Prolotherapy and Platelet Rich Plasma Therapies

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➲ Instructions for Use

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Related Commercial/Individual Exchange Policy
- Skin and Soft Tissue Substitutes

Community Plan Policy
- Prolotherapy and Platelet Rich Plasma Therapies

Medicare Advantage Policy
- Skin Substitutes Grafts/Cellular and Tissue-Based Products (Injections and/or Applications)

Application

UnitedHealthcare Commercial
This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange
This Medical Policy applies to Individual Exchange benefit plans.

Coverage Rationale

Due to insufficient evidence of efficacy, the following are unproven and not medically necessary for any condition or indication:
- Prolotherapy
- Platelet-rich plasma

Note: Refer to the Medical Policy titled Skin and Soft Tissue Substitutes for information related to amnion-derived fluid injections/therapy.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed

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HCPCS Code	Description
G0460	Autologous platelet rich plasma (PRP) or other blood-derived product for nondiabetic chronic wounds/ulcers (includes, as applicable: administration, dressings, phlebotomy, centrifugation or mixing, and all other preparatory procedures, per treatment)
G0465	Autologous platelet rich plasma (PRP) or other blood-derived product for diabetic chronic wounds/ulcers, using an FDA-cleared device for this indication, (includes as applicable: administration, dressings, phlebotomy, centrifugation or mixing, and all other preparatory procedures, per treatment)
M0076	Prolotherapy
P9020	Platelet rich plasma, each unit

Description of Services

Prolotherapy (proliferative therapy), also known as nonsurgical and ligament and tendon reconstruction and regenerative joint injection, is an orthopedic procedure that stimulates the body's healing processes to strengthen and repair injured and painful joints and connective tissue. Prolotherapy is injection of any substance (e.g., dextrose, saline, sarapin, procaine or lidocaine) that promotes growth of normal cells, tissues, or organs by stimulating the body's natural healing mechanisms to lay down new tissue in the weakened area. This is done by a very directed injection to the injury site, "tricking" the body to repair again. The mild inflammatory response, which is created by the injection, encourages growth of new, normal ligament or tendon fibers, resulting in a tightening of the weakened structure. Additional treatments repeat this process, allowing a gradual buildup of tissue to restore the original strength to the area. In the last several years, newer formulas include platelet-rich plasma (PRP) and autologous (from the same person) adult stem cell sources, typically taken from bone marrow or adipose (fat) tissue. Each treating physician tailors the selection of the appropriate formula according to the individual's need. The three types of prolotherapy are (1) growth factor injection prolotherapy; (2) growth factor stimulation prolotherapy; and (3) inflammatory prolotherapy. (AOAPRM, 2020; AAOM, 2020)

PRP is an autologous blood preparation with a high platelet concentration and concentrated platelet-derived growth factors and other cytokines, which may be the primary contributors to the benefits of PRP therapy. Introducing PRP to tissues with low healing potential, these growth factors and cytokines may stimulate regeneration and promote tissue repair. PRP preparations are not standardized and exhibit wide variability in platelet and white blood cell concentrations. It is unclear how these variations in PRP composition may affect clinical outcomes. (Hayes, 2021)

Clinical Evidence

Prolotherapy

The available studies on prolotherapy are limited to low-quality with a lack of prospective randomized comparison group that have cohorts that are matched, include short- to medium-term follow-up, and with no significant functional improvement compared with placebo. Also, there is a lack of standardized protocols to utilize either prolotherapy or PRP. Heterogeneous trials cannot draw any rational conclusions. Additional studies are needed to further define treatment parameters and determine whether a clinically significant improvement is achieved.

Low Back Pain

Yildirim Uslu (2024) conducted a retrospective study to compare the effectiveness of dextrose and steroid injections for low back pain related to superior cluneal nerve (SCS) entrapment neuropathy. This study included 16 participants who underwent ultrasound-guided steroid injections and 17 participants who underwent ultrasound-guided dextrose injection with the diagnosis of SCS neuropathy. Participants were evaluated with VAS and Roland-Morris Disability Questionnaire (RMDQ) scores before and after the procedure at week one. Participants with mechanical low back pain radiating to the iliac crest and hip for more than three months, tenderness observed on palpation in the posterior iliac crest, and numbness or increased pain complaints in the nerve distribution area on palpation were included in the diagnostic injection test with the preliminary diagnosis of SCS neuropathy. Five cc's of procaine were injected by targeting the apex of the posterior iliac crest with the in-plane technique under ultra-sound guidance. The test was considered positive in participants whose pain was relieved by 50% or more within 10 minutes after the injection. Participants with a positive diagnostic injection test, aged between 18 and 60 years, and pain unresponsive to oral medical treatments were included in the study. Nine individuals with concomitant lumbar radiculopathy, malignancy, chronic disease, or history of inflammatory diseases were excluded from the study. While VAS and RMDQ scores were similar in both groups before the procedure, VAS and RMDQ scores at week one was lower in the dextrose group. The author concluded that perineural dextrose injection appears to be a safe and effective alternative to steroid injections in the treatment of SCS

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neuropathy. This study is limited by its retrospective observations, small sample size, and short duration of follow-up. Well designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Chen and Suputtitada (2023) performed an observational study aimed to compare ultrasound-guided (USG) prolotherapy with 5% dextrose in water (D5W) in the multifidus muscle to USG mechanical needling and sterile water injections for the treatment of lumbar spinal stenosis (LSS). The data were extracted from the medical records of aging patients with LSS who received USG D5W in the multifidus muscle or USG mechanical needling and sterile water injections for the treatment of LSS by the first author. Low back pain (LBP) or axial pain and leg pain or radicular pain were assessed by the visual analog scale (VAS), and gait ability with walking distance was obtained at six different time points. Among the 211 older patients who were diagnosed with LSS, 104 received USG mechanical needling and sterile water injections over the course of 4 weeks, while the other 107 received D5W in the multifidus muscles in a single session. Chronic LBP, radiating pain, and the ability to walk all greatly improved at one and three months after the intervention compared with VAS measures taken at the start. Patients who underwent mechanical needling with injections of sterile water performed consistently better on all measures at one, three and six months than those who received prolotherapy in the multifidus muscles. The authors concluded that after receiving USG mechanical needling and sterile water, patients with LSS reported improvements in LBP, radicular pain, and ability to walk for at least 6 months. Prolotherapy with D5W in the multifidus muscle has a moderate effect for only 3 months. The authors stated that this study has several limitations. This was a retrospective examination of data from a single institution and an experienced injector, resulting in a potentially biased sample and restricted generalizability. Under ultrasound guidance, a needle must be inserted precisely to remove calcification and fibrosis from the facet joints, medial branch, and multifidus muscles. In addition, mechanical removal of calcification and fibrosis near the neurovascular bundle in these regions requires extreme caution. Long-term exposure, typically to D5W used in prolotherapy, is another area that requires investigation. In addition, calcification and fibrosis continue to exist because of degenerative joint diseases. It will be challenging to inject regenerative agents in the future. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Pereira Pires et al. (2023) conducted a randomized, blinded clinical trial with in-office participants with LBP. Participants with chronic LBP (> 12 weeks) who were nontraumatic and unresponsive to at least 1 month of physical therapy were selected. All participants were followed up at a return visit at 1, 3, and 6 months for pain assessment using validated pain questionnaires and scales. Nineteen participants were included in the conservative group, and 19 were included in the glucose group, with the majority being women (57.9%). The participants were between 47 and 59 years of age (39.5%), mixed race (76.33%), and married or in a committed relationship (73.7%) and had completed the study for 5.2 years. Overall, the mean body mass index (BMI) was 27.3 ±4.4 and higher in the conservative group (mean, 28.0 ±4.7). The groups had differences in VAS scores, with median and amplitude values close to each other between the time points evaluated and increasing values in the glucose group, which had higher values for this scale at the third evaluation ($p = 0.031$). When comparing the Roland-Morris Scale scores between the groups, a significant difference was observed only in the 3-m assessment ($p = 0.021$). In the follow-up assessment, both groups had significant improvement between T0 and the other assessment time points ($p < 0.05$) in all evaluations. The authors concluded that both groups improved on the evaluated scales during follow-up. Overall, no effects were attributable to the glucose components or the prolotherapy protocol. Limitations include the lack of standardization of the most effective dose; these values are not always available in other studies. In addition, the duration and frequency of follow-up may result in underreporting pain scores, and effective treatment may be complex without a multimodal and multidisciplinary approach. Further research is needed to determine the clinical relevance of these findings.

Sirh et al. (2022) conducted a retrospective chart review study aimed to evaluate the importance of the quadratus lumborum muscle and introduce an effective landmark-based blind injection technique combining trigger point injection (TPI) with prolotherapy for treating quadratus lumborum trigger points and enthesopathy. Adult patients (n = 17) with lower back and/or buttock pain were placed in the lateral decubitus position. Patients were, on average, aged 47.35 years (range, 28-70 years); 11 were men, and six were women. The duration of symptom onset ranged from 3 days to 3 years. The mean pain duration was 163.2 ±296.6 days. Among the 17 patients, 10 had bilateral lesions, and seven had unilateral lesions. Patients were not treated bilaterally at each treatment session. The quadratus lumborum muscle was palpated to accurately locate its lesions, including trigger points, taut bands, and tendon lesions, after five key landmarks had been identified. A newly designed, 60- to 90-mm 28G thin hypodermic needle was inserted at the tender points. The needle was typically advanced until its tip touched the transverse process to treat myofascial trigger points and tendon lesions in the iliolumbar and lumbocostal fibers, excluding superficial trigger points of the iliocostal fibers. Subsequently, lidocaine (0.5%) or a mixture of lidocaine (0.5%) and dextrose (12.5%-15%) was injected. The pretreatment VAS score in all 17 patients decreased from ≥ 4-8/10 (mean, 5.588) to 0-1/10 (mean, 0.294) after completion of all treatments. The total number of treatments was one to four in acute and subacute cases and two to eight in chronic cases. The mean follow-up period was 73.5 days (treatment period: range, 4 to 43 days and at least 60 days of follow-up). The authors concluded that TPI with prolotherapy for the treatment of trigger points and myofascial pain in the quadratus lumborum is safe and

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effective and can be used with or without steroids, fluoroscopy, or ultrasound guidance. This study has certain limitations. First, this study did not include an adequate number of patients for statistical comparative analysis. Second, the data were retrospectively reviewed. Additionally, this study is single arm, without a control group, and did not assess differences between acute, subacute, and chronic cases. The other limitation is that it lacked long-term follow-up. A larger, controlled, prospective study is needed in the future to evaluate the effects of the TPI an integrated injection technique, in patients with combined problems of various structures and the quadratus lumborum.

Osteoarthritis

Ustun and Çağlar (2023) conducted a single-center, parallel-group, randomized controlled, single-blinded study aimed to compare the therapeutic efficacy of prolotherapy and paraffin wax (PW) in hand osteoarthritis (OA). Participants with bilateral hand OA were divided into PW and prolotherapy treatment groups. The PW group was treated 5 days per week for 2 weeks. The prolotherapy group received an injection of dextrose solution into the ligaments of painful joints once weekly for 3 weeks. The VAS, Duruoz Hand Index (DHI) scale, hand dynamometer for grip strength, and pinch meter for lateral pinch were used for baseline and posttreatment follow-up assessments. Overall, 42 participants were included. The VAS scores decreased in both the PW and prolotherapy groups ($p = 0.024$ and $p = 0.014$). Baseline and third-month posttreatment VAS scores did not significantly differ ($p = 0.581$). The DHI scores improved in both groups ($p < 0.001$ and $p < 0.001$) and were higher in the prolotherapy than in the PW group ($p = 0.042$). Right- and left-hand grip strength increased in the PW and prolotherapy groups ($p < 0.001$, $p = 0.001$; $p = 0.013$, $p = 0.002$, respectively). The authors concluded that both treatment methods were effective regarding pain and grip strength; however, prolotherapy improved the hand functions more significantly. This study has limitations. First, it has a relatively small sample size. Second, it did not include male participants; thus, it may be difficult to generalize the findings to both sexes. Also, the study groups' baseline DHI scores were different, and the follow-up duration was relatively short. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Waluyo et al. (2023) conducted a systematic review to evaluate the efficacy of dextrose prolotherapy (DPT) compared with that of other interventions in the management of OA. Electronic databases, including PubMed, Google Scholar, Cochrane, and BioMed Central, were searched from inception to October 2021. Randomized controlled trials (RCTs) that compared the use of DPT with other interventions (injection, placebo, therapy, or conservative treatment) in the treatment of OA were included. Potential articles were screened for eligibility, and data were extracted by all authors. Risk of bias was assessed using the Cochrane Risk of Bias tool. Study population, methods, and results data were extracted and tabulated by three authors. Twelve studies reported that DPT was as effective or even more effective in improving functional outcomes than other interventions, while others found that hyaluronic acid (HA), platelet-rich plasma (PRP), erythropoietin, and autologous conditioned serum were more effective. Fourteen studies assessed the effectiveness of DPT, and 10 of them reported that DPT was more effective in reducing pain than other interventions. The authors concluded that DPT in OA confers potential benefits for pain and functional outcomes, but this systematic review found that the studies to date are at high risk of bias. Well-designed, adequately powered, prospective, controlled clinical trials of DPT in the management of OA are needed to further describe safety and clinical outcomes (or efficacy).

Gul et al. (2020) performed an RCT to determine the efficacy of prolotherapy injections vs exercise in the treatment of OA secondary to developmental dysplasia of the hip. The study consisted of 41 participants divided into two groups: treated with prolotherapy ($n = 20$) and exercise (control group; $n = 21$). Clinical outcomes were evaluated at baseline, 3 weeks, 3 months, 6 months, and a minimum of 1 year of follow-up. Prolotherapy injection recipients outperformed exercise controls for VAS pain change score at 6 months (-4.6 ±2.6 vs -2.8 ±2.5; $p = 0.016$) and 12 months (-4.5 ±2.4 vs -2.9 ±2.5; $p = 0.017$) and for Harris Hip score at 6 months (24.2 ±14.0 vs 14.8 ±12.4; $p = 0.007$) and 12 months (24.3 ±13.4 vs 16.5 ±11.3; $p = 0.018$). The authors concluded that prolotherapy is superior to exercise and may delay surgery. Limitations include a small sample size, which makes it difficult to decide whether these conclusions can be generalized to a larger population. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes. Further investigation is needed before the clinical usefulness of this procedure is proven.

