have failed. Blood taken from the patient by standard venesection is injected into the area around the damaged tendon. This approach is thought to promote healing by triggering stem cell recruitment, angiogenesis and fibroblast stimulation. A local anesthetic is usually used and ultrasound may provide guidance. Before injection, dry needling may be carried out. After the procedure, patients are instructed to avoid strenuous or excessive use of
Suresh and colleagues (2006) assessed if ultrasound guided autologous blood injection is an effective treatment for refractory medial epicondylitis. A total of 20 patients (13 men and 7 women) with symptom duration of 12 months underwent sonographic evaluation. Tendonosis was confirmed according to 3 sonographic criteria: (i) echo texture, (ii) interstitial tears and (iii) neovascularity. The tendon was then dry needled and autologous blood was injected. Patients were reviewed at 4 weeks and at 10 months. Visual analog scores (VAS) and modified Nirschl scores were assessed pre-procedure and post-procedure. There was significant reduction in VAS between pre-procedure and 10 months post-procedure when it had a median inter-quartile range (IQR) of 1.00 (1 to 1.75), range of 0 to 7. The median IQR Nirschl score, which at pre-procedure was 6.00 (5 to 7), range of 4 to 7, had decreased at 4 weeks to 4.00 (2.25 to 5), range of 2 to 7, and at 10 months to 1.00 (1 to 1.75), range of 0 to 7, revealing a significant decrease ($z = 3.763$, $p < 0.001$). The hypo-echoic change in the flexor tendon significantly decreased between pre-procedure, when there was a mean (SD) of 6.45 (1.47), and at 10 months, when it was 3.85 (2.37) ($p < 0.001$). Doppler ultrasound showed that neovascularity decreased between pre-procedure, when there was a mean (SD) of 6.10 (1.62), range of 4 to 9, and at 10 months, when it was 3.60 (2.56), range of 0 to 9 ($p < 0.001$). The authors concluded that the combined action of dry needling and autologous blood injection under ultrasound guidance appears to be an effective treatment for refractory medial epicondylitis as demonstrated by a significant decrease in VAS and a fall in the modified Nirschl scores.

Connell et al (2006) evaluated the effectiveness of autologous blood injection under sonographic guidance for the treatment of refractory lateral epicondylitis. A total of 35 patients (23 men and 12 women, mean age of 40.9 years, mean symptom duration of 13.8 months) underwent sonographic evaluation prior to dry needling the tendon and injection with autologous blood. Patients were reviewed, and measures of Nirschl and
VAS were taken pre-procedure and post-procedure, at 4 weeks and 6 months. Following autologous blood injections, significant reductions were reported for Nirschl scores, which decreased from a median IQR pre-procedure score of 6 (6 to 7), to 4 (2 to 5) at 4 weeks ($p < 0.001$), and to 0 (0 to 1) at 6 months ($p < 0.001$). Similarly, significant reductions were reported for VAS scores from a median IQR pre-procedure score of 9 (8 to 10), to 6 (3 to 8) at 4 weeks ($p < 0.001$), and to 0 (0 to 1) at 6 months ($p < 0.001$). Sonography demonstrated a reduction in the total number of interstitial cleft formations and anechoic foci; a significant reduction in tendon thickness from a mean (SD) of 5.15 mm (0.79) at baseline to 4.82 mm (0.62) at 6 months post-procedure ($p < 0.001$) was observed. Hypoechoic change significantly reduced from a median IQR of 7 (6 to 7) at baseline to 2 (1 to 3) at 6 months post-procedure ($p < 0.001$). Neovascularity also significantly decreased from a median (IQR) of 6 (4 to 7) at baseline to 1 (0 to 3) at 6 months post-procedure ($p < 0.001$), although sonographic abnormality remained in many asymptomatic patients. The authors concluded that autologous blood injection is a primary technique for the treatment of lateral epicondylitis. Sonography can be used to guide injections and monitor changes to the common extensor origin.

In a prospective, cohort study, James et al (2007) evaluated the effectiveness of ultrasound-guided dry needling and autologous blood injection for the treatment of refractory patellar tendonosis. A total of 47 knees in 44 patients (40 men and 7 women, mean age of 34.5 years, age range of 17 to 54 years) underwent sonographic examination of the patellar tendon following referral with a clinical diagnosis of patellar tendonosis (mean symptom duration of 12.9 months). Ultrasound guided dry needling and injection of autologous blood into the site of patellar tendonosis was performed on two occasions 4 weeks apart. Pre-procedure and post-procedure Victorian Institute of Sport Assessment (VISA) scores were collected to assess patient response to treatment. Follow-up ultrasound examination was done in 21 patients (22 knees). Therapeutic intervention led to a significant improvement in VISA score: mean pre-procedure
score of 39.8 (range of 8 to 72) versus mean post-procedure score of 74.3 (range of 29 to 100), \( p < 0.001 \); mean follow-up of 14.8 months (range of 6 to 22 months). Patients were able to return to their sporting interests. Follow-up sonographic assessment showed a reduction in overall tendon thickness and in the size of the area of tendonosis. A reduction was identified in interstitial tears within the tendon substance. Neovascularity did not reduce significantly or even increased. The authors concluded that dry needling and autologous blood injection under ultrasound guidance shows promise as a treatment for patients with patellar tendonosis.

In a single-blind, randomized, clinical study, Kazemi and colleagues (2010) compared local corticosteroid with autologous blood injections for the short-term treatment of lateral elbow tendinopathy. A total of 60 patients aged 27 to 64 years with a new episode of tennis elbow were recruited -- 30 patients were randomized to methylprednisolone and 30 to autologous blood group over 1 year. Severity of pain within last 24 hours; limb function; pain and strength in maximum grip; disabilities of the arm, shoulder, and hand quick questionnaire (Quick DASH) scores; modified Nirschl scores; and pressure pain threshold were evaluated before injection and at 4 and 8 weeks after injection. Data were analyzed with the chi and t test. Within-group analyses showed better results for autologous blood (all \( p \) values < 0.001 except for grip strength, \( p = 0.005 \)). In the corticosteroid group, differences in severity of pain (\( p = 0.008 \)) and grip strength (\( p = 0.001 \)) were significant. At 4 weeks, between-group analyses showed superiority of autologous blood for severity of pain (\( p = 0.001 \)), pain in grip (\( p = 0.002 \)), pressure pain threshold (\( p = 0.031 \)), and Quick DASH questionnaire score (\( p = 0.004 \)). There were no significant differences in modified Nirschl score, grip strength, and limb function. At 8 weeks, autologous blood was more effective in all the outcomes (all \( p \) values < 0.001). The authors concluded that autologous blood was more effective in short-term than the corticosteroid injection. The findings of this small, single-blind study need to be validated by further investigation with larger number of subjects and longer follow-up.
The available evidence regarding the effectiveness of autologous blood injection for the treatment of tendonopathies is largely based on non-randomized studies. Their findings need to be validated by well-designed studies. Furthermore, available guidelines from the American College of Occupational and Environmental Medicine, National Institute for Health and Clinical Excellence (NICE), and Work Loss Data Institute do not support the use of autologous blood injection for tendonopathies.

The American College of Occupational and Environmental Medicine (2007) did not recommend autologous blood injection for managing patients with elbow disorders. The NICE's guideline on autologous blood injection for tendinopathy (2009) states that current evidence on the safety and effectiveness of autologous blood injection for tendinopathy is inadequate in quantity and quality. In addition, the NICE Committee notes that some of the published studies involved the use of dry needling prior to the injection of autologous blood, but it was not possible to differentiate between effects of these two components of the procedure. The Committee also states that future research should be in the context of randomized controlled studies that define chronicity of tendinopathy and describe any previous or adjunctive therapies (e.g., physiotherapy and dry needling) as well as the tendons treated. These studies should address the role of ultrasound guidance and include functional and quality of life outcomes with a minimum follow-up of 1 year. It is also interesting to note that the Work Loss Data Institute's guideline on the management of acute and chronic shoulder disorders (2007) did not mention the use of autologous blood injection as a means of therapy.

The Work Loss Data Institute's guideline on elbow (acute and chronic) (2011) stated that autologous blood injection is currently under study and is not specifically recommended.

**Autologous Blood Injection for the Treatment of Cervical Radiculopathy:**
In a pilot study, Goni et al (2015) examined the effectiveness of epidural perineural injection of autologous conditioned serum (ACS) versus methylprednisone (MPS) in unilateral cervical radiculopathy patients. A total of 40 patients were equally allocated into ACS and MPS groups and were injected with 2.5 to 3 ml of ACS or MPS, respectively, under image guidance into the perineural area of the affected nerve root. They were followed-up for 6 months with VAS for pain, neck pain disability scale in Hindi language, neck disability index, and Short Form of Health Survey-12 (SF-12). Patients who had received injections of ACS and MPS both had improvements in the scores of the evaluation tools. The improvement in the ACS patients was gradual and sustained during the entire study period whereas that in the MPS group had some deterioration over time. No major complications were noted among the 2 groups; minor complications were noted in both the groups. The authors concluded that ACS can be considered an equally good or better modality of non-operative management in patients of unilateral cervical radiculopathy as MPS. They stated that this approach may be offered to affected patients before offering them surgery. The findings of this pilot study need to be validated by well-designed studies.