Hauser et al. (2016) conducted a systematic review to review dextrose (d-glucose) prolotherapy efficacy in the treatment of chronic musculoskeletal pain. Electronic databases, including PubMed, Healthline, OmniMedicalSearch, Medscape, and Embase, were searched from 1990 to January 2016. Prospectively designed studies that used dextrose as the sole active prolotherapy constituent were selected. Two independent reviewers rated studies for quality of evidence using the Physiotherapy Evidence Database assessment scale for RCTs and the Downs and Black evaluation tool for non-RCTs for level of evidence using a modified Sackett scale and for clinically relevant pain score difference using minimal clinically important change criteria. Study population, methods, and results data were extracted and tabulated. Fourteen RCTs, one case-control study, and 18 case series studies met the inclusion criteria and were evaluated. Pain conditions were clustered into tendinopathies, OA, spinal/pelvic, and myofascial pain. The RCTs were high-quality Level 1 evidence (Physiotherapy Evidence Database ≥ 8) and found dextrose injection to be superior to controls in (1) Osgood-Schlatter disease, lateral epicondylitis of the elbow, traumatic rotator cuff injury, KOA, finger OA, and myofascial pain and (2)

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biomechanical but not subjective measures in the temporomandibular joint (TMJ) and comparable in a short-term RCT but superior in a long-term RCT in LBP. Many observational studies were of high quality and reported consistent positive evidence in multiple studies of tendinopathies, KOA, sacroiliac pain, and iliac crest pain that received RCT confirmation in separate studies. Eighteen studies combined self-rating (subjective) of individuals with psychometric, imaging, and/or biomechanical (objective) outcome measurement and found both positive subjective and objective outcomes in 16 studies and positive objective but not subjective outcomes in two studies. All 15 studies solely using subjective or psychometric measures reported positive findings. The authors concluded that the use of DPT is supported for treatment of tendinopathies, knee and finger joint OA, and spinal/pelvic pain due to ligament dysfunction. Efficacy in acute pain, as first-line therapy, and in myofascial pain cannot be determined from the literature. Further research with RCTs is needed to validate these findings.

In a systematic review and meta-analysis, Hung and colleagues (2016) compared the effectiveness of DPT vs control injections and exercise in the management of OA pain. PubMed and Scopus were searched, from the earliest record until February 2016, and one single-arm study and five RCTs were included (n = 326). The investigators estimated the effect sizes of pain reduction before and after serial dextrose injections and compared the values between DPT, comparative regimens, and exercise 6 months after the initial injection. Regarding the treatment arm using DPT, the effect sizes compared with baseline were 0.65, 0.84, 0.85, and 0.87 after the first, second, third, and fourth or more injections, respectively. The overall effect of dextrose was better than that of control injections, demonstrating superiority when compared with local anesthesia and exercise. An insignificant advantage of dextrose over corticosteroids was observed, which was only estimated from one study. The authors concluded that dextrose injections decreased pain in individuals with OA but did not exhibit a positive dose-response relationship following serial injections. DPT was found to provide a better therapeutic effect than exercise, local anesthetics, and probably corticosteroids when individuals were retested 6 months following the initial injection. The researchers also noted that the effect of prolotherapy did not differ between hand OA and KOA. This study has several drawbacks, including but not limited to the minimal number of trials eligible for meta-analysis as well as heterogeneity in the patient populations, injection protocols, comparative regimens, and outcome assessment.

Knee

Teymouri et al. (2025) conducted a randomized controlled trial (RCT) aimed to compare dextrose prolotherapy (DPT) with intra-articular normal saline injection (IA-NS) to treat KOA in terms of effectiveness and patient-reported outcomes. The study was a double-blind RCT with an allocation ratio of 1:1. The authors used block randomization to assign participants to each treatment arm. Participants with a VAS of at least four for pain, and a Kellgren-Lawrence scale of grade two or three (mild or moderate disease) were selected and assessed according to eligibility criteria. The participants received either 5 ml of 50% dextrose water or 5 ml of 0.9% sodium chloride. The participants were followed up at two, four, and eight weeks. All results were reported with a confidence interval of 95%, and a p-value of less than 0.05 was considered significant. Overall, 55 patients were included in the study, however, only 50 completed the study process (25 patients in each treatment arm). The mean age of patients with knee OA was 62.98 ±5.37, ranging from 55 to 74 years. The authors observed improvement in both groups in terms of knee pain, function, and knee extension degree at all follow-up visits ($p < 0.001$). Although DPT was associated with better results than IA-NS, the difference was not statistically significant ($p > 0.05$). The adverse events were limited to injection-site pain and ecchymosis, which resolved by week four. The authors concluded that although they achieved slightly better results with DPT, this treatment technique was not clinically or statistically superior to IA-NS in terms of knee pain and function in the short-term. Therefore, both DPT and IA-NS are effective and well tolerated treatment options for KOA. Limitations of this study include a small sample size and short duration of follow-up. Further research with more RCTs is needed to validate these findings.

A systematic review conducted by Ewart et al. (2024) published by the U.S. Department of Veterans Affairs Health Services Research and Development Evidence Synthesis Program, funded in part to inform the Agency for Healthcare Research and Quality and the Veterans Affairs' understanding of prolotherapy, it was determined that the overall evidence base for prolotherapy was generally limited by methodological concerns and the inconsistent reporting of adverse events. Regarding KOA, DPT demonstrated little to no benefit for pain-related function or physical performance when compared to normal saline injections.

Mohamadi Jahromi et al. (2024) conducted a single-center, double-blind, parallel-group, RCT to compare the effectiveness of intra-articular and peri-articular DPT in patients with KOA without effusion. A total of 51 individuals including 27 cases (12 males, 15 females; mean age: 55.7 ±5.2 years; range, 38 to 70 years) in Group A and 24 cases (nine males, 15 females; mean age: 54.7 ±4.6 years; range, 38 to 70 years) in Group B were recruited. Group A received intra-articular DPT, while Group B received peri-articular DPT. Treatment was administered two times with two-week intervals. The VAS, Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Oxford Knee Scale (OKS) questionnaires were filled at baseline, and four and eight weeks after first injection. At four and eight weeks, the VAS, OKS, and WOMAC scores improved from baseline in both groups. There was no difference in the WOMAC and OKS

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scores between the two methods. The VAS scores showed superiority of intra-articular method ($p < 0.05$). The authors concluded that both peri-articular and intra-articular DPT were effective in individuals with KOA. There was no superiority in terms of functional improvement between the two groups. However, intra-articular prolotherapy was more effective in decreasing pain in these patients. This RCT has limitations. The sample size was calculated as 25. Although the authors selected 60 patients with KOA without effusion (30 in each group), nine participants (n = 3 in the intra-articular group and n = 6 in the peri-articular group) withdrew from the study and did not continue the injection due to poor attendance to follow-up visits (i.e., living in distant locations). The authors also planned two injection sessions, however a previous study with more sessions showed different results from their study. Thus, more injection sessions would be preferable. Furthermore, the follow-up period in this study was relatively short; therefore, further long-term studies are warranted. Finally, the authors followed participants by subjective assessments using mentioned questionnaires without evaluating the radiological changes after the injections. Lack of a placebo or control group was another limitation. Further multi-center, large-scale, long-term studies including control groups using objective assessment methods are needed.

Cheng et al. (2024) performed a systematic review and network meta-analysis to investigate the effects of the combination of pharmacological agents and exercise on KOA. RCTs that investigated the efficacy of pharmacological agents combined with exercise for KOA were searched in PubMed, Embase, and Cochrane Library. The network meta-analysis was performed in the frequentist framework. Standardized mean difference (SMD) with 95% CI was estimated for pain and function. Grading of recommendations, assessment, development, and evaluations were used to evaluate the certainty of evidence. In total, 71 studies were included. The combination therapy outperformed pharmacological or exercise therapy alone. Among the various pharmacological agents combined with exercise, mesenchymal stem cell injection was ranked the best for short-term pain reduction (SMD, -1.53; 95% CI, -1.92 to -1.13, high certainty), followed by botulinum toxin A, dextrose, and PRP. For long-term pain relief, DPT was most optimal (SMD, -1.76; 95% CI, -2.65 to -0.88, moderate certainty), followed by mesenchymal stem cells, platelet rich in growth factor, and PRP. The authors concluded that for patients undergoing exercise therapies, mesenchymal stem cells, dextrose, PRP, platelet rich in growth factor, and botulinum toxin A may be the optimal agents for the treatment of KOA. Limitations include small sample sizes and a short duration of follow-up. Further research is needed to determine the clinical relevance of these findings.

Fu et al. (2024) conducted a double-blinded RCT aimed to compare the efficacy of intra-articular prolotherapy (IG) combined with periarticular perineural injection (PG) in the management of KOA. A total of 60 participants with the diagnosis of KOA were included in this double-blinded RCT. The inclusion criteria were as follows: (1) age 48 to 80 years; (2) the diagnosis of KOA; (3) grade 2 and 3 on the Kellgren-Lawrence grading scale; and (4) the pain, crepitation, and knee joint stiffness continuing for a minimum of 3 months' duration or longer. The main exclusion criteria were as follows: (1) any infection involving the knee skin or (2) history of any influencing factors of disease. All participants were divided into three groups and received either IG, PG, or I + PG under ultrasound guidance, and the 2-, 4-, and 8-week follow-up data for participants were available (IG, n = 20; PG, n = 20; I + PG, n = 20). The VAS, WOMAC, and pressure pain threshold (PPT) were used as outcome measures at baseline and 2, 4, and 8 weeks. No statistically significant differences were observed in terms of age; sex; BMI; duration of current condition; and baseline assessments of pain intensity, WOMAC scores, and PPT. After treatment, the improvement of VAS activity, WOMAC, and PPT values was observed compared with prior to treatment in all groups ($p < 0.05$). At 4 and 8 weeks after treatment, the VAS and WOMAC scores of I + PG were lower than those of PG or IG, and the difference was statistically significant ($p < 0.05$). The PPT values of PG and I + PG were improved compared with those of IG at 2, 4, and 8 weeks after treatment. The authors concluded that the USG I + PG of 5% glucose seemed to be more effective in alleviating pain and improving knee joint function than single therapy in the short term. Clinical rehabilitators could clinically try this combination of I + PG to improve clinical symptoms in patients with KOA. Limitations include a small sample size and short observation time. Long-term evaluations of the results and prospective, randomized studies are still needed. In addition, the lack of a comparison group limits the conclusions that can be reached from this study.

Khateri et al. (2024) performed a systematic review and meta-analysis to assess the impact of DPT on individuals diagnosed with KOA. The findings of the study revealed that when the studies using the WOMAC were combined, individuals with KOA who received prolotherapy experienced an improvement in function compared with those who received other treatments [SMD, 0.20; 95% CI (1), -0.11 to 0.51; p value SMD, 0.221; I^2, 78.49%; p-heterogeneity < 0.001]. Additionally, a decrease in mean pain and stiffness was observed in individuals who received prolotherapy vs those who received other treatments or a placebo (SMD, -0.95; 95% CI, -1.14 to -0.76; p value SMD < 0.001; I^2, 59.35%; p-heterogeneity, 0.070 vs SMD, -0.21; 95% CI, -0.32 to -0.10; p value SMD < 0.001; I^2, 88.11%; p-heterogeneity < 0.001). Furthermore, based on VAS score, a reduction of 0.81 units out of 10 in mean pain was observed in individuals with KOA who received prolotherapy (SMD, -0.81; 95% CI, -5.63 to 4.10; p value SMD, 0.693; I^2, 48.54%; p-heterogeneity, 0.08). The authors concluded that DPT exhibits promising effectiveness in reducing joint pain and stiffness as well as improves functional performance in patients with KOA. Furthermore, it is recommended that forthcoming studies incorporate multicenter trials with a larger number of participants and follow-up periods to guide decisions concerning the duration of prolotherapy's effects.

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Yildiz et al. (2023) conducted a randomized, prospective study to compare the efficacy of HDP with conventional physiotherapy (CPT) in improving symptoms in female participants with KOA. This study included 60 participants with a diagnosis of KOA. The participants were randomly assigned to the HDP (n = 30) and CPT (n = 30) groups. The participants in the HDP group were treated with a dextrose injection into the knee joint (25% dextrose) and around the knee (15% dextrose) in two sessions for 1 month, while those in the CPT group received a hot pack, transcutaneous electrical nerve stimulation, and therapeutic ultrasound in five sessions a week for 4 weeks. Prior to commencing the treatment and at 1 and 3 months post treatment, all participants were evaluated using the VAS, WOMAC, goniometric measurement of active knee range of motion (ROM), 50-m walking test, and isokinetic knee muscle strength measurements. No statistically significant differences were observed between the two groups regarding the demographic characteristics prior to treatment ($p > 0.05$). However, at 1 and 3 months post treatment, the scores of all the outcome parameters were improved in the HDP group compared with the CPT group ($p < 0.05$ for all). In both groups, improvement was observed in the VAS scores, WOMAC total values, and ROM following the treatments, with the greatest improvement observed in the HDP group ($p < 0.001$). The isokinetic quadriceps peak torque measurements were increased in both groups following treatment. All scores exhibited improvement in the HDP group at both 1 and 3 months post treatment. The authors concluded that the results of this randomized, prospective study demonstrate that both HDP and CPT are effective treatment modalities to relieve pain and increase functionality and strength in patients with KOA. However, greater improvements in pain and functionality can be achieved with prolotherapy. The present study has several limitations. First, the present study did not examine whether the participants with OA performed the home-based exercise program regularly. Secondly, the participants were not questioned about their history of drug use. Thirdly, patients with mild and severe OA (Kellgren-Lawrence grade 1 and 4) were excluded from the study. Finally, the 3-month period of treatment may not have been sufficient for a definitive evaluation of muscle performance. Further investigation is needed before the clinical usefulness of this procedure is proven.

Cortez et al. (2022) conducted a systematic review to compare the effectiveness of DPT with other substances for pain relief in individuals with primary KOA. The literature screening was done in January 2021 through MEDLINE (PubMed), Embase, and the database of the National Institutes of Health based on the following criterion: randomized clinical trials that subjected individuals with primary KOA who underwent treatment with DPT and other substances for pain relief. Paired reviewers independently identified 3,381 articles and included eight trials that met the eligibility criteria. According to the findings of this review, individuals who underwent DPT had improvements between baseline and posterior assessments and when compared with individuals who received saline injections; however, when compared with individuals who received other substances, the results were not clear. The authors concluded that although DPT is a useful treatment method by itself, it is still not possible to clearly affirm that it is superior or inferior to its counterparts. Further studies are needed to bring more evidence to the field. The findings of this study need to be validated by well-designed studies. Further investigation is needed before the clinical usefulness of this procedure is proven.

Hsieh and Lee (2022) completed a prospective, randomized, double-blinded trial to determine whether intra-articular co-injection with hypertonic dextrose improves the outcome of HA prolotherapy in KOA. In total, 104 participants who fulfilled the American College of Rheumatology clinical and radiographic criteria for KOA, with a Kellgren-Lawrence grade of 2 or 3, were recruited (n = 104). The participants were block randomized to the treatment (HA and hypertonic dextrose) or control (HA and normal saline) group. USG knee intra-articular injections were administered once a week for 3 weeks. The primary outcomes were performance-based physical function measures (regular and fastest walking speed, stair climbing time, and chair rising time), and the secondary outcomes were the WOMAC and Knee Injury and Osteoarthritis Outcome Score (KOOS). The outcome measures were assessed before the injections and at 1 week and 1, 3, and 6 months after the injections. The data were analyzed through repeated-measures analysis of covariance. Significant intergroup difference-in-differences favoring the treatment group were observed for improvements in stair climbing time (-1.6; 95% CI, -8.56 to 4.16; $p = 0.38$) and WOMAC physical function (-21.2; 95% CI, -126.05 to 103.83; $p = 0.045$) at 6 months. The group × time interaction effects favored the treatment group for regular ($p = 0.001$) and fastest walking speed ($p = 0.001$) and chair rising time ($p = 0.038$); WOMAC stiffness ($p < 0.001$) and physical function ($p = 0.003$); and the KOOS for pain ($p = 0.035$), other symptoms ($p = 0.022$), and quality of life ($p = 0.012$). The authors concluded that compared with HA plus normal saline co-injections, HA plus dextrose co-injections resulted in more significant improvements in stair climbing time and physical function at 6 months, effectively decreased pain, and improved physical function and physical functional performance from 1 week to 6 months. HA plus dextrose co-injections could be a suitable adjuvant therapy for patients with KOA. Limitations to this study include a lack of a control, small sample size, and short-term follow-up. The findings of this study need to be validated by well-designed studies.

A systematic review and meta-analysis were performed by Wee et al. (2021) to summarize the evidence for DPT in KOA. The authors searched PubMed and Embase from inception to September 2020. All publications in the English language were included, without demographic limits. Randomized clinical trials comparing the effects of any active interventions or placebo vs DPT in individuals with KOA were included. Potential articles were screened for eligibility, and data were extracted independently. The risk of bias was assessed using the Cochrane Risk of Bias tool. A meta-analysis was

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performed on clinical trials with similar parameters. The Strength of Recommendation Taxonomy was used for evaluating the strength of recommendations. In total, 11 articles (n = 837) met the search criteria and were included. The risk-of-bias analysis revealed two studies to be of low risk. The overall effectiveness was calculated using a meta-analysis method. Prolotherapy was no different from PRP on the pain subscale at the 6-month time point. Prolotherapy was inferior to PRP at 6 months [mean difference (MD), 0.45; 95% CI, 0.06-0.85; p = 0.03] on the stiffness subscale. Prolotherapy was found to be safe, with no major adverse effects. The authors concluded that prolotherapy in KOA confers potential benefits for pain, but the studies are at high risk of bias. Based on two well-designed studies, DPT may be considered in KOA (strength of recommendation B). This treatment is safe and may be considered in patients with limited alternative options (strength of recommendation C). Limitations include heterogeneity in terms of study design, injection sites, and techniques; varying concentrations of DPT; and outcome measures used. Meta-analysis was limited to only two studies due to this heterogeneity. Well-designed, comparative studies are needed to further describe safety and clinical outcomes.[Authors Rabago et al. (2013), Rahimzadeh et al. (2014), and Sit et al. (2020), previously cited in this policy, are included in this review.]

Bae et al. (2020) performed a systematic review and meta-analysis to evaluate the effectiveness of prolotherapy compared with that of alternative treatment options for chronic musculoskeletal pain. Alternative options included steroid injections, saline injections, PRP injections, exercise, and extracorporeal shock wave therapy (ESWT). The review included 10 RCTs, involving a total of 750 individuals, including a prolotherapy group and comparator groups using exercise, saline, PRP, and steroid injection. The primary outcome was pain score change during daily life. Pain scores from 6 months to 1 year after DPT were reduced compared with those with saline injection (SMD, -0.44; 95% CI, -0.76 to -0.11; p = 0.008) and exercise (SMD, -0.42; 95% CI, -0.77 to -0.07; p = 0.02). No difference in pain scores for prolotherapy compared with PRP or steroid injection was observed. The authors concluded that prolotherapy is a more effective treatment for chronic pain than saline injection or exercise. The available evidence is limited, with overall poor-quality methodology and design and diversity in reporting outcome measures. Therefore, no conclusions can be made regarding the relative efficacy, effectiveness, or safety of treatment.

Rahimzadeh et al. (2018) investigated the effect of injecting intra-articular PRP vs prolotherapy on pain and function in KOA. In this randomized, double-blinded trial, 42 participants with KOA received intra-articular injections. “Patients in the PRP therapy group received 7 mL PRP solution and those in the PRL group received 7 mL 25% dextrose. Using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), levels of pain and knee function were evaluated and recorded for each patient immediately prior to the first injection as well as at 1 month (immediately prior to the second injection), 2 months (a month after the second injection), and 6 months later. During the first and second months, a rapid decrease in the overall WOMAC score was observed in both groups. The overall WOMAC score increased at the sixth month but was lower than the overall WOMAC score in the first month. Statistical analysis indicated that the overall WOMAC score significantly decreased in both groups of patients over 6 months.” The authors concluded that this study suggests that (1) a positive change in WOMAC score indicated an improvement in the quality of life of participants receiving either injection after the first injection and (2) PRP is more effective than prolotherapy in the treatment of KOA. However, they acknowledge that this study has limitations, including the “lack of a control group receiving placebo; lack of morphological assessment of cartilage, soft tissue, and structures in and around the knee joint; small sample size; and limited timeframe for patient assessment.”

Fingers

Khan et al. (2023) performed a systematic review and meta-analysis to evaluate the treatment effect and role of HA for available soft tissue indications. A search was conducted for all RCTs involving the use of HA for soft tissue indications. Two reviewers independently screened articles for eligibility and extracted data from included studies for analysis. Risk of bias for all included studies and pooled outcomes were assessed using a fixed-effects model. Outcomes (e.g., function, pain relief) were categorized to short-term (< 6 weeks, 6-12 weeks) and mid-term (> 12 weeks) data. The authors present effect estimates as MDs and SMDs and present the estimate of effect of HA for available indications in relation to available comparators. Of a total of 6,930 articles screened, 19 RCTs (n = 1,629) were eligible and included in this review. HA was evaluated across a variety of soft tissue indications, including rotator cuff disease, elbow pain, ankle sprains, Achilles tendinopathy, patellar tendinopathy, and trigger finger. Of the 19 RCTs, 11 were placebo controlled, and nine used active comparators (PRP, cortisone, prolotherapy, or ESWT). The pooled treatment effect of HA across most soft indications against placebo and active comparators demonstrated benefit in short-term pain of < 6 weeks (MD VAS, 2.48; 95% CI, 2.31-2.65) and 6 to 12 weeks (MD VAS, 2.03; 95% CI, 1.86-2.20). Relief of mid-term pain of > 12 weeks from administration (MD VAS, 3.57; 95% CI, 3.35-3.78) also favored HA over comparators across indications. High heterogeneity was present with rotator cuff (10 trials; I^2, 94%) and elbow tendinopathy (two trials; I^2, 99%). The authors identified uncertain benefit for trigger finger (two trials; I^2, 67%). Heterogeneity for ankle sprains, patellar tendinopathy, and Achilles tendinopathy could not be assessed, as they only had one trial each. The authors concluded that this systematic review and meta-analysis support HA’s efficacy in the treatment of a variety of soft tissue indications. Understanding the relative effects of HA to other injectable modalities requires additional large trials. This systematic review and meta-analysis has

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several limitations. Many of the included studies were of small sample sizes, and for some indications, only one or two RCTs provided information. Assessments for certain indications at various follow-up periods were not possible. Additionally, the authors identified a significant degree of heterogeneity across most outcomes, despite controlling for indication and comparator, thus limiting the ability to perform subgroup analyses on HA vs other injection types. This supports the need for large, high-quality studies to provide reliable estimates of effect for HA across various soft tissue indications. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Jahangiri et al. (2014) compared the advantages of prolotherapy in the treatment of first carpometacarpal OA with those of corticosteroid local injection in a double-blinded RCT. Sixty participants (60 hands) with OA of the first carpometacarpal joint were assigned equally to two groups. For the corticosteroid group, after two monthly saline placebo injections, a single dose of methylprednisolone acetate 40 mg (0.5 ml) mixed with 0.5 ml of 2% lidocaine was injected. For the dextrose group, 0.5 ml of 20% dextrose was mixed with 0.5 ml of 2% lidocaine, and the injection was repeated monthly for 3 months. Pain intensity, hand function, and the strength of lateral pinch grip were measured at baseline and 1, 2, and 6 months post treatment. The two groups were comparable at 2 months but significantly different at 1 month (better results for corticosteroid) and 6 months (more favorable outcome for dextrose). After 6 months of treatment, both groups had increased functional level, but dextrose seemed to be more effective. The authors concluded that for the long term, dextrose seemed to be more advantageous, while the two treatments were comparable in the short term. Further research with a large sample size is needed to compare possible complications of corticosteroid/lidocaine vs dextrose/lidocaine injections in the management of OA.

Lateral Epicondylosis

Lhee et al. (2025) conducted a prospective RCT to evaluate whether PRP, prolotherapy, and ESWT provide superior clinical outcomes at 24 months compared with physiotherapy alone in patients with chronic lateral epicondylosis. Adults older than 35 years with lateral elbow pain lasting greater than six months, diagnosed via physical examination and ultrasound, and refractory to at least three months of nonoperative treatment, were included. Exclusion criteria included recent corticosteroid or botulinum toxin injections and complete extensor tendon rupture. Patients were randomized into four treatment groups: physiotherapy, ESWT, prolotherapy, or PRP. The primary outcome was the Disabilities of the Arm, Shoulder and Hand (DASH) score, and the secondary outcome was the Subjective Satisfaction Score (SSS). Patients were followed for two years to assess the treatment efficacy. A total of 231 patients were enrolled, with 202 completing the study. Baseline DASH scores were comparable across the groups ($p = .526$). At 24 months, PRP reduced DASH scores by 31.18 points compared with physiotherapy (18.70 points) and ESWT (17.62 points) ($p < .01$). Prolotherapy (21.02 points) also showed noted improvement compared with physiotherapy at 18 months (15.61 points) ($p < .01$). PRP yielded the highest SSS (4.60 ±0.9), outperforming physiotherapy (3.00 ±1.9) and ESWT (3.43 ±1.7) ($p < .01$). Prolotherapy also yielded higher SSS (4.24 ±1.2) compared with physiotherapy ($p < .01$) and ESWT ($p < .01$) at 24 months. At 24 months, all groups demonstrated DASH score reductions exceeding the minimal clinically important difference of 10 points, indicating clinically meaningful improvement: PRP (31.18), prolotherapy (20.70), ESWT (17.62), and physiotherapy (18.70). The authors concluded that PRP and prolotherapy yielded better clinical and functional outcomes than ESWT and physiotherapy in chronic lateral epicondylosis over a two-year follow-up. The findings support the potential of these therapies as effective nonsurgical options for long-standing cases. Limitations include potential selection and attrition bias. The use of patient-reported DASH scores, although reliable, introduces subjectivity. Additionally, the SSS was assigned by physicians based on interviews, introducing potential observer bias. The absence of objective measures (e.g., grip strength, tendon imaging) limits structural interpretation. Finally, the potential contribution of needling itself, via local bleeding and inflammation, cannot be ruled out and warrants further investigation using dry-needling controls, especially given some previous studies showing that even normal saline injections may yield comparable effects, whereas others report superior outcomes with PRP. Further investigation is needed before the clinical usefulness of this procedure is proven.

Ciftci et al. (2023) conducted a double-blind, ultrasound guided RCT to investigate the effects of prolotherapy (PrT) on pain, functionality, clinical improvement and to compare the 5% low and 15% high-dose dextrose PrT in chronic lateral epicondylitis. Sixty patients (n = 60), aged 44.30 ±10.31 years old, with chronic lateral epicondylitis were allocated randomly into three groups. To Group one: 5% dextrose PrT, to Group two: 15% dextrose PrT, and to Group three: 0.9% saline injections were administered at three times (weeks zero, three, and six), to the entheses of forearm extensors and annular ligament. The primary outcomes were handgrip strength, visual analog scale-rest (VAS-R), visual analog scale-activity (VAS-A), pressure-pain threshold, and Quick Disability of the Arm, Shoulder and Hand (Q-DASH). The secondary outcomes were clinical improvement (Disease Global Assessment Questionnaire), side effects, and complications. Primary outcomes were collected at baseline week zero, week three, and 12. Secondary outcomes were collected at weeks three and 12. In Group two, VAS-A and VAS-R (at week three), handgrip strength and pressure-pain threshold (at week 12) were different than the other groups ($p < .05$). In Groups one and two, there was a difference in primary outcomes at week 12 than baseline ($p < .05$). In Group three, there was no difference in VAS-R, VAS-A, and handgrip

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strength at weeks three and 12 than baseline (p > .05). The authors concluded that in chronic lateral epicondylitis, 5% and 15% dextrose PrT is more effective in pain, handgrip strength, functionality, and clinical improvement than 0.9% saline. There was no difference in functionality, clinical improvement, side effects, and complications between the PrT groups. 15% dextrose PrT was more effective in handgrip strength and pressure-pain threshold at week 12 and pain at week three. The authors recommend 15% dextrose PrT for chronic lateral epicondylitis based on this study. This RCT has limitations. The effect of traumatization by the needle cannot be quantified and may have contributed to inflammation caused by dextrose PrT. Since it was an in vivo study, inflammation between the groups could not be evaluated objectively. All patients participating in the study were given exercise therapy in the form of a home program and the exercise therapy may also contribute to the improvement seen in PrT groups, which could not be distinguished in the study. There is a need for studies comparing PrT doses and supporting long-term follow-ups. Further investigation is needed before the clinical usefulness of this procedure is proven.