Autologous Blood Injection for the Treatment of Chronic Urticaria:

In a double-blind, parallel group RCT, Debbarman and colleagues (2014) evaluated the effectiveness of autologous serum therapy (AST) in chronic urticaria (CU) and also determined its usefulness in autoreactive urticaria (AU). A total of 54 patients were given AST and 57 patients were given injection normal saline (placebo), along with cetirizine in an on-demand basis in both groups. Autologous serum therapy/placebo was given weekly for 9 weeks and followed-up for a total period of 24 weeks. Autoreactive urticaria was diagnosed by autologous serum skin test. Urticaria total severity score (TSS), urticaria activity score (UAS), dermatologic life quality index (DLQI) was used as primary effectiveness variables. Safety parameters assessed were the spontaneously
reported adverse events and laboratory parameters. Urticaria total severity score showed significant improvement from baseline, 7(th) week and 8(th) week onwards in AST group and placebo group, respectively. Group comparison showed significant improvement 4(th) week onwards. Urticaria activity score showed similar results; DLQI showed significant improvement in AST group compared to placebo at the end of study. Both AU and non-AU patients showed comparable improvement of TSS. The authors concluded that AST shows promise in treatment of urticaria regardless of the autoreactive nature. These preliminary findings need to be validated by well-designed studies.

**Autologous Blood Injection for the Treatment of Patella Tendinopathy:**

In a pilot study, Resteghini and associates (2015) evaluated the effectiveness of autologous blood injections against saline in patients with chronic recalcitrant patella tendinopathy. Using 2 practitioners, patients were randomized to either receive autologous blood injections or saline injections. All patients completed the Short-Form McGill Pain Questionnaire (MPQ), VAS, and a Victoria Institute of Sport Assessment for Patella Tendinopathy scale over a 12-month period. A total of 22 patients completed the final review at 12 months and were included in the study. Subjects ranged in age from 22 and 61 years and were randomized to 11 in each autologous blood injection and saline groups. Autologous blood injection group had a mean duration of symptoms of 16.7 months, whereas that of the saline group was 19.2 months. The saline group mean VAS score was reduced from 7.9 to 4.5 at 1 month (p = 0.003) and 3.3 (p = 0.005) at 1 year. With autologous blood injections, the score was reduced from 7.5 to 4.5 (p = 0.005) at 1 month and 3.1 (p = 0.003) at 1 year. Victoria Institute of Sport Assessment for Patella Tendinopathy, MPQ, and VAS scores improved significantly in both groups. The authors concluded that the findings of this study demonstrated that both the autologous blood injection and saline groups experienced a significant improvement in symptoms. However, when the
results were compared, there was no statistical difference between the 2 groups.

**Autologous Blood Injection for the Treatment of Temporomandibular Joint Dislocation:**

Varedi and Bohluli (2015) reviewed the English literature about the safety and effectiveness of autologous blood injection in the treatment of patients suffering from chronic recurrent temporo-mandibular joint (TMJ) dislocation. These investigators highlighted the key trials and recent directions about this modality and discussed about the mechanism, advantages, and disadvantages of this approach. A literature search was performed using PubMed, Medline, and Ovid Medline databases to identify articles reporting on the injection of autologous blood for treatment of chronic recurrent dislocation of TMJ. Other references cited in the retrieved reports, as well as the "related articles" tool in PubMed Medline, were also checked to improve the search and, if relevant, were included in the study. The search was restricted to articles published in the English language. A total of 7 studies meeting the inclusion criteria were reviewed. The selected articles included 4 prospective clinical trials and 3 case report articles. The authors concluded that there are a few articles about the clinical use of autologous blood for treating patients with chronic recurrent TMJ dislocation. Reviewing of the literature showed that there are successful results about this modality, but there are still some concerns about it in terms of the effect of the injected blood on the articular cartilage and formation of fibrous or bony ankylosis. Well-designed studies are needed to ascertain the effectiveness of autologous blood injection in the treatment of TMJ dislocation.

**Autologous Blood Products in the Treatment of Lateral Epicondylitis and Plantar Fasciopathy:**

In a systematic review and meta-analysis, Tsikopoulos and associates (2016) compared the effectiveness of autologous whole blood with that of corticosteroid injections (CSIs) on
epicondylopathy and plantar fasciopathy. The databases of PubMed, Web of Science, CENTRAL, and Scopus were searched up to May 6, 2015. Randomized trials comparing the effects of autologous whole blood and CSIs on epicondylopathy or plantar fasciopathy were included. Trials exploring the effectiveness of PRP were excluded. The primary outcome was pain relief. The secondary outcome included the assessment of composite outcomes. All outcomes were assessed at 2 to 6 (short-term) weeks, 8 to 13 (intermediate-term) weeks and 24 to 26 (medium-term) weeks. Quality assessment was performed with the Cochrane risk of bias tool. A total of 9 trials were included. For pain relief, there was a statistically significant difference in favor of corticosteroids in the short-term (standardized mean difference [SMD] 0.52; 95 % CI: 0.18 to 0.86; I² = 53 %; p < 0.01). A statistically significant difference in favor of autologous whole blood was indicated in the medium-term assessment of pain relief on epicondylopathy. The authors concluded that corticosteroids were marginally superior to autologous whole blood in relieving pain on plantar fasciopathy at 2 to 6 weeks. They stated that autologous whole blood provided significant clinical relief on epicondylopathy at 8 to 24 weeks. Moreover, they stated that conclusions were limited by the risk of bias.

In a meta-analysis, Qian and colleagues (2016) compared the safety and effectiveness of autologous blood products (ABPs) and CSIs in the treatment of lateral epicondylitis. These investigators systematically searched Embase, PubMed, the Cochrane Library, and Web of Science to identify RCTs that compared ABPs with CSIs for the treatment of lateral epicondylitis without language and publication date restriction through April 2015. Two investigators independently included and assessed the quality of each eligible study according to the method recommended by the Cochrane Collaboration. Available data about the main outcomes were extracted from each study and heterogeneity was assessed using the Q statistic and the inconsistency index (I²). They also evaluated the publication bias and conducted a subgroup analysis. Review Manager 5.2 software was used for data syntheses and
analyses, and the standardized mean difference (SMD) or mean difference (MD) was estimated by using random effects models with a 95 % CI. To investigate the effectiveness among different trial durations, the follow-up times were divided into short periods (2 to 4 weeks), intermediate periods (6 to 24 weeks) and long-term periods (greater than or equal to 24 weeks). A total of 10 RCTs (n = 509) were included in this meta-analysis. The pooled analysis showed that CSIs were more effective than ABPs for pain relief in the short-term (SMD = 0.88; 95 % CI: 0.31 to 1.46 %; p = 0.003). However, in the intermediate-term, ABPs exhibited a better therapeutic effect for pain relief (SMD = -0.38; 95 % CI: -0.70 to -0.07 %; p = 0.02), function (SMD = -0.60; 95 % CI: -1.13 to -0.08 %; p = 0.03), disabilities of the arm, shoulder, and hand (MD = -11.04; 95 % CI: -21.72 to -0.36 %; p = 0.04), and Nirschl stage (MD = -0.81; 95 % CI: -1.11 to -0.51 %; p < 0.0001). In the long-term, ABPs were superior to CSIs for pain relief (SMD = -0.94; 95 % CI: -1.32 to -0.57 %; p < 0.0001) and Nirschl stage (MD = -1.04; 95 % CI: -1.66 to -0.42 %; p = 0.001). Moreover, for grip strength recovery, no significant difference was found between the 2 therapies (p > 0.05). The authors concluded that limited evidence supported the conclusion that CSIs are superior to ABPs for pain relief in the short-term; however, this result was reversed in the intermediate- and long-term. They stated that ABPs appeared to be more effective at restoring function in the intermediate-term; however, because of the small sample size and the limited number of high-quality RCTs, more high-quality RCTs with large sample sizes are needed to validate this result.

Platelet-Rich Plasma Injection and Platelet Gel:

Besides autologous blood injection, other blood product injection therapies for the treatment of patients with tendonopathies include platelet-rich plasma (PRP) and bone marrow plasma.

Growth factors are groups of proteins capable of stimulating cellular growth, proliferation and cellular differentiation. They occur in a wide range of tissues and are important for
regulating a variety of cellular processes. Platelets are small, regularly-shaped clear cell fragments that circulate in the blood and play a fundamental role in hemostasis (cessation of bleeding); a natural source of growth factors. Platelet-Derived Growth Factor (PDGF) is a protein that is secreted by platelets which attracts fibroblasts and macrophages and plays a role in the proliferation phase of wound healing by contributing to the repair of connective tissue, glial and smooth muscle cells.

Growth factors that are derived from platelets assist in the process of blood vessel formation (angiogenesis) and can be obtained either by using recombinant DNA technology or through centrifuged autologous blood. Autologous growth factors, including autologous platelet-derived growth factors (PDGF), autologous platelet concentrate (APC) and autologous platelet gel (APG), also known as platelet-rich plasma (PRP) or "buffy coat," are harvested from a patient’s own (autologous) blood. APC and APG are topically applied to wounds or systemically administered to purportedly accelerate healing and reduce complications of chronic nonhealing wounds that fail to respond to conventional methods of wound treatment or used as an adjunct (addition) to surgery to promote hemostasis and reduce wound complications.

In a pilot study, Mishra and Pavelko (2006) reported their findings on the treatment of chronic elbow tendonosis with PRP. A total of 140 patients were evaluated in this study. Subjects were initially given a standardized physical therapy protocol and various non-operative treatments. Twenty of these patients had significant persistent pain (mean of 82 of 100; range of 60 to 100 of 100 on VAS) for a mean of 15 months despite these interventions. All patients were considering surgery. This cohort of patients was then given either a single percutaneous injection of PRP (n = 15) or bupivacaine (n = 5). Eight weeks after the treatment, the PRP-injected patients noted a 60% improvement in their VAS versus 16% improvement in bupivacaine-treated patients (p = 0.001). Three of 5 of the control subjects (bupivacaine-treated) withdrew or sought other treatments after the 8-week
period, preventing further direct analysis. Thus, only PRP-treated patients were available for continued evaluation. At 6 months, PRP-treated subjects noted a 81% improvement in their VAS ($p = 0.0001$). At final follow-up (mean of 25.6 months; range of 12 to 38 months), the PRP-treated patients reported a 93% reduction in pain compared with before the treatment ($p < 0.0001$). The authors concluded that treatment of patients with chronic elbow tendinosis with PRP reduced pain significantly. Moreover, they stated that further evaluation of this novel treatment is warranted.

In a randomized controlled trial (RCT), Peerbooms and associates (2010) examined the effectiveness of PRP compared with corticosteroid injections in patients with chronic lateral epicondylitis. A total of 100 patients with chronic lateral epicondylitis were randomly assigned in the PRP group ($n = 51$) or the corticosteroid group ($n = 49$). A central computer system carried out randomization and allocation to the trial group. Patients were randomized to receive either a corticosteroid injection or an autologous platelet concentrate injection through a peppering technique. The primary analysis included VAS and DASH Outcome Measure scores (DASH: Disabilities of the Arm, Shoulder, and Hand). Successful treatment was defined as more than a 25% reduction in VAS or DASH score without a re-intervention after 1 year. The results showed that, according to the VAS, 24 of the 49 patients (49%) in the corticosteroid group and 37 of the 51 patients (73%) in the PRP group were successful, which was significantly different ($p < 0.001$). Furthermore, according to the DASH scores, 25 of the 49 patients (51%) in the corticosteroid group and 37 of the 51 patients (73%) in the PRP group were successful, which was also significantly different ($p = 0.005$). The corticosteroid group was better initially and then declined, whereas the PRP group progressively improved. The authors concluded that treatment of patients with chronic lateral epicondylitis with PRP reduces pain and significantly increases function, exceeding the effect of corticosteroid injection. They stated that future decisions for application of the PRP for lateral epicondylitis should be confirmed by further follow-up from this trial and should take
into account possible costs and harms as well as benefits.

In a stratified, block-randomized, double-blind, placebo-controlled trial, de Vos and colleagues (2010) examined if a PRP injection would improve outcome in chronic mid-portion Achilles tendinopathy. A total of 54 randomized patients aged 18 to 70 years with chronic tendinopathy 2 to 7 cm above the Achilles tendon insertion were included in the study. Subjects received eccentric exercises (usual care) with either a PRP injection (PRP group) or saline injection (placebo group); randomization was stratified by activity level. The validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which evaluated pain score and activity level, was completed at baseline and 6, 12, and 24 weeks. The VISA-A score ranged from 0 to 100, with higher scores corresponding with less pain and increased activity. Treatment group effects were evaluated using general linear models on the basis of intention-to-treat. After randomization into the PRP group (n = 27) or placebo group (n = 27), there was complete follow-up of all patients. The mean VISA-A score improved significantly after 24 weeks in the PRP group by 21.7 points (95 % confidence interval [CI]: 13.0 to 30.5) and in the placebo group by 20.5 points (95 % CI: 11.6 to 29.4). The increase was not significantly different between both groups (adjusted between-group difference from baseline to 24 weeks, -0.9; 95 % CI: -12.4 to 10.6). This CI did not include the pre-defined relevant difference of 12 points in favor of PRP treatment. The authors concluded that among patients with chronic Achilles tendinopathy who were treated with eccentric exercises, a PRP injection compared with a saline injection did not result in greater improvement in pain and activity. They do not recommend this treatment for chronic mid-portion Achilles tendinopathy.

In a pilot study, Sampson et al (2010) evaluated the clinical effects of intra-articular PRP injections in a small group of patients with primary and secondary osteoarthritis (OA). A total of 14 patients with primary and secondary knee OA who met the study criteria received 3 PRP injections in the affected
knee at approximately 4-week intervals. Outcome measures included the Brittberg-Peterson Visual Pain (VAS), Activities, and Expectations score and the Knee Injury and Osteoarthritis Outcome Scores at pre-injection visit at 2-, 5-, 11-, 18-, and 52-week follow-up visits. Musculoskeletal ultrasound was used to measure cartilage thickness. There were no adverse events reported. The study demonstrated significant and almost linear improvements in Knee Injury and Osteoarthritis Outcome Scores, including pain and symptom relief. Brittberg-Peterson VAS showed many improvements including reduced pain after knee movement and at rest. Cartilage assessment was limited because of the small sample size. The majority of the patients expressed a favorable outcome at 12 months after treatment. The authors concluded that the positive trends and safety profile demonstrated could potentially be used to inspire a larger, blinded, and randomized clinical trial to determine whether PRP is safe and effective for the treatment of knee OA.

Filardo et al (2011) examined the effects of intra-articular PRP injections for the treatment of degenerative cartilage lesions and osteoarthritis of the knee. Of the 91 patients evaluated in the previous 12-month follow-up study, 90 were available for the 2-year follow-up (24 patients presented a bilateral lesion, in a total of 114 knees treated). All of the patients presented a chronic knee degenerative condition and were treated with 3 intra-articular PRP injections. International Knee Documentation Committee (IKDC) and EQ-VAS scores were used for clinical evaluation. Complications, adverse events and patient satisfaction were also recorded. All of the evaluated parameters worsened at the 24-month follow-up: these parameters were at significantly lower levels with respect to the 12-month evaluation (the IKDC objective evaluation fell from 67 to 59 % of normal and nearly normal knees; the IKDC subjective score fell from 60 to 51), even if they remained higher than the basal level. Further analysis showed better results in younger patients (p = 0.0001) and lower degrees of cartilage degeneration (p < 0.0005). The median duration of the clinical improvement was 9 months. The authors concluded that these findings indicated that treatment with PRP injections can
reduce pain and improve knee function and quality of life with short-term efficacy. They stated that further studies are needed to confirm these results and understand the mechanism of action, and to find other application modalities, with different platelet and autologous blood growth factors concentrations and injection timing, which provide better and more durable results.

Schepull et al (2011) noted that animal studies have shown that local application of PRP stimulates tendon repair. Preliminary results from a retrospective case series have shown faster return to sports. In a randomized controlled trial, these researchers hypothesized that autologous PRP stimulates healing of acute Achilles tendon ruptures. A total of 30 patients were recruited consecutively. During surgery, tantalum beads were implanted in the Achilles tendon proximal and distal to the rupture. Before skin suture, randomization was performed, and 16 patients were injected with 10 ml PRP (10 times higher platelet concentration than peripheral blood) whereas 14 were not. With 3-dimensional radiographs (roentgen stereophotogrammetric analysis; RSA), the distance between the beads was measured at 7, 19, and 52 weeks while the patient resisted different dorsal flexion moments over the ankle joint, thereby estimating tendon strain per load. An estimate of elasticity modulus was calculated using callus dimensions from computed tomography. At 1 year, functional outcome was evaluated, including the heel raise index and Achilles Tendon Total Rupture Score. The primary effect variables were elasticity modulus at 7 weeks and heel raise index at 1 year. The mechanical variables showed a large degree of variation between patients that could not be explained by measuring error. No significant group differences in elasticity modulus could be shown. There was no significant difference in heel raise index. The Achilles Tendon Total Rupture Score was lower in the PRP group, suggesting a detrimental effect. There was a correlation between the elasticity modulus at 7 and 19 weeks and the heel raise index at 52 weeks. The authors concluded that these findings suggested that PRP is not useful for treatment of Achilles tendon ruptures. The variation in
elasticity modulus provides biologically relevant information, although it is unclear how early biomechanics is connected to late clinical results.

In a prospective, randomized, observer-blind controlled pilot study, Horstmann et al (2011) examined the effects of autologous platelet gel (APG), prepared from the buffy coat of a unit of autologous blood, after total knee arthroplasty (TKA) on blood loss, wound healing, pain, range of motion, and hospital stay. A total of 40 patients with only osteoarthritis of the knee were scheduled to have a TKA, and they were randomized into 2 groups. Patients in the treatment group were all treated with the application of APG after the prosthesis was implanted. Patients in the control group were treated with the same protocol but no APG was used. Pre-operative and post-operative hemoglobin levels showed no significant difference and allogeneic blood transfusions were not given in either group. Hematomas were significantly larger in the control group than in the platelet gel group (p = 0.03). The pain score at rest was higher in the control group on the 3rd day (p = 0.04). Wound healing disturbances were seen in 4 patients in the control group and in no patients in the APG group (n.s.). Range of motion of the knee was similar post-operatively. Hospital stay was 6.2 days in the APG and 7.5 days in the control group (n.s.). The authors noted that differences in favor of the use of APG were found, but these were subjective evaluations, marginal in effect, or did not reach statistical significance. The use of drains might have decreased the concentration of delivered platelets and may have diminished the effect. However, in this study, a statistically significant clinically important effect in favor of APG application was not found. They concluded that further studies with larger numbers of patients, and without the use of drains, are needed to investigate the possible benefits of APG in total knee arthroplasty.