A systematic review and meta-analysis by Zhu et al. (2022) were performed to evaluate the effectiveness of HDP on pain intensity and physical function in individuals with lateral elbow tendinosis (LET) compared with other active nonsurgical treatments. A systematic search of the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Web of Science, PubMed, Dimensions, Global Health, NHS Health Technology Assessment, Allied and Complementary Medicine, and Ovid nursing database from inception to June 15, 2021, was performed, without language restrictions. Two reviewers independently identified parallel or crossover RCTs that evaluated the effectiveness of DPT in LET. The search identified 245 records; data from eight studies (354 individuals) were included. Two reviewers independently extracted data and assessed included studies. The Cochrane Risk of Bias 2 tool was used to evaluate risk of bias. The Grading of Recommendations Assessment, Development, and Evaluation approach was used to assess the quality of the evidence. Pooled results favored the use of DPT in reducing tennis elbow pain intensity compared with active controls at 12 weeks post enrollment, with an SMD of -0.44 (95% CI, -0.88 to -0.01; p = 0.04) and moderate heterogeneity (I^2, 49%). Pooled results also favored the use of DPT on physical functioning compared with active controls at 12 weeks, with Disabilities of the Arm, Shoulder, and Hand (DASH) scores achieving an MD of -15.04 (95% CI, -20.25 to -9.82; p < 0.001), with low heterogeneity (I^2, 0.0%). No major related AEs have been reported. The authors concluded that DPT is superior to active controls at 12 weeks for decreasing pain intensity and functioning by margins that meet criteria for clinical relevance in the treatment of LET. Although existing studies are too small to assess rare AEs, for individuals with LET, especially those who have disease refractory to first-line treatments, DPT can be considered a nonsurgical treatment option in carefully selected individuals. Limitations include a small sample size and small number of studies in most comparisons. The time frame of 12 to 16 weeks available for data pooling was short; therefore, longer-term effects remain uncertain. Well-designed, comparative studies are needed to further describe safety and clinical outcomes. The study is also limited due to a heterogeneous population of individuals across trials. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes. [Authors Bayat et al. (2019) and Rabago et al. (2013), previously cited in this policy, are included in this review].

Gupta et al. (2022) conducted a prospective comparison study to evaluate the efficacy of prolotherapy using local injection of 25% dextrose and local corticosteroid injection in tennis elbow. From December 2020 to December 2021, a total of 260 participants aged 18 to 60 years were included in the study. The eligible participants were divided into two categories based on lottery. The first group of participants was given prolotherapy with 25% dextrose (group A), and the second group was given the local corticosteroid triamcinolone (group B). Participants were followed up at regular intervals, and outcome measures were monitored using the VAS and Mayo Elbow Performance Scale (MEPS). Scores were assessed and documented before injection and post injection at 6 weeks, 12 weeks, 24 weeks, and 1 year. All participants had improvement in VAS score and MEPS score following DPT, including participants injected with steroids. VAS scoring performed prior to injection and at 6 weeks, 12 weeks, 24 weeks, and 1 year showed improvement in scores for both groups of participants, that is, those receiving injection of 25% dextrose and those receiving injection of triamcinolone; however, on comparison of scores using a paired *t* test, participants receiving 25% dextrose had greater improvement of scores at 6 weeks, 12 weeks, and 24 weeks, which was statistically significant. However, at 1 year, it was insignificant. MEPS scores again showed a much-improved outcome in participants receiving prolotherapy with 25% dextrose compared with triamcinolone injection. The scores were statistically significant at 6 weeks, 12 weeks, 24 weeks, and 1 year. MEPS scoring, which is a more comprehensive scoring, also proved that 25% DPT improved outcomes in participants with tennis elbow. The authors concluded that functional outcomes in participants in the prolotherapy and steroid injection groups improved during early follow-ups. However, in the prolotherapy group, this improvement persisted for a longer time frame compared with participants treated with steroids. The authors stated that prolotherapy using dextrose had better functional outcome and longer effects in the management of tennis elbow. Sample size is a limitation of this progressive study. Age-matched participants with similar preinjection scores in both groups could have been compared for better evaluation of results. In the future, age- and gender-matched participants with similar comorbidities can be studied to further impress upon the results.

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Kaya et al. (2022) conducted a single-blinded RCT to compare the efficacy of the wrist splint and the injection of corticosteroid, autologous blood, and hypertonic dextrose in the treatment of lateral epicondylitis. A total of 120 participants (43 male participants, 77 female participants; mean age, 45.7 ±7.7 years; range, 18-65 years) diagnosed with lateral epicondylitis between December 2013 and June 2015 were included in the study and randomized into four groups. The first group was administered 20 mg methylprednisolone acetate plus 2 mL 2% prilocaine; the second group received 2 mL venous blood plus 0.5 mL prilocaine; and the third group received 2 mL 30% dextrose plus 0.5 mL prilocaine injections. A second injection was administered to the third group 1 month later. The fourth group was recommended to use only a wrist splint. Pretreatment and posttreatment evaluations of the participants were carried out at 1 and 6 months by the VAS in terms of pain, by Patient-Rated Tennis Elbow Evaluation (PRTEE) questionnaire in terms of functional level, and by the Jamar dynamometer in terms of grip strength. In all groups, VAS values at 1 and 6 months after treatment were found to be lower compared with baseline. Except for the splint group, improvement was observed in all three injection groups in terms of grip strength and PRTEE values at 6 months compared with the baseline values. In the comparison of the groups, no difference was observed in terms of improvement in VAS scores and grip strength. While corticosteroid injection was effective in terms of PRTEE pain, function, and total scores only at 1 month, the autologous injection was effective in terms of PRTEE function and total scores at only 6 months after treatment. No differences for splint and prolotherapy groups were observed in terms of PRTEE scores. The authors concluded that corticosteroid injection, autologous blood injection, and prolotherapy are effective and safe long-term methods in lateral epicondylitis treatment. The main limitation of this study is the lack of an imaging modality such as ultrasonography for diagnosis and treatment. Another limitation is the short-term follow-up (6 months), which did not allow for assessment of intermediate- and long-term outcomes. The final limitation is the lack of selection of participants according to occupation or the kind of sports activity that may affect outcomes. Further investigation is needed before the clinical usefulness of this procedure is proven.

A randomized clinical trial was conducted by Bayat et al. (2019) comparing the efficacy of DPT to that of steroid injection in the treatment of chronic lateral epicondylitis. Thirty participants were randomly assigned to either the hypertonic dextrose group or the methylprednisolone group. “Participants were assessed through Quick DASH and VAS scores, once before injection, and then after 1- and 3-months follow-up. Two patients were excluded due to not completing the follow-up timepoints.” “In both groups VAS scores revealed significant improvement during the first month follow-up [mean difference (MD) = 1.9 ±3.3, versus 1.5 ±1.9 for the prolotherapy and steroid groups, respectively]. This declining trajectory continued at the third month visit in the prolotherapy group and MD reached 4.4 ±2.9, while it did not change remarkably in the steroid group (MD = 1.9 ±3.4). In fact, comparing VAS scores between the 1st- and 3rd-month time points did not reveal a significant improvement in the steroid group ($p = 0.6$). Also, the Quick DASH index showed a similar pattern and improved remarkably in both groups during the first visit. However, only the efficacy in the prolotherapy group persisted after 3-month follow-up (MD = 9.5 ±21.6, $p = 0.044$). One month after injections no preference between the two interventions was observed ($p = 0.74$ for VAS and 0.14 for Quick DASH score). However, the 3rd-month follow-up revealed a meaningful superiority ($p = 0.03$ for VAS and $p = 0.01$ for Quick DASH score) favoring the prolotherapy method.” The authors concluded that while both methods appeared to be effective in the short-term treatment of chronic lateral epicondylitis, the DPT injections appeared to be slightly more efficacious over a longer period. This study is limited by the small study population and suboptimal data analysis.

Rotator Cuff Tendinopathies

A systematic review conducted by Ewart et al. (2024) published by the U.S. Department of Veterans Affairs Health Services Research and Development Evidence Synthesis Program, funded in part to inform the Agency for Healthcare Research and Quality and the Veterans Affairs’ understanding of prolotherapy, it was determined that the overall evidence base for prolotherapy was generally limited by methodological concerns and the inconsistent reporting of adverse events. Regarding shoulder pain related to bursitis and rotator cuff issues, DPT resulted in worse physical performance outcomes compared to corticosteroid injections.

Lin et al. (2022) completed a randomized, double-blinded, controlled study to investigate the effect of hypertonic dextrose injection on pain and disability in participants with chronic supraspinatus tendinosis. The secondary aim was to evaluate its effect on the tendon ROM and morphology. A total of 57 participants with symptomatic chronic supraspinatus tendinosis were enrolled. Participants were randomly administered USG injections of 20% hypertonic dextrose (study group, n = 29) or 5% normal saline (control group, n = 28). The primary outcome measure was VAS scores for pain and Shoulder Pain and Disability Index (SPADI) scores. Secondary outcomes included the ROM and ultrasound examination findings of the supraspinatus tendon at baseline and at 2, 6, and 12 weeks post intervention. The study group exhibited improvements in the VAS (MD, -2.1; 95% CI, -2.7 to -1.4; $p < 0.001$) and SPADI (MD, -11.6; 95% CI, -16.5 to -6.7; $p < 0.001$) scores compared with baseline scores at week 2. However, the effect was not sustained to week 6. Flexion ROM increased at weeks 2 (MD, 14.1; 95% CI, 5.7-22.5; $p < 0.001$) and 6 (MD, 8.9; 95% CI, 2.4-15.4; $p = 0.003$) compared with baseline. The thickness of the supraspinatus tendon improved at weeks 6 (MD, .50; 95% CI, .26-.74; $p < 0.001$) and 12 (MD, .61; 95% CI, .37-.84; $p < 0.001$) compared with baseline. The ratio of histograms also improved at weeks 6 (MD,

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.19; 95% CI, .06-.32; p = 0.002) and 12 (MD, .26; 95% CI, .10-.41; p < 0.001) compared with baseline. The authors concluded that hypertonic dextrose injection could provide short-term pain and disability relief in patients with chronic supraspinatus tendinosis. Ultrasound imaging at week 6 revealed changed tendon morphology. Limitations include a lack of pain evaluation immediately after intervention, an objective functional assessment, and tendon biopsy to confirm changes in tenocyte structure. Further research with RCTs is needed to validate these findings.

Chang et al. (2021) performed a double-blinded RCT to determine whether DPT offers clinical benefits in participants with shoulder pain and bursitis. The study consisted of participants (n = 50) in an outpatient rehabilitation department of a single medical center with a diagnosis of shoulder pain and bursitis. Participants were randomly assigned to 15% dextrose injection (group 1) or placebo (group 2) to receive either 15% dextrose injection or normal saline injection. The primary outcome was maximal pain relief while performing activities. The secondary outcomes included resting pain level, function, and disability assessment results and ultrasonographic parameters. Participants were followed up for 3 months post treatment. Following observation of time effects for all outcome parameters minus elastographic parameters, the authors concluded that dextrose bursal injection was not associated with greater improvements in clinical outcomes compared with normal saline injection. However, data indicated a greater increase in tissue stiffness of the supraspinatus tendon with bursal dextrose injection. Limitations include a small sample size and short duration of follow-up.

Giovannetti de Sanctis et al. (2021) performed a systematic review to compare injectable corticosteroids with other drugs in the treatment of partial rotator cuff tears and the effectiveness in terms of pain and shoulder functionality. Nine prospective RCTs were included in the review, with a total of 494 individuals. Of the 494 individuals, 232 underwent corticosteroid infiltration, 90 with PRP and 47 with glucose prolotherapy; 125 underwent an infiltrative cycle with lidocaine or other local anesthetic as placebo. Corticosteroid VAS scores were as follows: prior to operation, 5.6 ±0.66; short term, 2.73 ±1.08; midterm, 2.93 ±0.89; and long term, 4.09 ±0.38. PRP VAS scores were as follows: prior to operation, 6.2 ±1.2; short term, 3.51 ±1.86; midterm, 3.9; and long term, 2.04 ±0.76. Prolotherapy VAS scores were as follows: prior to operation, 5.3 ±0.81; short term, 4.37 ±1.16; midterm, 4.27 ±1.36; and long term, 3.1 ±1.52. The authors concluded that all treatments showed improvement compared with baseline; however, no differences in terms of pain control were observed. PRP was better in terms of shoulder function. Prolotherapy could not be analyzed due to the small number of studies. Limitations include a small sample size, which makes it difficult to decide whether these conclusions can be generalized to a larger population. The findings of this study need to be validated by well-designed studies, and further investigation is needed before the clinical usefulness of these procedures is proven.