Guadilla et al (2012) described a non-invasive arthroscopic procedure as an alternative to open surgery for avascular necrosis (AVN) of the hip. Patients with grade I or IIA AVN of
the hip were treated by core decompression performed by drilling under fluoroscopic guidance. Liquid PRP was delivered through a trocar, saturating the necrotic area. In more severe conditions, the necrotic bone is decompressed and debrided, through a cortical window at the head-neck junction. A composite graft made of autologous bone and PRP was delivered by impactation through the core decompression track. Fibrin membranes were applied to enhance healing of the head-neck window and arthroscopic portals. Platelet-rich plasma was infiltrated in the central compartment. This arthroscopic approach aided in making diagnosis of the labrum and articular cartilage and permitted intra-operative treatment decisions. Visual control allowed the precise localization and treatment for the necrotic area allowing cartilage integrity to be preserved. The authors concluded that arthroscopic management of AVN of the femoral head is viable and has significant advantages. They stated that clinical studies should justify the theoretical additional benefits of this approach. An UpToDate review on "Osteonecrosis (avascular necrosis of bone)" (Jones, 2012) does not mention the use of PRP as a therapeutic option.

Sanchez et al (2012) evaluated the safety and symptomatic changes of intra-articular (IA) injections of PRP in patients with OA of the hip. A total of 40 patients affected by monolateral severe hip OA were included in the study. Each joint received 3 IA injections of PRP, which were administered once-weekly. The primary end point was meaningful pain relief, which was described as a reduction in pain intensity of at least 30 % from baseline levels as evaluated by the WOMAC subscale at 6-months post-treatment. The VAS and Harris hip score subscale for pain were used to verify the results. Secondary end points included changes in the level of disability of at least 30 % and the percentage of positive responders, namely, the number of patients that achieved a greater than 30 % reduction in pain and disability. Statistically significant reductions in VAS, WOMAC and Harris hip subscores for pain and function were reported at 7 weeks and 6 months (p < 0.05). Twenty-three (57.5 %) patients reported a clinically relevant reduction of pain
(45%, range of 30 to 71%) as assessed by the WOMAC subscale. Sixteen (40%) of these patients were classified as excellent responders who showed an early pain reduction at 6 to 7 weeks, which was sustained at 6 months, and a parallel reduction of disability. Side effects were negligible and were limited to a sensation of heaviness in the injection site. The authors concluded that this preliminary non-controlled prospective study supported the safety, tolerability and efficacy of PRP injections for pain relief and improved function in a limited number of patients with OA of the hip. These findings need to be validated by prospective RCTs.

Bocanegra-Perez et al (2012) described the results of using PRP in the management of bisphosphonate-associated necrosis of the jaw. A total of 8 patients with a diagnosis of bisphosphonate-associated necrosis of the jaw were surgically treated for debridement and removal of necrotic bone, followed by application of autologous platelet concentrate enriched with growth factors and primary suture of the wound. Patients underwent periodic clinical and radiological follow-up examinations. All patients showed clinical improvement and oral lesions resolved 2 to 4 weeks following treatment. After an average 14-month follow-up period, patients remained asymptomatic. The authors concluded that although not conclusive, the combination of necrotic-bone curettage and PRP to treat refractory osteonecrosis of the jaw yielded promising results.

Gross et al (2013) performed a systematic review of clinical outcomes following injectable therapy of non-insertional Achilles tendinosis, identified patient-specific factors that are prognostic of treatment outcomes, provided treatment recommendations based on the best available literature, and identified knowledge deficits that require further investigation. These investigators searched Medline (1948 to week 1 of March 2012) and Embase (1980 to week 9 of 2012) for clinical studies evaluating the efficacy of injectable therapies for non-insertional Achilles tendinosis. Specifically, they included RCTs and cohort studies with a comparative control group.
Data abstraction was performed by 2 independent reviewers. The Oxford Level of Evidence Guidelines and GRADE recommendations were used to rate the quality of evidence and to make treatment recommendations. A total of 9 studies fit the inclusion criteria for this review, constituting 312 Achilles tendons at final follow-up. The interventions of interest included PRP (n = 54), autologous blood injection (n = 40), sclerosing agents (n = 72), protease inhibitors (n = 26), hemodialysate (n = 60), corticosteroids (n = 52), and prolotherapy (n = 20). Only 1 study met the criteria for a high-quality RCT. All of the studies were designated as having a low-quality of evidence. While some studies showed statistically significant effects of the treatment modalities, often studies revealed that certain injectables were no better than a placebo. The authors concluded that the literature surrounding injectable treatments for non-insertional Achilles tendinosis has variable results with conflicting methodologies and inconclusive evidence concerning indications for treatment and the mechanism of their effects on chronically degenerated tendons. They stated that prospective, randomized studies are needed to guide Achilles tendinosis treatment recommendations using injectable therapies.

In a RCT, Kesikburun and associates (2013) examined the effect of PRP injections on pain and shoulder functions in patients with chronic rotator cuff tendinopathy. A total of 40 patients, 18 to 70 years of age, with (i) a history of shoulder pain for greater than 3 months during overhead-throwing activities, (ii) MRI findings of rotator cuff tendinopathy or partial tendon ruptures, and (iii) a minimum 50% reduction in shoulder pain with subacromial injections of an anesthetic were included in this placebo-controlled, double-blind RCT. Patients were randomized into a PRP group (n = 20) or placebo group (n = 20). Patients received an ultrasound-guided injection into the subacromial space that contained either 5 ml of PRP prepared from autologous venous blood or 5 ml of saline solution. All patients underwent a 6-week standard exercise program. Outcome measures (Western Ontario Rotator Cuff Index [WORC], Shoulder Pain and Disability Index [SPADI], 100-mm
VAS of shoulder pain with the Neer test, and shoulder range of motion) were assessed at baseline and at 3, 6, 12, and 24 weeks and 1 year after injection. Comparison of the patients revealed no significant difference between the groups in WORC, SPADI, and VAS scores at 1-year follow-up (p = 0.174, p = 0.314, and p = 0.904, respectively). Similar results were found at other assessment points. Within each group, the WORC, SPADI, and VAS scores showed significant improvements compared with baseline at all time-points (p < 0.001). In the range of motion measures, there were no significant group \times time interactions. The authors concluded that at 1-year follow-up, a PRP injection was found to be no more effective in improving quality of life, pain, disability, and shoulder range of motion than placebo in patients with chronic rotator cuff tendinopathy who were treated with an exercise program.

In a randomized, double-blinded, placebo and active-controlled, half-head, parallel-group study, Trink et al (2013) evaluated the safety and effectiveness of PRP for the treatment of alopecia areata (AA). A total of 45 AA patients were randomized to receive intra-lesional injections of PRP, triamcinolone acetonide (TA) or placebo on 50% of their scalp. The other 50% was not treated. A total of 3 treatments were given for each patient, with an interval of 1 month from each other. The end-points were hair regrowth, hair dystrophy as measured by dermoscopy, burning/itching sensation and cell proliferation as measured by Ki-67 evaluation. Patients were followed for 1 year. Platelet-rich plasma was found to significantly increase hair regrowth and decrease hair dystrophy and burning/itching sensation when compared with TA or placebo, and Ki-67 levels, which served as markers for cell proliferation, were significantly higher. No side effects were noted during treatment. The authors concluded that in this pilot study, which is the first to investigate the effects of PRP on AA, suggested that PRP may serve as a safe and effective treatment option in AA, and calls for more extensive controlled studies with this method.

In a single-center, parallel-group, participant-blinded RCT, Griffin et al (2013) examined the effectiveness of PRP therapy in
the management of patients with a typical osteoporotic fracture of the hip. In this study, 200 of 315 eligible patients aged 65 years and over with any type of intra-capsular fracture of the proximal femur were included. Patients were excluded if their fracture precluded internal fixation. Participants underwent internal fixation of the fracture with cannulated screws and were randomly allocated to receive an injection of PRP into the fracture site or not. Main outcome measure was failure of fixation within 12 months, defined as any revision surgery. Primary outcome data were available for 82 of 101 and 78 of 99 participants allocated to test and control groups, respectively; the remainder died prior to final follow-up. There was an absolute risk reduction of 5.6 % (95 % CI: -10.6 % to 21.8 %) favoring treatment with PRP therapy ($\chi^2$ test, $p = 0.569$). An adjusted effect estimate from a logistic regression model was similar (odds ratio [OR] = 0.71, 95 % CI: 0.36 to 1.40, z test; $p = 0.325$). There were no significant differences in any of the secondary outcome measures excepting length of stay favoring treatment with PRP therapy (median difference 8 days, Mann-Whitney U test; $p = 0.03$). The number and distribution of adverse events were similar. Estimated cumulative incidence functions for the competing events of death and revision demonstrated no evidence of a significant treatment effect (hazard ratio [HR] 0.895, 95 % CI: 0.533 to 1.504; $p = 0.680$ in favor of PRP therapy). The authors concluded that there was no evidence of a difference in the risk of revision surgery within 1 year in participants treated with PRP therapy compared with those not treated. However, the authors cannot definitively exclude a clinically meaningful difference.

Kumar et al (2013) evaluated the effectiveness of PRP in chronic cases of plantar fasciitis. Patients with plantar fasciitis not responded to a minimum of 1 year standard conservative management were offered PRP therapy. Injections were performed in theatre as a day case. Roles-Maudsley (RM) scores, VAS, AOFAS scores and “would have injection again” were collated pre-operatively, 3 and 6 months post-operatively. Prospective data were collected of 50 heels (44 patients). At 6 month review, RM score improved from mean 4 to 2 ($p <$
0.001), VAS improved from 7.7 to 4.2 (p < 0.001) and AOFAS improved from 60.6 to 81.9 (p < 0.001). A total of 28 patients (64%) were very satisfied and would have the injection again. No complications were reported. The authors concluded that in these chronic cases, PRP produced an efficacy rate, approaching 2 out of every 3. The procedure was safe with no reported complications. The authors felt that PRP may have some role in treatment, and merits further study with a prospective randomized trial.

Osterman et al (2015) noted that PRP has anti-inflammatory effects with potential applications in the treatment of OA. In a controlled laboratory study, these researchers used an in-vitro co-culture model of OA in human cartilage and synovium to investigate the anti-inflammatory effects of 2 different PRP preparations. A co-culture system was created using osteoarthritic cartilage and synovium from 9 patients undergoing total knee arthroplasty. Interleukin-1β (IL-1β) was added to each co-culture to induce inflammation. Two PRP preparations were obtained -- one yielding low white blood cell and platelet concentrations (PRPLP) and one yielding high platelet and white blood cell concentrations (PRPHP). Either PRPLP, PRPHP, or medium was added to the co-culture wells. Control wells contained OA cartilage and synovium but neither IL-1β nor PRP. Normal, non-OA cartilage was obtained to establish baseline gene expression levels. Quantitative polymerase chain reaction was used to measure changes in markers of inflammation in the tissues (a disintegrin and metalloproteinase with thrombospondin motifs-5 [ADAMTS-5], tissue inhibitor of metalloproteinases-1 [TIMP-1], vascular endothelial growth factor [VEGF], aggrecan, and type I collagen) at 0, 24, 48, and 72 hours. Treatment with PRPLP or PRPHP significantly decreased expression of TIMP-1 and ADAMTS-5 in cartilage, increased aggrecan expression in cartilage, and decreased ADAMTS-5, VEGF, and TIMP-1 expression in synovium compared with control co-cultures (p < 0.05). There was significantly less nitric oxide production in the PRPLP and PRPHP groups compared with controls (p < 0.05). There were significant differences in gene expression in the normal
cartilage compared with all 4 groups of OA cartilage at all 4 time points. Treatment with either PRPLP or PRPHP returned some gene expression to the same levels in normal cartilage but not for all markers of inflammation. The authors concluded that this co-culture model assessed 2 different PRP preparations and their anti-inflammatory effects over time on human OA cartilage and synovium. Both had a significant anti-inflammatory effect on gene expression; however, there was no difference in the anti-inflammatory effect between the 2 preparations. These investigators stated that OA is a leading cause of chronic disability, and less invasive treatment methods are needed; these findings suggested that PRP injections may be an effective alternative anti-inflammatory agent in the treatment of OA.

On behalf of the Osteoarthritis Section of the French Society for Rheumatology, Ornetti et al (2016) stated that PRP has been generating considerable attention as an intra-articular treatment to alleviate the symptoms of OA. Activated platelets release a host of soluble mediators such as growth factors and cytokines, thereby inducing complex interactions that vary across tissues within the joint. In-vivo, PRP may promote chondrocyte proliferation and differentiation. The available data are somewhat conflicting regarding potential effects on synovial cells and angiogenesis modulation. Platelet-rich plasma probably exerts an early anti-inflammatory effect, which may be chiefly mediated by inhibition of the NF-κB pathway, a hypothesis that requires confirmation by proof-of-concept studies. The authors stated that it is far too early to draw conclusions about the effectiveness of PRP as a treatment for hip OA.

Nourissat et al (2015) stated that although tendinopathies constitute a heterogeneous group of conditions, they are often treated by similar combinations of local and systemic symptomatic interventions. The vast number of causes, pathophysiological mechanisms, and histological changes that characterizes tendinopathies may explain that the standard treatment fails in some patients. Platelet-rich plasma (PRP),
which contains a host of soluble mediators including growth factors, has been suggested as a second-line treatment for refractory tendinopathy, with the goal of expediting tendon healing or remodeling. These investigators reported a systematic literature review of basic research data from humans and animals that support the clinical use of PRP in tendinopathies and of clinical studies in the most common tendinopathies (elbow, knee, shoulder, and Achilles tendon). The objective was to clarify the role for this new injectable treatment, which is garnering increasing attention. The level of evidence remains low, as few well-designed randomized controlled trials have been published. The available scientific evidence does not warrant the use of PRP for the first-line treatment of tendinopathy. PRP therapy may deserve consideration in specific tendinopathy subtypes, after failure of ultrasound-guided corticosteroid injections. Nevertheless, further studies are needed to define these potential indications and the optimal treatment protocols.

Balasubramaniam et al (2015) systematically reviewed the literature regarding PRP therapy in chronic tendinopathy. The databases used in the search include the Elton B. Stephens Co. (EBSCO) database, Medline, the Cochrane library, Ovid, and Embase (the Excerpta Medica database). A total of 389 articles were reviewed from Feb 2010 to April 2014, for possible inclusion. Of these articles, a total of 9 randomized controlled trials (RCTs) met the inclusion criteria. Only 1 RCT was excluded due to previous surgery in both the trial and control groups. Each article was reviewed independently by 2 authors. Each article was analyzed using the Cochrane Criteria checklist. Where any discrepancy occurred in results, a 3rd independent reviewer was consulted. The review found that PRP was most effective in patellar and lateral epicondylar tendinopathy, with both RCTs in the patellar section of the study supporting the use of PRP in pain reduction at 3 and 12 months, whereas 2 of 4 studies in the lateral epicondylar section showed improvements in pain and disability at 6 and 12 months. There was a lack of evidence to support the use of PRP in Achilles and rotator cuff tendinopathy. The authors concluded that although the results
of this review showed promise for the use of PRP in chronic tendinopathy, the analysis highlighted the need for more controlled clinical trials comparing PRP with placebo.

Di Matteo et al (2015) PRP has been introduced in the clinical practice to treat a growing number of different musculoskeletal pathologies. It is currently applied in the treatment of Achilles and patellar tendinopathies, which are common sport-related injuries very challenging to manage. Aim of the present paper was to review systematically the available clinical evidence concerning the application of PRP in the treatment of patellar and Achilles tendinopathy. A systematic review of the literature was performed according to the following inclusion criteria for relevant articles: (i) clinical reports of any level of evidence, (ii) written in the English language, (iii) with no time limitation, and (iv) on the use of PRP to treat conservatively Achilles and patellar tendinopathy. A total of 22 studies were included and analyzed. Two studies on patellar tendinopathy were RCTs, whereas just 1 RCT was published on Achilles tendon. All the papers concerning patellar tendon reported positive outcome for PRP, which proved to be superior to other traditional approaches such as shock-wave therapy and dry needling. In the case of Achilles tendon, despite the encouraging findings reported by case series, the only RCT available showed no significant clinical difference between PRP and saline solution. The main finding of this study was the paucity of high-level literature regarding the application of PRP in the management of patellar and Achilles tendinopathy. However, the authors noted that clinical data currently available, although not univocal, suggest considering PRP as a therapeutic option for recalcitrant patellar and Achilles tendinopathies.

Gholami et al (2016) examined the effectiveness of PRP in improving sports injuries and subsequently threw some light on these controversies. These researchers performed a systematic review of the literature and meta-analysis of results. All related databases, such as PubMed, Cochrane Database of Systematic Reviews, DARE, and EMBASE, were searched on the use of PRP on athletes and in sports medicine. The search was conducted
from June 2013 to February 2014. The search retrieved 905 studies, of which 13 RCTs met inclusion criteria for systematic review and meta-analysis. All articles were appraised by Critical Appraisal Skills Program (CASP) check-list for RCTs. The analysis of the results of pain scores and physical activity/functions did not show any superiority for PRP as opposed to the other options. The authors concluded that this meta-analysis showed no more effectiveness for PRP application in sports-related injuries in terms of physical function improvement and pain relief. Therefore, they stated that the extensive use of PRP for such injuries should be limited; well-designed RCTs are needed to support the findings.

An UpToDate review on “Overview of the management of overuse (chronic) tendinopathy” (Khan and Scott, 2016) lists “Dry needling and autologous blood/platelet rich plasma injection” as investigational treatments. It states that “small randomized trials of patients with mid-portion Achilles tendinopathy demonstrated no benefit from platelet rich plasma (PRP) or autologous blood injection when added to an eccentric training program. A similar study performed in patients with rotator cuff tendinopathy also reported no benefit from PRP when performed in patients treated with standard physical therapy”.

**Platelet-Rich Plasma Injection for the Treatment of Ankle Sprain:**

Rowden et al (2015) noted that over 23,000 people per day require treatment for ankle sprains. Platelet-rich plasma is an autologous concentration of platelets that is thought to improve healing by promoting inflammation through growth factor and cytokine release. Studies to-date had shown mixed results, with few randomized trials. In a prospective, double-blind, randomized, placebo-controlled study, these researchers determined patient function among patients randomized to receive standard therapy plus PRP, compared to patients who receive standard therapy plus sham injection (placebo). Patients with severe ankle sprains were randomized. Severity was
graded on degree of swelling, ecchymosis, and ability to bear weight; PRP with lidocaine and bupivacaine was injected at the point of maximum tenderness by a blinded physician under ultrasound guidance. The control group was injected in a similar fashion with sterile 0.9 % saline. Both groups had VAS pain scores and Lower Extremity Functional Scale (LEFS) on days 0, 3, and 8; LEFS and a numeric pain score were obtained via phone call on day 30. All participants were splinted, given crutches, and instructed to not bear weight for 3 days; at this time patients were re-evaluated. There were 1,156 patients screened and 37 were enrolled. Four withdrew before PRP injection was complete; 18 were randomized to PRP and 15 to placebo. There was no statistically significant difference in VAS and LEFS scores between groups. The authors concluded that in this small study, PRP did not provide benefit in either pain control or function over placebo.