Nasiri et al. (2021) performed an RCT to compare the effectiveness of prolotherapy injection(s) with that of corticosteroid injection(s) in participants with rotator cuff dysfunction. Overall, 33 participants were randomly allocated in two groups: prolotherapy group (n = 17) and corticosteroid group (n = 16). The VAS and SPADI were evaluated for both groups at baseline and 3 and 12 weeks after injections. Improvement in VAS and SPADI scores in 3 and 12 weeks after injections compared with preinjection times was shown in both groups. The authors concluded that both therapies, when administered with a home exercise program, are effective in the management of pain related to rotator cuff dysfunction. However, due to side effects from corticosteroids, prolotherapy is the suggested alternative. Limitations include small sample size and short duration of follow-up. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

A retrospective case series by Ryu et al. (2018) investigated prolotherapy with polydeoxyribonucleotide (PDRN) as a possible viable treatment option for chronic rotator cuff tendinopathy. “The records of patients with chronic rotator cuff tendinopathy (n = 131) were reviewed retrospectively, and the patients treated with PDRN prolotherapy (n = 32) were selected. The main outcome of the shoulder pain and disability index score on a numerical rating scale of average shoulder pain was measured. The authors concluded that compared to baseline data, significant improvements were shown in the shoulder pain and disability index and pain visual analog scale scores at one week after the end of treatment at one month and three months later.” They also concluded that “additional randomized multidisciplinary effectiveness trials that include imaging outcomes such as ultrasound are required to verify the effect of PDRN for chronic RCT compared with current therapies, including prolotherapy with PDRN.” The findings are limited by the lack of a comparison group.

Seven et al. (2017) evaluated the efficacy of prolotherapy in treating chronic refractory rotator cuff lesions through a randomized, prospective, comparative trial. Participants with chronic rotator cuff lesions and symptoms that persisted for > 6 months were divided into two groups: the control group (n = 60), treated with exercise three times weekly for 12 weeks, and the prolotherapy group (n = 60), which received two to six USG prolotherapy injection sessions, in addition to the three-times-weekly home exercise program. A total of 101 participants out of 120 were included in the results. Clinical assessment of shoulder function was performed using the VAS for pain, SPADI, Western Ontario Rotator Cuff Index, participant satisfaction, and shoulder ROM. Participants were examined at baseline; weeks 3, 6, and 12; and last follow-up (minimum of 1 year). At 1 year, 92.9% vs 56.8% of participants reported excellent or good outcomes overall in the

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prolotherapy and control groups, respectively. No AEs were reported. Limitations of this study include but are not limited to small sample size and lack of a placebo control. The investigators concluded that prolotherapy is an easily applicable and satisfying auxiliary method in the treatment of partial rotator cuff lesions that reduces pain and improves both shoulder function and patient satisfaction. Larger studies with longer follow-up times are needed.

Bertrand and colleagues (2016) compared the effect of DPT on pain levels and degenerative changes in painful rotator cuff tendinopathy. In this blinded RCT, 72 participants who received three monthly injections of 0.1% lidocaine with DPT [entheses dextrose (Enth-Dex group)] or one of two control injections [entheses saline injection without dextrose (Enth-Saline group) or superficial saline injection (Superfic-Saline group)] were included in the 9-month follow-up data. All participants received concurrent physical therapy. The primary outcome measure was achieving an improvement in maximal current shoulder pain of ≥ 2.8 (twice the MCID for VAS pain score). At 9 months, the Enth-Dex group maintained a 2.9-point improvement in pain compared with 1.8 and 1.3 for the Enth-Saline and Superfic-Saline groups, respectively. The use of prolotherapy in the Enth-Dex group resulted in a significant improvement compared with the Superfic-Saline group [16 (59%) vs 7 (27%)]; however, the difference between the Enth-Dex group and the Enth-Saline group did not reach clinical significance. The authors concluded that prolotherapy may provide an effective and welcome addition to the management of patients with painful rotator cuff tendinopathy. Additional larger clinical trials with more complete functional assessment tools are required to determine the clinical utility of this technology.

Groin Pain

Bisciotti et al. (2020) performed a systematic review of conservative treatment for long-standing adductor-related groin pain syndrome (GPS). The review consisted of 19 studies and 440 individuals. Seven types of therapeutic interventions were reviewed, including compression clothing therapy, manual therapy combined with strengthening exercise, prolotherapy, corticoid injection, PRP therapy, intratissue percutaneous electrolysis, and pulse-dose radiofrequency (RF). Prolotherapy, described in two studies, was performed on 24 individuals with long-standing GPS. Follow-up assessments were completed at 6 months and 32 months. The VAS was assessed for pain during sports activity, and the Nirschl Pain Phase Scale was assessed for functional impairment caused by pain. Thirty-two months after therapy, VAS scores improved from 6.3+/-1.4 to 1.0+/2.4 ($p < 0.001$), and Nirschl Pain Phase Scale scores changed from 5.3+/-0.7 to 0.8+/-1.9 ($p < 0.001$). Only one study reviewed PRP for GPS, with a total of 41 individuals. The authors concluded that strength of evidence (SOE) for prolotherapy is a moderate level (C) and a recommendation of conflicting strength (D) for PRP. The available data are relatively weak and inconclusive and derived primarily from uncontrolled or poorly controlled studies. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Temporomandibular Joint Disorders

Bahgat et al. (2025) conducted a systematic review to highlight the current knowledge of the efficacy of dextrose as a prolotherapy agent in managing temporomandibular joint internal derangement (TMJ-ID). A "Population, Intervention, Comparison, Outcome" (PICO) strategy was executed using an electronic search through PubMed/MEDLINE, Cochrane databases, and Google Scholar from their inception to August 2022. Only randomized clinical trials investigating the treatment of TMJ-ID with hypertonic dextrose prolotherapy (HDPT) were included. Two independent reviewers assessed the eligibility of the studies with subsequent data extraction. The systematic search identified 392 studies, and only eight articles were considered eligible for selection, with a total of 286 individuals; 72% were females, and 28% were males. The extracted data showed positive effects of dextrose on joint pain and maximum mouth opening (MMO) with high patient satisfaction. The authors concluded that HDPT can be effective in relieving TMJ symptoms as it reduces pain, improves joint dysfunction, and increases MMO up to 12 months. Meta-analysis was not performed, which presents a limitation of this systematic review. Quantitative analysis was not done due to the lack of standardization between studies regarding the dextrose concentrations used, the control or comparative interventions applied, variation in the follow-up intervals, and the statistical tests applied. Further research is needed to determine the clinical relevance of these findings.

Saramantos et al. (2025) conducted a systematic review with meta-analysis to investigate the existing quality of clinical evidence on the efficacy of prolotherapy versus placebo and other active comparators, such as autologous blood products or botulinum toxin, in improving the outcomes of TMJ disorders. A literature search in MEDLINE, Scopus, and Cochrane databases was performed, following the PRISMA statement guidelines, to identify RCTs of individuals with TMJ disorders receiving prolotherapy. The maximal incisor opening (MIO), VAS for pain, and frequency of dislocations were analyzed as the outcomes. The weighted mean difference was used to pool outcomes. The risk of bias was recorded for the studies included. Six studies comparing prolotherapy to placebo were identified. Prolotherapy is uniformly more efficient in reducing the VAS for pain when compared to the placebo (mean difference = 1.20, 95% CI: 0.56-1.84, $p < 0.001$). Perceived jaw mobility was improved among prolotherapy patients, (mean difference = 0.47, 95% CI: 0.05-0.90, $p = 0.003$) when compared to the placebo. Regarding MIO (mean difference = 0.84, 95% CI: -2.12-3.80, $p = 0.58$), a beneficial effect for prolotherapy was not confirmed. The authors concluded that prolotherapy appears to be more efficient

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than autologous blood products in reducing VAS for pain (mean difference = 0.49, 95% CI: 0.11-0.87, p = 0.01). Prolotherapy was found to be more effective in reducing pain, MIO, and clicking when compared to an occlusal splint in a single study. The authors also stated that prolotherapy is a promising modality for TMJ disorders, despite the limited number of RCTs. Existing evidence supports its use to reduce TMJ-related pain, even against other modalities. Limitations of the present study include a small number of available RCTs, with few participants in each one of them. Not all included studies used the same diagnostic RDC/TMJ criteria to classify included patients. In addition, the follow-up time rarely exceeded six months, with the median being three months; therefore, future studies may need to address the long-term efficacy of prolotherapy in VAS for pain outcomes. Further research is needed to better describe the benefit of prolotherapy for other outcomes.

Gibaly et al. (2024) conducted an RCT to compare the combined effect of Prolotherapy and Deep Dry Needling (DDN) versus DDN effect on relieving the symptoms of TMJ anterior disc displacement apart from the impact of the penetrating needle. The clinical trial randomly allocated 40 individuals. The (control group) individuals received four intraarticular and masseteric DDN sessions, while the (study group) individuals were subjected to the exact technique followed by prolotherapy solution injection. The baseline preoperative measurements included MIO, auscultation of the presence of clicking, and VAS, which were repeated for postoperative measurements after one, two, five, and eight months. By the end of the study, all individuals expressed apparent improvement in pain, MIO and clicking. The inter- and intragroup comparison revealed that the pain score values of the control group after five and eight months were higher than those of the study group. The study group demonstrated more significant MIO calibration than the control group, with insignificant differences between both groups regarding the presence of clicking at any time interval. The associations between clicking and VAS values, between clicking and MIO, and between VAS values and increased MIO were positive in the test group and negative in the control group. The authors concluded that dextrose prolotherapy and DDN were beneficial. However, prolotherapy demonstrated more sustained, and correlated long-term alleviation of symptoms and increased MIO. A limitation of this RCT includes the small sample size (40 patients). Further research is needed to determine the clinical relevance of these findings.

Zhou et al. (2024) conducted a systematic review and meta-analysis to investigate the efficacy of dextrose prolotherapy versus placebo and other active interventions, like autologous blood injection (ABI) and botulinum toxin (BTX), in improving the outcomes of TMJ hypermobility. An extensive database search was performed. Maximal mouth opening (MMO), pain, and frequency of dislocations were analyzed. Eight RCTs were included. In comparison with placebo, dextrose prolotherapy was associated with significantly reduced pain and MMO. Comparison of dextrose with ABI revealed no difference in MMO. Qualitative analysis showed no difference in outcomes in patients who received DPT and BTX. The authors concluded that low-quality evidence suggests that dextrose prolotherapy may reduce MMO and improve pain scores compared to placebo in patients with TMJ hypermobility. Low-quality evidence also suggests that there may be minimal differences in outcomes between dextrose vs ABI and BTX. This study has limitations. The small number of studies in each meta-analysis and limited comparative studies impact the strength of the conclusions. All the included studies did not clearly specify the inclusion criteria and there was limited data on the disease severity and history of failed treatments. Inadequate reporting of outcomes and numerical data is a major drawback of the included studies. Furthermore, pain and MMO were the only two outcomes that could be examined in the meta-analysis. Pain is a very subjective outcome and can be affected by the patient's pain threshold, the placebo effect, the time of measurement, etc. Also, there was a substantial methodological heterogeneity amongst trials in terms of the study sample, concentration of dextrose, number of injections, and site of injections. Due to the limited data, the authors could not examine how these variables could influence the study outcomes. This may limit precise comparisons and adequate conclusions. Therefore, the current results must be interpreted with caution. Furthermore, all included studies were only from three countries, namely, India, Turkey, and Egypt, which seriously limits the generalization of the conclusions. Further investigation is needed before clinical usefulness of this procedure is proven.

Chęciński et al. (2023) performed a systematic review to identify primary studies on autologous blood injection for the treatment of TMJ hypermobility and assess the therapy for effectiveness. RCTs comparing dislocation episode rates, ROM in the TMJ, or articular pain intensity were adopted as the eligibility criteria. The results of the individual studies were tabulated, and syntheses were illustrated in graphs. Overall, 22 studies involving 982 individuals were included in the qualitative analysis, of which seven involving 390 individuals were subject to quantitative analysis. None of the included RCTs presented a high risk of bias; 75% of them caused some concerns. In a 3-month observation, administration of autologous blood was more efficient in limiting TMJ dislocations than hypertonic dextrose (one study, 32 individuals; relative risk, 0.33; odds ratio, 0.29), and no difference in outcomes was observed between intracavitary and pericapsular administration compared with pericapsular injection alone (two studies, 70 individuals; relative risk, 1.00; odds ratio, 1.00). The authors concluded that injections of autologous blood into the TMJs were effective in preventing further TMJ dislocation episodes in 75% of 94% of individuals. This study has limitations. Six of the eight RCTs caused some concerns about the risk of bias. A study by Machon et al. (2018) consisted of a single intervention, and all other RCTs allowed repeated injections until success, subject to consent of the individuals. The different number of repetitions of the

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intervention makes it difficult to draw conclusions about the effectiveness of a single administration. The inhomogeneity of the control groups makes it difficult to compare autologous blood injections for TMJs with other interventions. Further research with RCTs is needed to validate these findings.

Mohammed et al. (2023) conducted a prospective clinical study to evaluate the effect of DPT in treating internal derangement of the TMJ. A total of 20 participants with TMJ internal derangement were enrolled in the study. The diagnosis of internal derangement was confirmed by magnetic resonance imaging (MRI). The posterior and anterior disk attachment as well as the most tender part of the masseter muscle were injected with 12.5% dextrose. Pain, maximum mouth opening, clicking, and deviation were assessed immediately before treatment as well as at 2, 4, and 12 weeks post treatment. Improvement in the four clinical variables at the three time intervals was observed. Pain at 2 weeks was reduced by 60% (6 vs 3.75) and by 200% (6 vs 1.9) at 4 weeks. The maximum mouth opening was increased by 6.4 mm at 2 weeks and 7.85 mm at 4 weeks. The percentage of participants with clicking decreased from 70% prior to operation to 50% at 2 weeks, 15% at 4 weeks, and 5% at 12 weeks. The ratio of participants with deviation decreased from 80% prior to operation to 35% at 2 weeks, 15% at 4 weeks, and 5% at 12 weeks. The authors concluded that prolotherapy is a safe and effective treatment for alleviating the symptoms of internal derangement of the TMJ. Limitations of this study are the absence of a positive or negative control group, relatively small sample size, and short follow-up period. In addition, no postinjection MRI of the joint was performed to correlate the clinical improvement of symptoms with imaging changes in the joint and disk position. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Dasukil et al. (2021) conducted a clinical trial to study the efficacy of prolotherapy and to establish it as an effective procedure in participants with TMJ disorders to provide a long-term solution to chronic TMJ pain and dysfunctions. A total of 25 participants with various TMJ disorders treated with prolotherapy, the solution consisting of one part of 50% dextrose (0.75 ml), two parts of lidocaine (1.5 ml), and one part of warm saline (0.75 ml), were included. The standard program is to repeat the injections three times at 2-week intervals, which totals four injection appointments over 6 weeks with a 3-month follow-up. Appreciable reduction in tenderness in the TMJ and masticatory muscles was observed, with improvement in mouth opening. The effect of the treatment in improving clicking and deviation of the TMJ was found to be statistically significant ($p < 0.05$). No permanent complications were observed. The authors concluded that prolotherapy is an effective therapeutic modality that reduces TMJ pain and improves joint stability and ROM in a majority of patients. It can be a first-line treatment option, as it is safe, economical, and an easy procedure that is associated with minimal morbidity. This was a nonrandomized study design without a control group. High-quality evidence demonstrating a beneficial impact of prolotherapy on health outcomes in patients with TMJ disorders is lacking. Further research with RCTs is needed to validate these findings.