Platelet-Rich Plasma Injection for the Treatment of Cerebral Palsy:

Alcaraz et al (2015) reported the case of a cerebral palsy (CP) patient who received intravenous PRP. These investigators administered an intravenous injection of concentrated PRP (25 cc) in a 6-year old boy with perinatal CP, cognitive impairment, and marked and severe generalized spasticity. They performed follow-up at 3 and 6 months after the injection. All serum samples for determination were obtained by ELISA technique. Cognitive scales (Bayley, Battelle, M.S.C.A, Kaufman ABC, and Stanford-Binet Intelligence scale) were used before and after treatment. The determination protocol that was applied before the analysis was performed manually and the auto-transfusion was considered suitable for treatment. These researchers determined the plasma levels of factor similar to insulin-1 (IGF-1), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor B (TGF-B) before and during treatment monitoring. No adverse effects were observed in the patient except for a small hematoma in the area channeling venous access. These investigators observed a clear improvement in the cognitive
sphere (memory, ability to perform more complex tasks, and acquisition of new skills) and in language, maintaining stable levels of growth factor in plasma 3 to 5 times higher than average for his age group at both 3- and 6-month follow-up. Positron emission tomography (PET) images showed an evident increased demarcation in the cerebral cortex. The authors proposed that this therapy is useful in these patients to harness the neurostimulative and neuroregenerative power of endogenous growth factors derived from platelets. The findings of this single case study needs to be validated by well-designed studies.

**Platelet-Rich Plasma Injection for the Treatment of Crohn’s Disease-Related Perianal Fistula:**

In a prospective, pilot study, Gottgens et al (2015) attempted to improve healing rates of Crohn’s disease (CD)-related high perianal fistulas by combining the well-known mucosal advancement flap with PRP. Consecutive patients with primary or recurrent CD-related high perianal fistulas, defined as involving the middle and/or upper third parts of the anal sphincter complex, were included. A staged procedure was performed with non-cutting seton treatment for 3 months first, followed by a mucosal advancement flap with injection of PRP into the fistula tract. A total of 10 consecutive patients were operated on between 2009 and 2014; 50 % of the patients had undergone previous fistula surgery. Mean follow-up was 23.3 months (SD 13.0). Healing of the fistula was 70 % (95 % CI: 33 to 89 %) at 1 year. One (10 %) patient had a recurrence, and in 2 (20 %) patients, the fistula was persistent after treatment. An abscess occurred in 1 (10 %) patient. The median post-operative Vaizey score was 8.0 (range of 0 to 21), indicating a moderate to severe continence impairment. The authors concluded that the results of combining the mucosal advancement flap with PRP in patients with CD-related high perianal fistulas are moderate with a healing rate of 70 %. They stated that further investigation is needed to determine the benefits and risks on continence status for this technique in this patient population.
Platelet-Rich Plasma Injection for the Treatment of Hamstring Injury:

In a randomized, 3-arm (double-blind for the injection arms), parallel-group trial, Hamilton et al (2015) evaluated the effectiveness of a single PRP injection in reducing the return to sport duration in male athletes, following an acute hamstring injury (HI). A total of 90 professional athletes with MRI positive HI were randomized to injection with PRP-intervention, platelet-poor plasma (PPP-control) or no injection. All received an intensive standardized rehabilitation program. The primary outcome measure was time to return to play, with secondary measures including re-injury rate after 2 and 6 months. The adjusted HR for the PRP group compared with the PPP group was 2.29 (95 % CI: 1.30 to 4.04; p = 0.004); for the PRP group compared with the no injection group 1.48 (95 % CI: 0.869 to 2.520; p = 0.15), and for the PPP group compared with the no injection group 1.57 (95 % CI: 0.88 to -2.80; p = 0.13). The adjusted difference for time to return to sports between the PRP and PPP groups was -5.7 days (95 % CI: -10.1 to -1.4; p = 0.01); between the PRP and no injection groups -2.9 days (95 % CI: -7.2 to 1.4; p = 0.189) and between the PPP and no injection groups 2.8 days (95 % CI: -1.6 to 7.2; p = 0.210). There was no significant difference for the secondary outcome measures. No adverse effects were reported. The authors concluded that these findings indicated that there is no benefit of a single PRP injection over intensive rehabilitation in athletes who have sustained acute, MRI positive HI. Intensive physiotherapy led rehabilitation remains the primary means of ensuring an optimal return to sport following muscle injury.

In a meta-analysis, Pas and colleagues (2015) updated and re-analyzed the effectiveness of conservative treatments HI. PubMed, EMBASE, Web of Science, Cochrane library, CINAHL and SPORTDiscus were searched till mid-February 2015. Randomized controlled trials on the effect of conservative interventions versus a control group or other intervention for HI were included. The search results were screened independently by 2 authors. Risk of bias assessment was performed using a
modified Downs and Black scale with a maximum score of 28. Meta-analysis was performed, where possible. A total of 10 RCTs (526 participants), including 6 new RCTs, were identified. Two RCTs were of good/excellent quality, the rest were fair or poor (median Downs and Black score 16 (IQR 9)). Meta-analysis of 2 studies on rehabilitation (lengthening) exercises showed a significantly reduced time to return to play (HR 3.22 (95 % CI: 2.17 to 4.77), p < 0.0001) but no difference in risk of re-injury. Meta-analysis of 3 studies investigating PRP showed no effect when compared to control (HR 1.03 (95 % CI: 0.87 to 1.22), p = 0.73). Limited evidence was found that progressive agility and trunk stability training may reduce re-injury rates. The authors concluded that meta-analysis showed superior effectiveness for rehabilitation exercises; PRP injection had no effect on acute HI.

Brukner (2015) stated that not all HI are the same and that certain types of injuries require prolonged rehabilitation and return to play. The slow stretch type of injury and injuries involving the central tendon both require longer times to return to play. A number of factors have been proposed as being indicators of time taken to return to play, but the evidence for these is conflicting. Recurrence rates remain high and it is now thought that strength deficits may be an important factor. Strengthening exercise should be performed with the hamstrings in a lengthened position. The author stated that there is conflicting evidence regarding the effectiveness of PRP injection in the treatment of HI so at this stage their use is not advised.

Platelet-Rich Plasma Injection for the Treatment of Temporomandibular Joint Osteoarthritis:

In a RCT, Comert et al (2015) compared the long-term clinical and radiologic outcomes of temporomandibular joint OA (TMJ-OA) treated with arthrocentesis plus PRP versus arthrocentesis alone. The sample was composed of 30 consecutive patients with TMJ-OA treated randomly with arthrocentesis alone (control group) or initial arthrocentesis plus PRP injection and then 4 consecutive PRP injections (study
group). The predictor variable was treatment technique. The outcome variables were VAS evaluations (masticatory efficiency, joint sounds, and pain complaints), maximal inter-incisal opening, and cone-beam computed tomographic (CBCT) findings. Outcome variables were recorded pre-operatively and 12 months post-operatively. Descriptive and bivariate statistics were computed, and significance was set at a “p” value less than 0.05. The paired-t and Student-t tests were used for intra-group and inter-group comparisons, respectively. The sample was composed of 47 joints of 30 patients with OA (control group: 15 joints of 12 patients; mean age of 35.08 ± 14.84 years; study group: 32 joints of 18 patients; mean age of 32.22 ± 14.32 years). Joint sounds and general pain complaints decreased statistically in the 2 groups, whereas masticatory efficiency, painless inter-incisal opening, and lateral motion increased statistically only in the study group. However, only masticatory efficiency showed statistically greater improvement in the study group compared with the control group. Cone-beam CT evaluations showed that reparative re-modeling of the osseous abnormalities occurred at rates of 87.5 and 46.6 % in the study and control groups, respectively. The authors concluded that these findings suggested that arthrocentesis and PRP injections provided a safe and promising method for the treatment of TMJ-OA that is superior to arthrocentesis alone. These preliminary findings need to be validated by well-designed studies.

Platelet-Rich Plasma Injection for the Treatment of Anterior Cruciate Ligament Surgery:

In a systematic review, Figueroa et al (2015) evaluated the current literature for evidence that would substantiate the use of PRP in the treatment of anterior cruciate ligament (ACL) ruptures. These researchers performed a systematic search in PubMed and Embase of studies written in the English and Spanish languages that compared the use of PRP with a control group in patients with ACL injuries assessing graft to-bone healing, graft maturation, and/or clinical outcomes and were RCTs or prospective cohort studies. A total of 11 studies
fulfilled the inclusion criteria, comprising 516 patients (266 ACL reconstructions using PRP and 250 ACL reconstructions without PRP); 6 studies reported a statistically significant difference (4 studies) or tendency toward faster graft maturation in the platelet group (2 studies); 1 study found no differences. Regarding tunnel healing/widening, 1 study showed faster healing in the PRP group and 5 studies showed no differences between the 2 groups. Considering clinical outcomes, 1 study showed better clinical outcomes with PRP use and 5 studies showed no benefits with the use of PRP. The authors concluded that concerning ACL graft maturation, there is promising evidence that the addition of PRP could be a synergic factor in acquiring maturity more quickly than grafts with no PRP, with the clinical implication of this remaining unclear. Regarding tunnel healing, it appeared that there is not an improvement with the addition of PRP. They stated that there is no proof that clinical outcomes of ACL surgery are enhanced by the use of PRP.