Sit et al. (2021) performed a systematic review of RCTs to determine the efficacy of HDP for TMJ disorders. Overall, 10 full-text RCTs were included in the study, with sample sizes ranging from 12 to 72, with a total of 336 individuals. The study period ranged from 4 weeks to 1 year post enrollment. The primary outcome was pain intensity. Secondary outcomes included maximum interincisal mouth opening (MIO) and disability score. A meta-analysis of five RCTs revealed decreased TMJ pain compared with placebo (SMD, -0.76; 95% CI, -1.19 to -0.32; I^2, 0%). No statistical differences were noted for changes in MIO and functional scores. The Cochrane Risk of Bias 2 tool revealed “some” to “high” risk of bias. The authors concluded that prolotherapy has a positive effect on TMJ pain compared with placebo injections. The significance of this study is limited by a small sample size and short follow-up period.

An RCT conducted by Louw et al. (2019) studied the effect of hypertonic dextrose injection (prolotherapy) for the treatment of temporomandibular dysfunction. Overall, 42 participants (54 joints) were randomized to three monthly intra-articular injections of 20% dextrose/0.2% lidocaine or to 0.2% lidocaine. This was followed by injections of dextrose/0.2% lidocaine as needed through 1 year. Facial pain and jaw dysfunction, MIO, percentage of joint with 50% or more improvement in pain/function, and participant satisfaction were the primary and secondary outcome measures. “Randomization produced a control group with more female participants ($p = .03$), longer pain duration ($p = .01$), and less MIO ($p = .01$). Upon 3-month analysis, including pertinent covariates, dextrose group participants reported decreased jaw pain (4.3 ±2.9 points vs 1.8 ±2.7 points; $p = .02$), jaw dysfunction (3.5 ±2.8 points vs 1.0 ±2.1 points; $p = .008$), and improved MIO (1.5 ±4.1 mm vs −1.8 ±5.1 mm; $p = .006$). Control group participants received dextrose injections beginning at 3 months. No between-group differences were noted at 12 months; pooled data suggested that jaw pain, jaw function, and MIO improved by 5.2 ±2.7 points (68%), 4.1 ±2.8 points (64%), and 2.1 ±5.5 mm, respectively. Pain and dysfunction improved by at least 50% in 38 of 54 (70%) and 39 of 54 (72%) jaws, respectively.” The authors concluded that prolotherapy results in substantial improvement in jaw pain, function, and MIO compared with masked control injection at 3 months, with clinical improvements enduring to 12 months. This study is limited by the small patient population and suboptimal data analysis.

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Zhou and colleagues (2014) conducted a single-center case series of 45 individuals, introducing a modified technique of prolotherapy using an injection of lignocaine and 50% dextrose at a single site in the posterior periarticular tissues. The criteria for inclusion in this study were open lock of the jaw more than twice in the past 6 months and no long-standing dislocation of the TMJ. Individuals were followed up for at least 1 year. Appreciable improvements in the number of episodes of dislocation and clicking after the injection were observed. The overall success rate, defined as the absence of any further dislocation or subluxation for more than 6 months, was 41 of 45 (91%). Of the 41 rehabilitated individuals, 26 (63%) required a single injection, 11 (27%) had two treatments, and four (10%) needed a third injection. All individuals tolerated the injections well. The authors concluded that the modified DPT is simple, safe, and cost-effective for the treatment of recurrent dislocation of the TMJ. Study limitations include small study size and the lack of a control group.

Lower Limb Tendinopathies

Bello Baez et al. (2023) conducted a longitudinal, observational study to add to the small but growing body of evidence on the effectiveness of USG Achilles intratendinous hyperosmolar DPT and introduce a novel, preceding step of paratenon hydrodissection with lidocaine in patients with chronic Achilles tendinosis resistant to rehabilitation therapy. A total of 27 consecutive patients diagnosed with Achilles tendinosis, in whom conservative treatment (e.g., physiotherapy, shock wave therapy) had failed, were included. A 2% lidocaine paratenon anesthesia and hydrodissection were followed by USG intratendinous injections of 25% glucose every 5 weeks. The VAS was used for pain assessment at rest, for activities of daily living, and after moderate exercise at the beginning and at the end of the treatment. Moreover, tendon thickness and vascularization were recorded at baseline and the final treatment consultation. Effectiveness was estimated from scoring and relative pain reduction using a 95% CI. The nonparametric Wilcoxon test and a general linear model for repeated measures were applied. Statistical significance was established as $p < 0.05$. A median of five (one to 11) injection consultations per patient was required. Pain scores decreased in all three conditions ($p < 0.001$). Relative reductions were 75% in pain at rest (95% CI, 61%-93%), 69% in pain with daily living activities (95% CI, 55%-83%), and 70% in pain after moderate exercise (95% CI, 57%-84%). Tendon neovascularization was significantly reduced ($p < 0.001$). The authors did not observe significant changes in tendon thickness ($p = 0.083$). The authors concluded that Achilles tendinosis treatment with paratenon lidocaine hydrodissection and subsequent prolotherapy with hyperosmolar glucose solution is safe, effective, inexpensive, and virtually painless, with results maintained over time. This study has limitations, including the lack of a control group or groups with other therapies that would allow comparison. There are no clinical trials that assess the use of 25% glucose vs placebo or that mask patients for pain evaluation before and after treatment, considering the subjectivity of pain perception. All study patients had undergone other therapies without success and had a high degree of pain and high level of neovascularization. Further clinical studies comparing hyperosmolar dextrose injections with other therapies and with no therapy are required.

Kazempour Mofrad et al. (2022) performed an uncontrolled, before-after study to evaluate the effectiveness of extra-articular neurofascial DPT in chronic ankle ligament injury. Participants with chronic ankle ligament injury entered this uncontrolled before-after study based on eligibility criteria. Participants who consented to participate in the study filled out the prepared questionnaire containing demographic data, the Cumberland Ankle Instability Tool (CAIT), and the VAS. The initial CAIT score of less than 25 indicated functional instability following an ankle sprain. Participants underwent neurofascial prolotherapy with dextrose 12.5%. Two injections were performed in 1 month. The CAIT was completed 1, 3, and 6 months after the intervention. Overall, 25 participants with chronic ankle ligament injury were investigated. The mean CAIT score was 1.88 (±2.35) before the intervention, which increased significantly over the study ($p < 0.001$). The CAIT score reached 21.84 (±6.04) in the sixth month after the intervention. Moreover, the VAS score decreased significantly over the study from 6.12 (±2.35) before the intervention to 1.24 (±0.43) in the sixth month after the intervention ($p < 0.001$). The authors concluded that their findings revealed the therapeutic effectiveness of dextrose neurofascial prolotherapy in decreasing pain and functional instability in patients with chronic ankle pain due to ligamentous injury accompanied by chronic ankle instability. This study is limited by its uncontrolled and unblinded design and small sample size. Further research with RCTs is needed to validate these findings.

Because the efficacy of and potential AEs with sclerotherapy and prolotherapy are unclear, Morath et al. (2018) conducted a systematic review and meta-analysis of available published literature on these therapies for treating Achilles tendinopathy in athletes. While the initial search yielded 1,104 entries, only 13 were human studies. Four RCTs were ranked as having a low risk of selection bias. Three of those reported a statistically significant drop in VAS score. Positive results regarding pain relief and participant satisfaction were identified in 12 of the 13 studies. The authors stated that the meta-analysis was clearly in favor of the intervention. Only one serious AE and two minor AEs were reported in the entire body of literature. The researchers concluded that both sclerotherapy and prolotherapy are safe and may be effective treatment options for Achilles tendinopathy; however, long-term studies and RCTs are still needed to support their recommendation. The conclusions are limited by a mix of human and animal studies, controlled and uncontrolled studies, and questionable choice of comparator groups.

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Platelet-Rich Plasma Therapies

PRP preparations are heterogeneous and lack standardization and evidence fails to substantiate clinical efficacy and safety for this form of treatment. While some available studies are promising, the majority of evidence on platelet-derived blood or plasma therapies compared with other standard treatments is highly variable regarding efficacy or improved health outcomes for a wide range of conditions. Evidence to draw firm conclusions about safety is insufficient; the limited published evidence indicates that intra-articular PRP is safe and well tolerated. Long-term effects of PRP therapy beyond one year, however, have not been established and safety remains a concern (Hayes, 2022). Higher-quality studies with longer follow-up as well as standardization of best practices are needed to determine the benefit of this technology.

Knee Osteoarthritis

Qaio et al. (2023) conducted a systematic review and meta-analysis on injectable treatments for KOA, including PRP. Overall, 35 RCTs comprising 3,104 individuals were included. Outcomes were measured by VAS and WOMAC scores as well as treatment-related AEs. In the included studies, treatment ranged from 3 to 24 months. All studies reported 3-month outcomes, with 31 reporting 6-month, 14 reporting 9-month, and 14 reporting 12-month outcomes. The results showed that at 3 months, 15 WOMAC scores were reported, and the groups receiving PRP reported the best outcomes. Among all follow-up times, the best improvement in WOMAC scores was seen in the individuals receiving PRP. With regard to VAS scores, PRP showed the second-best outcomes at the 3-month follow-up, with a decrease at 6 and 12 months when compared with other injectables. The authors concluded that PRP is an effective pain-relieving treatment with the lowest incidence of adverse effects. These results are limited by heterogeneity of data between studies as well as inconsistent numbers of injections reported and follow-up times. Furthermore, adverse effects were not mentioned. Additional high-quality research is needed to validate these findings.

A randomized clinical trial by Bennell et al. (2021) was conducted to evaluate the effects of intra-articular PRP injections compared with placebo saline injection on symptoms and joint structure in participants with symptomatic, mild to moderate, radiographic medial KOA. This randomized, two-group, placebo-controlled, participant-blinded, injector-blinded, assessor-blinded clinical trial enrolled community-based participants (n = 288) aged 50 years or older with symptomatic medial KOA (Kellgren-Lawrence grade 2 or 3) in Sydney and Melbourne, Australia, from August 24, 2017, to July 5, 2019. The 12-month follow-up was completed on July 22, 2020. Interventions involved three intra-articular injections at weekly intervals of either leukocyte-poor (LP) PRP using a commercially available product (n = 144) or saline placebo (n = 144). The two primary outcomes were 12-month change in overall average knee pain scores (11-point scale; range, 0-10, with higher scores indicating worse pain; MCID of 1.8) and percentage change in medial tibial cartilage volume, as assessed by MRI. Thirty-one secondary outcomes (25 symptom related and six MRI assessed; MCID not known) evaluated pain, function, quality of life, global change, and joint structures at the 2-month and/or 12-month follow-up. Among 288 participants who were randomized (mean age, 61.9 [SD, 6.5] years; 169 [59%] women), 269 (93%) completed the trial. In both groups, 140 participants (97%) received all three injections. After 12 months, treatment with PRP vs placebo injection resulted in a mean change in knee pain scores of -2.1 vs -1.8 points, respectively (difference, -0.4 points; 95% CI, -0.9 to 0.2; p = 0.17). The mean change in medial tibial cartilage volume was -1.4% vs -1.2%, respectively (difference, -0.2%; 95% CI, -1.9% to 1.5%; p = 0.81). Of 31 prespecified secondary outcomes, 29 showed no between-group differences. The authors concluded that among participants with symptomatic, mild to moderate, radiographic KOA, intra-articular injection of PRP, compared with injection of saline placebo, did not result in a difference in symptoms or joint structure at 12 months. These findings do not support the use of PRP for the management of KOA. This study has multiple limitations. PRP preparations are heterogeneous and lack standardization. Results from this trial may not be generalizable to other PRP preparations. This trial included participants with mild to moderate, radiographic KOA because prior evidence suggested that they may have greater benefits from PRP, and the results may not be generalizable to more severe disease. Further investigation is needed before the clinical usefulness of this procedure is proven.

Dório et al. (2021) performed a double-blinded, placebo-controlled, randomized clinical trial to evaluate the efficacy of intra-articular PRP and plasma to improve pain and function in participants with KOA over 24 weeks. The study included a randomized, double-blinded, placebo-controlled trial with three groups (n = 62): PRP (n = 20), plasma (n = 21), and saline (n = 21). Two USG knee injections were performed, with a 2-week interval. The primary outcome was a VAS of 0 to 10 cm for overall pain at week 24, with intermediate assessments at weeks 6 and 12. Main secondary outcomes were the KOOS, Outcome Measures in Rheumatology-Osteoarthritis Research Society International criteria, and Timed Up and Go test. At baseline, 92% of participants were female, with a mean age of 65 years, mean BMI of 28.0, and mean VAS pain of 6.2 cm. Changes in pain from baseline at week 24 were -2.9 cm (SD, 2.5), -2.4 cm (SD, 2.5), and -3.5 cm (SD, 3.3) for PRP, plasma, and saline, respectively (p intergroup = 0.499). No differences between the three groups at weeks 6 and 12 were observed. Similarly, no differences between groups regarding secondary outcomes were observed. The PRP group had higher frequency of AEs (65% vs 24% and 33% for plasma and saline, respectively; p = 0.02), mostly a mild transitory increase in pain. The authors concluded that PRP and plasma were not superior to placebo for pain and function improvement in KOA over 24 weeks. The PRP group had a higher frequency of a mild transitory increase in pain.