**Platelet-Rich Plasma Injection As Adjunctive Material to Bone Graft:**

In a systematic review and meta-analysis, Pocaterra et al (2016) evaluated the scientific evidence on the effectiveness of PRP as an adjunctive material in the sinus floor elevation technique. The following databases were searched for relevant published studies: Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, Science Direct, ISI Web of Knowledge, and SCOPUS. Only RCTs comparing a group receiving PRP as an adjunctive material to a control group without PRP, involving adult human subjects (age greater than 18 years) with no systemic disease, were included. Of the studies identified, only 1 reported a significant difference in bone augmentation in favor of the adjunctive use of PRP, while 4 studies did not find any significant difference. None of the studies included reported a significant difference in the implant survival rate. The authors concluded that further RCTs are needed to clarify the effectiveness of adjunctive PRP.
In a systematic review and meta-analysis, Lemos et al (2016) evaluated the effect on bone formation and implant survival of combining PRP with bone grafts in maxillary augmentation. A comprehensive review of articles listed in the PubMed/Medline, Embase, and Cochrane Library databases covering the period January 2000 to January 2015 was performed. The meta-analysis was based on bone formation for which the mean difference (MD, in millimeters) was calculated. Implant survival was assessed as a dichotomous outcome and evaluated using the risk ratio (RR) with 95% CI. The search identified 3,303 references. After inclusion and exclusion criteria were applied, 17 studies were selected for qualitative analysis and 13 for quantitative analysis. A total of 369 patients (mean age of 51.67 years) and 621 maxillary sinus augmentations were evaluated. After the data analysis, additional analyses were performed of the implant stability quotient, marginal bone loss, and alveolar bone height measured by MD. The results showed no significant difference in implant stability (p = 0.32, MD 1.00, 95% CI: -0.98 to 2.98), marginal bone loss (p = 0.31, MD 0.06, 95% CI: -0.05 to 0.16), alveolar bone height (p = 0.10, MD -0.72, 95% CI: -1.59 to 0.14), implant survival (p = 0.22, RR 1.95, 95% CI: 0.67 to 5.69), or bone formation (p = 0.81, MD -0.63, 95% CI: -5.91 to 4.65). The authors concluded that the results of this meta-analysis indicated no influence of PRP with bone graft on bone formation and implant survival in maxillary sinus augmentation.

**Platelet-Rich Plasma Injection for the Treatment of Chronic Wounds:**

In a meta-analysis, Martinez-Zapata et al (2016) examined if autologous PRP promotes the healing of chronic wounds. In June 2015, for this first update, these investigators searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library); Ovid Medline; Ovid Medline (In-Process & Other Non-Indexed Citations); Ovid Embase; and EbSCO CINAHL. They also searched for ongoing and unpublished clinical trials in the WHO International Clinical Trials Registry Platform (ICTRP) (searched
January 2015). They did not impose any restrictions with respect to language, date of publication, or study setting. These researchers included RCTs that compared autologous PRP with placebo or alternative treatments for any type of chronic wound in adults. They did not apply any date or language restrictions. They used standard Cochrane methodology, including 2 reviewers independently selecting studies for inclusion, extracting data, and assessing risk of bias. The search identified 1 new RCT, making a total of 10 included RCTs (442 participants, 42% women). The median number of participants per RCT was 29 (range of 10 to 117); 4 RCTs recruited people with a range of chronic wounds; 3 RCTs recruited people with venous leg ulcers, and 3 RCTs considered foot ulcers in people with diabetes. The median length of treatment was 12 weeks (range of 8 to 40 weeks). It is unclear whether autologous PRP improves the healing of chronic wounds generally compared with standard treatment (with or without placebo) (RR 1.19, 95% CI: 0.95 to 1.50; I(2) = 27%, low quality evidence, 8 RCTs, 391 participants). Autologous PRP may increase the healing of foot ulcers in people with diabetes compared with standard care (with or without placebo) (RR 1.22, 95% CI: 1.01 to 1.49; I(2) = 0%, low quality evidence, 2 RCTs, 189 participants). It is unclear if autologous PRP affects the healing of venous leg ulcers (RR 1.02, 95% CI: 0.81 to 1.27; I(2) = 0%). It is unclear if there is a difference in the risk of adverse events in people treated with PRP or standard care (RR 1.05, 95% CI: 0.29 to 3.88; I(2) = 0%, low quality evidence from 3 trials, 102 participants). The authors concluded that PRP may improve the healing of foot ulcers associated with diabetes, but this conclusion is based on low quality evidence from 2 small RCTs. It is unclear whether PRP influences the healing of other chronic wounds. The overall quality of evidence of autologous PRP for treating chronic wounds is low. There are very few RCTs evaluating PRP, they are under-powered to detect treatment effects, if they exist, and are generally at high or unclear risk of bias. They stated that Well designed and adequately powered clinical trials are needed.

Platelet-Rich Plasma Injection for the Treatment of
Osteoarthritis:

Knop et al (2016) conducted a comprehensive and systematic search of the literature on the use of PRP in the treatment of osteoarthritis, using the Medline, Lilacs, Cochrane and SciELO databases, from May 2012 to October 2013. A total of 23 studies were selected, with 9 being controlled trials and, of these, 7 randomized, which included 725 patients. In this series, the group receiving PRP showed improvement in pain and joint function compared to placebo and hyaluronic acid. The response lasted up to 2 years and was better in milder cases. However, it was found that there was no standardization in the PRP production method, neither in the number, timing, and volume of applications. Furthermore, the populations studied were not clearly described in many studies. Thus, the authors concluded that these results should be analyzed with caution, and further studies with more standardized methods are needed for a more consistent conclusion about the PRP role in osteoarthritis.

Platelet-Rich Plasma Injection for the Treatment of Rotator Cuff Injuries:

In a meta-analysis, Fu and colleagues (2016) examined the effectiveness of PRP and platelet-rich fibrin (PRF) matrix for improving healing of rotator cuff injuries. A meta-analysis of eligible studies was performed after searching Medline, Cochrane, and EMBASE on December 14, 2015. Databases were searched using the keywords "PRP or platelet-rich plasma", "PRFM or platelet-rich fibrin matrix", "rotator cuff" and "platelet-rich" for studies comparing outcomes of patients with rotator cuff injuries that did and did not receive a platelet-rich product. The primary outcome was a functional score change from pre- to post-treatment (Scorepost-Scorepre). The secondary outcome was a VAS pain score change from pre- to post-treatment (VASpost-VASpre). A total of 11 studies were included in the meta-analysis. The total number of patients that received PRP or PRF matrix was 320 and the number of control patients was 318. The standard
difference in means of the functional scores was similar between patients administered PRP/PRF matrix and patients in the control group (standard difference in means for functional scores = 0.029; 95% CI: -0.132 to 0.190; p = 0.725). The standard difference in means was similar between patients administered PRP and the controls (standard difference in means = 0.142; 95% CI: -0.080 to 0.364; p = 0.209). The authors concluded that the results of this meta-analysis did not support the use of PRP/PRF matrix in patients with rotator cuff injuries.

Platelet-Rich Plasma Combined with Stem Cells

Stem cells are unspecialized cells that when injected into a specific area of the body, may take on the characteristics of surrounding cells. Cell-based substitutes include, but may not be limited to, stem cells that have been combined with PRP (e.g., Regenexx). The injection of stem cells or cell-based substitutes is suggested to promote the healing of wounds and injuries.

Bone Marrow Plasma Injection/Bone Marrow Derived Mesenchymal Stromal Cells Administration:

Moon and colleagues (2008) hypothesized that iliac bone marrow plasma injection after arthroscopic debridement of degenerative tissue will bring along biological cure. Thus, it will not only reduce pain but also improve function in patients with resistant elbow tendonitis. A total of 24 patients (26 elbows) with significant persistent pain for a mean of 15 months, despite of standard rehabilitation protocol and a variety of other non-surgical modalities were treated arthroscopically. These researchers examined the effects of autologous iliac bone marrow plasma injection following arthroscopic debridement. Bone marrow plasma is produced by centrifugation of iliac bone marrow blood at 1,800 rpm for 20 to 30 minutes. Patients were allowed full range of motion exercise after 2 to 3 days. Cytokine analyses for this injective material were done. Outcome was rated by post-operative sonography, VAS and Mayo elbow performance scores (MEPS)
at 8 weeks and 6 months follow-up. All patients in this study reported improvement both in their VAS and MEPS; no complication was observed. Evidence of tendon healing was observed in post-operative sonographic examination. Predominant cytokines of this study were interleukin-12, interferon-gamma-inducible protein-10 and RANTES (regulated upon activation, normal T-cell expressed and secreted). The authors concluded the injection of iliac bone marrow plasma after arthroscopic debridement in severe elbow tendinosis demonstrated early recovery of daily activities and clear improvement.

In a phase I clinical trial, Duijvestein et al (2010) examined the safety and feasibility of autologous bone marrow derived mesenchymal stromal cells (MSCs) therapy in patients with refractory Crohn's disease. A total of 10 adult patients with refractory Crohn's disease (2 males and 8 females) underwent bone marrow aspiration under local anesthesia. Bone marrow MSCs were isolated and expanded ex vivo. Mesenchymal stromal cells were tested for phenotype and functionality in vitro. Overall, 9 patients received 2 doses of 1-2×10^6 cells/kg body weight, intravenously, 7 days apart. During follow-up, possible side effects and changes in patients' Crohn's disease activity index (CDAI) scores were monitored. Colonoscopies were performed at weeks 0 and 6, and mucosal inflammation was assessed by using the Crohn's disease endoscopic index of severity. Mesenchymal stromal cells isolated from patients with Crohn's disease showed similar morphology, phenotype and growth potential compared to MSCs from healthy donors. Importantly, immunomodulatory capacity was intact, as Crohn's disease MSCs significantly reduced peripheral blood mononuclear cell proliferation in vitro. Infusion of MSCs was without side effects, besides a mild allergic reaction probably due to the cryopreservant DMSO in 1 patient. Baseline median CDAI was 326 (224 to 378); 3 patients showed clinical response (CDAI decrease greater than or equal to 70 from baseline) 6 weeks post-treatment; conversely 3 patients required surgery due to disease worsening. The authors concluded that administration of autologous bone marrow derived MSCs
appears safe and feasible in the treatment of refractory Crohn's disease. No serious adverse events were detected during bone marrow harvesting and administration. These preliminary findings of a phase I study need to be validated by well-designed studies.