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Limitations include a small sample size and heterogeneous participant population. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Filardo et al. (2021) completed a meta-analysis of RCTs to evaluate the effectiveness of PRP injections for KOA compared with placebo and other intra-articular treatments. On January 17, 2020, the authors searched PubMed, Cochrane Library, Scopus, Embase, and Web of Science as well as the gray literature. RCTs comparing PRP injections with placebo or other injectable treatments in humans, in any language, were included. Risk of bias was assessed following the Cochrane guidelines; quality of evidence was graded using the GRADE guidelines. Overall, 34 RCTs, including 1,403 knees in the PRP groups and 1,426 in the control groups, were selected. The WOMAC score favored PRP, with a statistically and clinically significant difference vs placebo at the 12-month follow-up ($p = 0.02$) and vs HA at the 6-month ($p < 0.001$) and 12-month ($p < 0.001$) follow-ups. A clinically significant difference favoring PRP vs steroids was documented for VAS pain ($p < 0.001$), KOOS pain ($p < 0.001$), function in daily activities ($p = 0.001$), and quality of life ($p < 0.001$) at the 6-month follow-up. However, superiority of PRP did not reach the MCID for all outcomes, and the quality of evidence was low. The authors concluded that the effect of platelet concentrates goes beyond their mere placebo effect and that PRP injections provide better results than other injectable options. The authors stated that this benefit increases over time, becoming clinically significant after 6 to 12 months. However, although substantial, the improvement remains partial and supported by a low level of evidence. This finding urges further research to confirm benefits and identify the best formulation and indications for PRP injections in KOA. Limitations include a lack of standardization, lack of key data, heterogeneity, and high-level clinical trials. Only 20 out of 33 studies were double blinded; given the relevance of the placebo effect in the field of knee injections, this factor could have influenced the results, although the overall results were in line with those from the sensitivity analysis of double-blinded trials. Further research is needed to determine the clinical relevance of these findings. [Authors Lin et al. (2019) and Rahimzadeh et al. (2018), previously cited in this policy, are included in this review].

An updated 2021 Hayes Comparative Effectiveness Review of PRP for KOA stated that intra-articular PRP is a minimally invasive treatment associated with few complications that may be appealing when more conservative therapies (e.g., oral medications, physical therapy) are contraindicated, unavailable, or fail to provide adequate relief. Current evidence suggests that a difference in efficacy from intra-articular HA at up to 6 months is limited but that intra-articular PRP may be associated with better outcomes at the 1-year follow-up. If intra-articular PRP can be conclusively shown to provide benefits over intra-articular HA at 1 year, it has the potential to displace intra-articular HA. Future research should consider the role of PRP preparation protocols upon efficacy, as they vary considerably across studies. No standardization or consensus as to best practices is available nor is there clear understanding of which steps and factors (if any) are associated with better outcomes. These factors are likely to bear upon acceptance of PRP as an alternative to intra-articular corticosteroids or intra-articular HA in the future. The annual review identified five new key RCT studies. The evidence remains unchanged. [Author Di Martino A et al. (2018), previously cited in this policy, is included in this review].

An ECRI Clinical Evidence Assessment (2020) report on PRP therapy for KOA was published following a systematic review and meta-analysis. The report concentrated on PRP's effectiveness and safety compared with those of HA and corticosteroids. Pain relief, knee function, and AEs were assessed. In terms of pain relief, a meta-analysis of data from 30 RCTs reported that PRP yielded better pain score improvements than HA, corticosteroids, and placebo at 3, 6, and 12 months. In terms of knee function, PRP had better WOMAC scores than HA, corticosteroids, and placebo at 3, 6, and 12 months. No serious AEs occurred. More complications with PRP alone than with PRP plus HA were reported as well as more local AEs with leukocyte-rich (LR) PRP. The authors concluded that there is insufficient comparative data, and evidence is inconclusive. Limitations include varied PRP preparation, injection methods, and number of injections. Time between injections varied (weekly to monthly). Analysis was limited to 3-, 6-, and 12-month outcomes; data were not available for longer follow-up. Other limitations in the evidence base include the lack of blinding in some studies, a need for long-term follow-up, a primarily single-center focus, and no reporting on a treatment's ability to postpone knee replacement. (ECRI, 2020; updated 2022)

Trams et al. (2020) performed a systematic review and meta-analysis to evaluate PRP efficacy in the recovery of knee disorders and during knee surgery. A total of 83 clinical studies with 5,323 individuals were included in this review. The mean follow-up period was 12 months (ranging from 10 days to 3 years), and the mean number of individuals included was 62 (ranging from 20 to 315). The study included patellar tendinitis (four studies/137 individuals), muscle injuries around the knee (four studies/224 individuals), high tibial osteotomy (two RCTs/80 individuals), total knee arthroplasty (six RCTs/621 individuals), arthroscopy (four RCTs/199 individuals), anterior cruciate ligament reconstruction (ACLR; 16 RCTs/740 individuals), meniscal repair (two RCTs/five non-RCTs), and OA (38 studies/2,962 individuals). In total, seven areas of meta-analysis reported a positive effect of PRP. Among them, 10 sub analyses revealed differences in favor of PRP when compared with the control groups ($p < 0.05$). The study showed positive effects of PRP, both on the recovery of knee disorders and during knee surgery. The authors concluded that PRP improves outcomes in OA applications, arthroscopic treatment of cartilage degeneration, and meniscus healing; leads to faster return to sport after muscle

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injuries; and reduces blood loss after total knee replacement. Limitations include the need for further prospective and randomized studies with a higher number of participants, with lower biases.

A randomized, double-blinded, triple-parallel, placebo-controlled trial by Lin and colleagues (2019) prospectively compared the efficacy of intra-articular injections of PRP and HA with a sham control group (normal saline solution) for KOA. A total of 87 osteoarthritic knees (53 participants) were assigned to one of three groups receiving three weekly injections of either LP-PRP (31 knees), HA (29 knees), or normal saline (27 knees). The WOMAC Index score and International Knee Documentation Committee (IKDC) subjective score were collected at baseline and at 1, 2, 6, and 12 months after treatment. All three groups had statistically significant improvements in both outcome measures at 1 month; however, only the PRP group sustained the significant improvement in both the WOMAC and IKDC scores at 12 months, with improvements of 21% and 40%, respectively. No significant difference in both functional outcomes between the HA and normal saline groups was observed at any time point. Only the PRP group reached the MCID in the WOMAC score at every evaluation. Study limitations include a small sample size; additionally, the trial did not include imaging studies for the evaluation of joint cartilage post injection. The authors concluded that intra-articular injections of LP-PRP can provide clinically significant functional improvement for at least 1 year in patients with mild to moderate KOA. Future long-term studies with larger sample sizes encompassing all stages of degeneration, with the inclusion of imaging evaluation and biomarker analysis of the knee joints, are warranted to further elucidate these findings. These findings need to be reproduced in additional large, high-quality studies to assess the implications for clinical care.

Delanois and colleagues (2019) conducted a systematic review and analysis of reports evaluating (1) PRP injections; (2) bone marrow–derived mesenchymal stem cells; (3) adipose-derived mesenchymal stem cells; and (4) amnion-derived mesenchymal stem cells in the management of KOA. Of 1,009 studies identified in the last 5 years, 123 met inclusion criteria. Although the majority of PRP reports demonstrated improvements in pain and/or function, some revealed no substantial improvements. Similar findings were noted for the other therapy. The reviewers concluded that although some promising early results for PRP, bone marrow–derived mesenchymal stem cell, adipose-derived mesenchymal stem cell, and amnion-derived mesenchymal stem cell therapies were identified, the majority of level I studies have multiple problems, including but not limited to small sample sizes, potentially inappropriate control cohorts, and short-term follow-up. Despite the limitations, they indicate that there still appears to be evidence justifying their use for KOA management. More high-level, larger human studies using standardized protocols are needed.

Annaniemi et al. (2018) conducted a retrospective study of 190 patients to compare PRP vs viscosupplements in terms of symptom relief and time to arthroplasty in patients with KOA. Patients received either intra-articular injections of PRP (94 patients), which the authors label as “an experimental treatment in osteoarthritis,” or HA (86 patients) between January 2014 and October 2017. The WOMAC, the VAS, and ROM were measured before injection and at 15 days, 6 months, 12 months, and final follow-up. Patients treated with HA experienced a higher arthroplasty rate (36% vs 5.3%), lower ROM, worse VAS and WOMAC Index scores, and increased risk of any arthroplasty occurrence than those treated with PRP. Cox proportional hazards analysis revealed a tendency to decrease the risk of knee arthroplasty for the patients treated with PRP. When adjusted for propensity score in matched pairs (n = 78), the PRP group still showed significant improvement over the HA group in arthroplasty rate (12.8% vs 41%) and VAS and WOMAC scores but not in ROM during the mean follow-up of 16.7 months. Authors found that in comparison to HA, intra-articular injections of PRP are associated with better outcomes and prolonged time to arthroplasty and are a valid therapeutic option in select patients with KOA who are unresponsive to conventional treatments. A limitation of the retrospective study design was cited by the authors, who concluded that further larger studies are needed to validate this promising treatment modality. Additionally, the findings are limited by lack of randomization between interventions, which could have introduced biases and multiple comparisons.

Hip Osteoarthritis

Gazendam et al. (2020) performed a systematic review and network meta-analysis of RCTs to compare the efficacy of various intra-articular injectable treatments in treating hip OA at up to 6 months of follow-up. The intra-articular injectables included corticosteroids, HA, and PRP. Eleven studies, which included 1,353 individuals, were reviewed. Treatment groups included intra-articular placebo injection with or without local anesthetic (n = 314), HA (n = 596), corticosteroids (n = 237), PRP (n = 155), a combined HA and PRP injection (HA + PRP, n = 31), and a control group with no injection (n = 20). There was a high risk of bias due to deviations from the intended interventions and missing outcome data. Results revealed that none of the hip injections demonstrated improvement in pain or function scores compared with saline hip injection at 2 to 4 months and 6 months, except for HA + PRP and the control group. The authors concluded that no treatment was found to have a clinically meaningful benefit beyond placebo. Limitations include small sample size. Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

A 2019 Hayes Health Technology Assessment of published literature on the use of PRP for the treatment of hip OA identified four RCTs representing 303 individuals who were treated with intra-articular PRP or intra-articular HA. They

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stated that the small body of low-quality evidence suggests that pain and function outcomes may improve after treatment with USG PRP and remain better than pretreatment status up to 1 year. Intra-articular PRP outcomes do not appear to be different from those obtained with intra-articular injection with intra-articular HA, a common treatment alternative for which there is uncertainty regarding the clinical significance of treatment benefits. Evidence to draw firm conclusions about safety is insufficient; the limited published evidence indicates that intra-articular PRP is safe and well tolerated. Long-term effects of PRP therapy beyond 1 year have not been established. The report concludes that there is a potential but unproven benefit of PRP for hip OA. Future studies may help determine whether intra-articular PRP is more efficacious than placebo or other active treatments and provide additional information regarding potential harms (Hayes, 2019). The October 19, 2020, annual review identified four new abstracts, which included one RCT and three systematic reviews and meta-analyses. The evidence remains unchanged (Hayes, 2020). Authors Dallari et al. (2016) and Battaglia et al. (2013), previously cited in this policy, are included in this report.

Soft Tissue (Tendon, Joint, and Other Soft Tissue Areas of the Body)

Balasubramaniam et al. (2015) systematically reviewed the literature regarding PRP therapy in chronic tendinopathy. A total of 389 articles were reviewed from February 2010 to April 2014, with nine RCTs meeting inclusion criteria. Each article was reviewed independently by two authors. Each article was analyzed using the Cochrane Criteria checklist. 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 two of four studies in the lateral epicondylar section showed improvements in pain and disability at 6 and 12 months. Evidence to support the use of PRP in Achilles and rotator cuff tendinopathy was lacking. 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. The findings are limited by the small number of quality studies for each indication and inconsistent results of the intervention.

Moraes et al. (2014) conducted a Cochrane review to assess the effect of platelet-rich therapy (PRT) for musculoskeletal soft tissue injuries. Nineteen studies were found that compared PRT with placebo, autologous whole blood, dry needling or no PRT (n = 1,088). The trials covered eight types of injury, some of which were treated surgically: rotator cuff tears, shoulder impingement syndrome, tennis elbow, knee ligament reconstruction using autologous and donor grafts, patellar tendonopathy, Achilles tendinopathy, and acute rupture of the Achilles tendon. The available evidence base comprised a diverse collection of small trials that applied PRT in various ways for treating tendinopathies or as an augmentation procedure for surgically treated soft tissue injuries. There was very-low-quality evidence from a subset of the trials for a marginal short-term benefit in pain from PRT; however, other very-low-quality evidence indicated that using PRT did not appear to have a clinically relevant effect on short-term or long-term function. Very low-quality evidence showed no difference in AEs between the PRT and the various control interventions. Overall, and for the individual conditions, researchers concluded that evidence to support the use of PRT for treating these injuries is currently insufficient.

Knee

Irshad et al. (2024) conducted a prospective comparative analysis to compare the efficacy of intra-articular administration of PRP and corticosteroids (CSs) in the treatment of KOA. This prospective comparative study was performed among 100 individuals diagnosed with KOA for one year. Participants were divided into two equal groups through simple random sampling. Group A (n = 50) participants received an intra-articular injection of PRP solution whereas group B (n = 50) participants received an intra-articular injection of CSs. Informed consent and ethical approval were also acquired prior to data collection. A self-designed proforma based on interviews was used to collect data. The data analysis was carried out via descriptive statistics and an independent t-test. Women (n = 71, 71%) had a higher prevalence of KOA than men (n = 29, 29%). The means of study variables like age, VAS score, and WOMAC score were 56.10 ±8.70 years, 8.08 ±1.6, and 70.08 ±8.76 respectively. The frequency of KOA on the right side was 62% (n = 62) while it was 38% (n = 38) on the left side. In the study population, 69% (n = 69) patients had grade II KOA, and 31% (n = 31) patients had grade III KOA. At the first-month, second month, and third-month follow-up visits, there were differences in the mean scores of the WOMAC and VAS between the study groups. However, at the first-month follow-up visit, mean scores of VAS and WOMAC were lower in group B than in group A while these were lower in group A as compared to group B, at the second month and third-month follow-up appointments. The authors concluded that intra-articular infiltration of both PRP and CSs was efficacious in the treatment of KOA-related pain and functional limitations; however, overall improvement in the PRP group was higher than CS group. This study has limitations including its small sample size, follow-up visits at short time intervals, single intra-articular injection sessions of both PRP and CSs, and administration of intra-articular injections without ultrasound guidance. Therefore, the results of this study can only be extended to local populations and could have bias. To make these findings generalized and unbiased about the use of intra-articular injections of PRP and CSs in the treatment of KOA, research studies with larger sample sizes, follow-up appointments at longer intervals, and multiple sessions of ultrasound guided intra-articular injections are needed.