Gupta and colleagues (2012) noted that OA is a degenerative disease of the connective tissue and progresses with age in the older population or develops in young athletes following sports-related injury. The articular cartilage is especially vulnerable to damage and has poor potential for regeneration because of the absence of vasculature within the tissue. Normal load-bearing capacity and biomechanical properties of thinning cartilage are severely compromised during the course of disease progression. Although surgical and pharmaceutical interventions are currently available for treating OA, restoration of normal cartilage function has been difficult to achieve. Since the tissue is composed primarily of chondrocytes distributed in a specialized extra-cellular matrix bed, bone marrow stromal cells (BMSCs), also known as bone marrow-derived "mesenchymal stem cells" or "mesenchymal stromal cells", with inherent chondrogenic differentiation potential appear to be ideally suited for therapeutic use in cartilage regeneration. Bone marrow stromal cells can be easily isolated and massively expanded in culture in an undifferentiated state for therapeutic use. Owing to their potential to modulate local micro-environment via anti-inflammatory and immunosuppressive functions, BMSCs have an additional advantage for allogeneic application. Moreover, by secreting various bioactive soluble factors, BMSCs can protect the cartilage from further tissue destruction and facilitate regeneration of the remaining progenitor cells in situ. The authors described the advances made during the last several years in BMSCs and their therapeutic potential for repairing cartilage damage in OA.

General Reviews:

Rompe and colleagues (2008) stated that the management of Achilles tendinopathy is primarily conservative. Although many
non-operative options are available, few have been tested under controlled conditions. Surgical intervention can be successful in refractory cases. However, surgery does not usually completely eliminate symptoms and complications are not rare. The authors stated that further studies are needed to discern the optimal non-operative and surgical management of mid-portion Achilles tendinopathy.

In a systematic review, Rabago et al (2009) appraised existing evidence for prolotherapy, polidocanol, autologous whole blood, and PRP injection therapies for lateral epicondylosis (LE). Results of 5 prospective case series and 4 controlled trials (3 prolotherapy, 2 polidocanol, 3 autologous whole blood and 1 PRP) suggested each of the 4 therapies is effective for LE. In follow-up periods ranging from 9 to 108 weeks, studies reported sustained, statistically significant (p < 0.05) improvement on VAS and disease specific questionnaires; relative effect sizes ranged from 51% to 94%; Cohen's d ranged from 0.68 to 6.68. Secondary outcomes also improved, including biomechanical elbow function assessment (polidocanol and prolotherapy), presence of abnormalities and increased vascularity on ultrasound (autologous whole blood and polidocanol). Subjects reported satisfaction with therapies on single-item assessments. All studies were limited by small sample size. The authors concluded that there is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood, and PRP injections in the treatment of LE. However, rigorous studies of sufficient sample size, assessing these injection therapies using validated clinical, radiological and biomechanical measures, and tissue injury/healing-responsive biomarkers, are needed to determine long-term safety and effectiveness, and whether these techniques can play a definitive role in the management of LE and other tendonopathies.

van Ark et al (2011) reviewed the different injection treatments, their rationales and the effectiveness of treating patellar tendinopathy. A computerized search of the Medline, Embase, CINAHL and Web of Knowledge databases was conducted on
May 1, 2010 to identify studies on injection treatments for patellar tendinopathy. A total of 11 articles on 7 different injection treatments (dry needling, autologous blood, high-volume, PRP, sclerosis, steroids and aprotinin injections) were found: 4 RCTs, 1 non-RCT, 4 prospective cohort studies and 2 retrospective cohort studies. All studies reported positive results. The Delphi scores of the 4 RCTs ranged from 5 to 8 out of 9. Different and sometimes contradictory rationales were used for the injection treatments. The authors concluded that all 7 different injection treatments seem promising for treating patellar tendinopathy. Unlike the other injection treatments, steroid treatment often shows a relapse of symptoms in the long-term. They stated that results should be interpreted with caution as the number of studies is low, few high-quality studies have been conducted and the studies are hard to compare due to different methodology. They stated that more high-quality studies using the same cross-cultural reliable and valid outcome measure are needed, as well as further research into the pathophysiology.

Pak et al (2013) stated that mesenchymal stem cells from several sources (bone marrow, synovial tissue, cord blood, and adipose tissue) can differentiate into variable parts (bones, cartilage, muscle, and adipose tissue), representing a promising new therapy in regenerative medicine. In animal models, mesenchymal stem cells have been used successfully to regenerate cartilage and bones. However, there have been no follow-up studies on humans treated with adipose-tissue-derived stem cells (ADSCs) for the chondromalacia patellae. To obtain ADSCs, lipo-aspirates were obtained from lower abdominal subcutaneous adipose tissue. The stromal vascular fraction was separated from the lipo-aspirates by centrifugation after treatment with collagenase. The stem-cell-containing stromal vascular fraction was mixed with calcium chloride-activated PRP and hyaluronic acid, and this ADSCs mixture was then injected under ultrasonic guidance into the retro-patellar joints of all 3 patients. Patients were subjected to pre- and post-treatment magnetic resonance imaging (MRI) scans. Pre- and post-treatment subjective pain scores and physical therapy
assessments measured clinical changes. One month after the injection of autologous ADSCs, each patient’s pain improved 50 to 70%. Three months after the treatment, the patients' pain improved 80 to 90%. The pain improvement persisted over 1 year, confirmed by telephone follow-ups. Also, all 3 patients did not report any serious side effects. The repeated MRI scans at 3 months showed improvement of the damaged tissues (softened cartilages) on the patellae-femoral joints. The authors concluded that in patients with chondromalacia patellae who have continuous anterior knee pain, percutaneous injection of autologous ADSCs may play an important role in the restoration of the damaged tissues (softened cartilages). They stated that ADSCs treatment presents a glimpse of a new promising, effective, safe, and non-surgical method of treatment for chondromalacia patellae. These preliminary findings need to be validated by well-designed studies.

In summary, there is currently insufficient evidence to support the use of various blood product injection therapies (e.g., autologous blood, PRP, bone marrow plasma) for the treatment of tendonopathies.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

<table>
<thead>
<tr>
<th>CPT codes not covered for indications listed in the CPB:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0232T Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed.</td>
</tr>
<tr>
<td>38232 Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38241 Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
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Other CPT codes related to the CPB:
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
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**HCPCS codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>P9020</td>
<td>Platelet rich plasma, each unit</td>
</tr>
<tr>
<td>S9055</td>
<td>Procuren or other growth factor preparation to promote wound healing</td>
</tr>
</tbody>
</table>

**ICD-10 codes not covered for indications listed in the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>G80.0</td>
<td>Cerebral palsy</td>
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<tr>
<td>G80.9</td>
<td></td>
</tr>
<tr>
<td>K50.00</td>
<td>Crohn's disease [regional enteritis]</td>
</tr>
<tr>
<td>K50.919</td>
<td></td>
</tr>
<tr>
<td>L50.8</td>
<td>Other urticaria [chronic]</td>
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<tr>
<td>L63.0</td>
<td>Alopecia areata</td>
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<tr>
<td>L63.9</td>
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<tr>
<td>M15.0</td>
<td>Osteoarthritis</td>
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<td>M19.93</td>
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<tr>
<td>M22.40</td>
<td>Chondromalacia patellae</td>
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<td>M22.42</td>
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<tr>
<td>M26.62</td>
<td>Arthralgia of temporomandibular joint</td>
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<tr>
<td>M26.69</td>
<td>Other specified disorders of temporomandibular joint [dislocation or osteoarthritis]</td>
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<tr>
<td>M54.12</td>
<td>Radiculopathy, cervical region</td>
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<td>M76.50</td>
<td>Patellar tendinitis</td>
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<td>M76.52</td>
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<tr>
<td>M70.031</td>
<td>Other soft tissue disorders</td>
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<td>M79.9</td>
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<td>M84.459</td>
<td>Pathological fracture, hip</td>
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<td>M84.559</td>
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<td>M84.659</td>
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<td>M87.051</td>
<td>Idiopathic aseptic necrosis of femur [hip]</td>
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<td>M87.08</td>
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<td>M87.180</td>
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<td>Code</td>
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<td>S72.001 - S72.046</td>
<td>Fracture of neck of femur [hip]</td>
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<td>S76.301+ - S76.319+</td>
<td>Strain of muscle, fascia and tendon of the posterior muscle group at thigh level [hamstring injury]</td>
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<tr>
<td>S83.401+ - S83.409+</td>
<td>Sprains and strains of other specified sites of knee and leg [Gastrocnemius tear]</td>
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<td>S83.8X1+ - S83.8X9+</td>
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<td>S86.111+ - S86.119+</td>
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<tr>
<td>S86.211+ - S86.219+</td>
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<tr>
<td>S86.311+ - S86.319+</td>
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<tr>
<td>S86.811+ - S86.819+</td>
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<tr>
<td>S93.401+ - S93.499+</td>
<td>Sprain of ankle</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:


5. American College of Occupational and Environmental...


33. Griffin XL, Achten J, Parsons N, Costa ML. Platelet-rich therapy in the treatment of patients with hip fractures: A single centre, parallel group, participant-blinded,
44. Gottgens KW, Smeets RR, Stassen LP, et al. Treatment of Crohn's disease-related high perianal fistulas combining the mucosa advancement flap with platelet-rich plasma:


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0784
Blood Product Injections for Selected Indications

There are no amendments for Medicaid