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A systematic review and meta-analysis were performed by Barman et al. (2022) to assess the efficacy of autologous PRP injections in the treatment of patellar tendinopathy. The PubMed, MEDLINE, Embase, CINAHL, and Cochrane Central Register of Controlled Trials databases were searched for clinical trials that compared PRP injection with other "active treatment" interventions ("Non-PRP" injection and "No-injection" treatments) or "No-active treatment" interventions. Randomized and nonrandomized clinical trials that had been published up to November 15, 2021, were included in the meta-analysis. The primary outcome, pain relief, was measured on the VAS. Secondary outcomes were knee functional activities and quality of life. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed throughout the study. A total of eight comparative studies were identified for inclusion in the meta-analysis. Assessment of these studies revealed no differences in pain relief, functional outcomes, and quality of life in the short, medium, and long term between PRP injection and non-PRP injection interventions. Similarly, comparison of PRP injection with the no-active treatment intervention showed no differences in short- and medium-term pain relief. However, when PRP injection was compared with the no-injection treatment intervention ESWT, the former was found to be more effective in terms of pain relief in the medium term (MD, -1.50; 95% CI, -2.72 to -0.28) and long term (MD, -1.70; 95% CI, -2.90 to -0.50) and functional outcomes in the medium term (MD, 13.0; 95% CI, 3.01-22.99) and long term (MD, 13.70; 95% CI, 4.62-22.78). The authors concluded that in terms of pain relief and functional outcomes, the PRP injection did not provide greater clinical benefit than non-PRP injections in the treatment of patellar tendinopathy. However, in comparison to ESWT, a benefit in favor of PRP injection was observed. Limitations include heterogeneous treatment modalities in the control groups; additionally, in the eight studies included most of the findings in the subgroup analysis were based on one clinical trial only, and the total number of participants in each study was low. Further investigation is needed before the clinical usefulness of this procedure is proven. [Author Dragoo et al. (2014), previously cited in this policy, is included in this review].

A systematic review and meta-analysis by Migliorini et al. (2022) were performed to evaluate whether PRP augmentation in combination with arthroscopic meniscal repair would lead to greater patient-reported outcome measures (PROMs) and accelerate the healing process. This meta-analysis compared arthroscopic meniscal repair performed in isolation or augmented with PRP. The present study was conducted according to PRISMA 2020 guidelines. PubMed, Web of Science, Google Scholar, and Embase were accessed in August 2021. All the clinical trials, which compared arthroscopic meniscal repair performed in isolation or augmented with PRP, were included. Overall, 837 individuals were included; 38% (318 of 837 individuals) were women. The mean age of the individuals was 35.6 years (range, 20.8-64.3 years); the mean follow-up was 26.2 months (range, 6-54 months). Similarity was found in the analog scale (VAS; $p = 0.5$), Lysholm ($p = 0.9$), and IKDC scores ($p = 0.9$). Similarity was found in the rate of failure ($p = 0.4$) and rate of revision ($p = 0.07$). The authors concluded that the current published scientific evidence does not support PRP augmentation for arthroscopic meniscal repair. Limitations include the small number of studies included in the review, heterogeneity in PRP preparation and processing protocols, and timing of the PRP injection (i.e., during meniscal repair or after the meniscal suture). Well-designed, comparative studies with larger patient populations are needed to further describe safety and clinical outcomes.

Zhu et al. (2022) performed a systematic review and meta-analysis of RCTs to evaluate the effects of PRP on patient-reported functional scores, clinical assessments of knee function and structure, and complications following ACLR. The authors searched nine online databases for RCTs published in English or Chinese that examined the effects of PRP on ACLR. The primary outcome measures were the VAS for pain and IKDC scores. The secondary outcomes included the KT-1000 arthrometer, pivot-shift test, Lysholm and Tegner scores, tunnel widening, graft characterization, and complications. Subgroup analyses were performed according to time of assessments. Fixed- and random-effects models were selected for data analysis. A total of 14 studies were included. When PRP was injected into graft tunnels, the pooled VAS scores of the two groups were similar ($p = 0.31$), and the subgroup analysis found that VAS and IKDC only improved at 3 months post operation ($p = 0.0003$ and $p < 0.00001$, respectively). When PRP was used at the bone-patellar tendon-bone harvest sites, the VAS was decreased in the first 6 months post operation ($p < 0.00001$), whereas the IKDC score was not remarkably different ($p = 0.07$). After PRP injection, the Lysholm scores at 3 months post operation were different between the two groups ($p < 0.00001$), but Tegner scores ($p = 0.86$), KT-1000 measurements ($p = 0.12$), positive rate of the pivot-shift test ($p = 0.64$), enlargement of tunnels (femoral, $p = 0.91$; tibial, $p = 0.80$), and characterization of grafts ($p = 0.05$) were not different. No difference in complications was found in either group. The authors concluded that PRP applied alongside ACLR could reduce postoperative pain and improve knee function in the short and medium terms but is ineffective in the long term. PRP does not improve knee stability and the enlargement of tunnels and does not accelerate the healing of grafts. Limitations are that the volume, concentration, intensity, and number of injections of PRP varied across the different studies as well as graft types (allografts and autografts) and fixation techniques, all of which may have affected the results. Further research with RCTs is needed to validate these findings.

An updated 2022 Hayes Comparative Effectiveness Review on PRP for the treatment of ligament injuries and tendinopathies of the knee identified one good-quality systematic review and meta-analysis with findings from four RCTs and two quasi-RCTs assessing the efficacy of PRP vs that of no PRP in ACLR surgery or at the patellar graft donor site. Two additional primary RCTs were identified that supplemented these data. Two primary RCTs were identified that

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examined the use of PRP vs no PRP in individuals with PT. No studies of PRP use in medial collateral ligament injuries were found. The use of PRP in ACLR may not yield different functional outcomes from ACLR without PRP. However, limited evidence from individuals who received PRP for patellar donor site morbidity suggests that function may improve more by 12 months compared with that in individuals who did not receive PRP treatment and that use of PRP may reduce graft donor site pain more than no PRP. With regard to PT, limited and conflicting evidence precludes conclusions regarding functional improvement and pain reduction for PRP relative to some active controls. There is a paucity of evidence regarding the use of PRP to treat other ligament injuries or tendinopathies of the knee. The overall quality rating of the evidence was low to very low due to study limitations and inconsistency in the data, and the report concluded that no proven benefit was observed for this indication. [Author Dragoo et al. (2014), previously cited in this policy, is included in this review]. The 2020 annual review identified one new key RCT study. This updated annual review identified two new primary RCTs; however, the evidence remains unchanged.

An ECRI Clinical Evidence Assessment (2021) on PRP for patellar tendinopathy assessed one systematic review with RCTs and two RCTs not included in the systematic review. PRP safety and effectiveness were compared with those of alternative therapies. Primary outcomes were pain, function, and AEs. The authors reported no significant differences in PRP-treated individuals compared with saline-treated individuals after 1 year and with dry-needling individuals after 6 months. PRP-treated individuals had greater pain relief than those undergoing ESWT at 1 year and receiving high-volume image-guided saline injections at 6 months. A meta-analysis of all four RCTs found no significant differences in pain. PRP with autologous expanded bone marrow mesenchymal stem cells revealed that pain improved in both groups after 6 months, with no differences between groups. The authors reported no significant differences in function, measured using Victorian Institute of Sport Assessment-Patella (VISA-P) scores, in PRP-treated individuals compared with saline-treated individuals after 1 year and with dry-needling individuals after 6 months. Two other RCTs reported that PRP-treated individuals had greater function improvement than individuals undergoing ESWT at 1 year and high-volume image-guided saline injections at 6 months. A meta-analysis of all four RCTs found no significant differences in VISA-P. No AEs were reported. The authors concluded that PRP injections may improve pain and function in patients with patellar tendinopathy, based on inconclusive evidence. Limitations include the small study size, short follow-up period, and potential bias risks. Larger RCTs with longer follow-up that compare PRP with other treatments treating patellar tendinopathy and report patient-oriented outcomes are needed. (ECRI, 2021)

Lopez-Royo et al. (2020) performed a systematic review and meta-analysis of RCTs to determine the effectiveness of minimally invasive techniques (MITs) in individuals with patellar tendinopathy. The study included a total of 10 RCTs and 326 individuals. Five RCTs were included in the meta-analysis. The primary outcome was functionality using the VISA-P questionnaire. The secondary outcome was focused on pain. The study revealed that MITs, including PRP, skin-derived tenocyte-like cells, and dry needling combined with exercise lasting over 6 weeks, resulted in better results in pain and functionality than other short-term treatments. Long-term results revealed that skin-derived tenocyte-like cells and dry needling are more effective than PRP. The authors concluded that while PRP was effective post treatment, the improvements were not maintained over time and may have secondary effects. In addition, the authors concluded that it will be necessary to develop RCTs that not only analyze the effect but also compare efficacy between different MITs. Limitations include the short-term follow-up, which did not allow for assessment of intermediate- and long-term outcomes. Further investigation is needed before the clinical usefulness of this procedure is proven.

Achilles Tendinitis and Plantar Fasciitis

Fucaloro et al. (2025) performed a systematic review and meta-analysis to investigate complications of PRP injections for foot and ankle pathologies to better inform clinical decision making. A systematic review of the PubMed, Embase, Web of Science, and Cochrane databases was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to identify randomized controlled trials documenting complications after PRP injections for foot and ankle pathologies. Condition studied, demographic characteristics, and complications were extracted. Complication rates and the number needed to harm were calculated, and random-effects models were generated to compare complications using odds ratios, with $p < .05$ indicating significance. Sixteen studies assessing Achilles tendon injuries, plantar fasciitis, ankle osteoarthritis, and osteochondral lesions of the talus were identified, with 674 participants receiving PRP and 749 participants received alternative treatments (corticosteroid injection, saline solution injection, dry needling, hyaluronic acid injection, prolotherapy, and stromal vascular fraction injection). Twelve studies reported no complications. Four studies reported 277 complications in the PRP group (complication rate, 41.1%) and 249 complications in the comparison group (complication rate, 33.7%) ($p < .01$). Treatment-site pain was the most common complication, occurring at a higher rate in the PRP group (15.1% vs 10.2%, $p < .01$), and metadata showing higher odds of pain after PRP injection (odds ratio = 2.23, $I2 = 0.0\%$, $p < .01$). For PRP treatment, the number needed to harm was 13. One patient receiving PRP injections for Achilles tendinopathy experienced severe pain that resolved with surgical debridement. No other serious complications or infections occurred. The authors concluded that PRP injections in the foot and ankle have higher rates of post-injection pain versus comparison treatments, and an estimated 13 participants needed to receive PRP injections to experience any complication over an alternative injection. Only one

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participant experienced an event that necessitated surgical intervention. This systematic review and meta-analysis have limitations. The inclusion criteria did not select for specific PRP preparations and administration protocols. These less stringent inclusion criteria allowed for inclusion of a greater number of RCTs for analysis; however, it resulted in increased heterogeneity of PRP use procedures. Additionally, this study did not assess safety regarding multiple PRP injections in the series. Furthermore, with follow-up being limited to 36 months, complications related to treatment failure for which the decision was made to pursue surgical intervention may not be reflected in this review. In addition, this review was primarily limited by the accuracy and consistency of reported complications in each included study. Adverse event reporting was not standardized across RCTs, which resulted in ambiguity regarding duration and severity of non-serious complications. The findings of this review need to be validated by well-designed studies. Further investigation is needed before the clinical usefulness of this procedure is proven.

Herbert et al. (2024) performed a systematic review and meta-analysis to compare the effectiveness of PRP to other conservative treatment options for the management of plantar fasciitis (PF). A systematic search of PubMed and Google Scholar was performed for RCTs comparing PRP to other treatment modalities. Studies met inclusion criteria if mean and standard deviations for VAS pain scores, plantar fascia thickness (PFT), Foot Function Index (FFI), or American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score were reported. Mean differences (MD) were used to compare VAS pain, PFT, FFI, and AOFAS between PRP and other treatments. Ultimately, 21 RCTs which altogether included 1356 patients were included in the meta-analysis. PRP demonstrated greater improvements in VAS pain scores compared to extracorporeal shock wave therapy (ESWT) [SMD: 0.86; CI: (0.30, 1.41); p = 0.002], corticosteroid injections (CSI) [SMD: 1.08; CI: (0.05, 2.11); p = 0.04], and placebo [SMD: 3.42; CI: (2.53, 4.31); p < 0.00001]. In terms of FFI, no differences existed among PRP, ESWT, CSI, dextrose prolotherapy (DPT), and meridian trigger points (MTP) in enhancing foot functionality. However, PRP demonstrated an advantage over phonophoresis, showing improvement in FFI scores (SMD: 3.07, 95% CI: 2.34-3.81). PRP did not demonstrate superiority over ESWT, CSI, or MTP for improving PFT, but it was more effective than phonophoresis (SMD: 3.18, 95% CI: 2.43-3.94). PRP demonstrated improvements in AOFAS scores over CSI [SMD: 3.31, CI: (1.35, 5.27), p = 0.0009] and placebo [SMD: 3.75; CI: (2.81, 4.70); p < 0.00001]. The authors concluded that PRP is more effective than CSI, ESWT, and placebo in reducing VAS and more effective than CSI and placebo in improving AOFAS. PRP did not demonstrate a consistent advantage across all outcome measures, such as PFT and FFI. These findings underscore the complexity of PF treatment and call for a more standardized approach to PRP preparation and outcome measurement. This study has limitations. There was a high degree of heterogeneity among the included studies, with I2 values ranging from 87 to 97%. Studies also varied in their methods of PRP preparation. Additionally, the overall quality of existing RCTs evaluating the effectiveness of various treatments for PF is low. Further research is needed to determine the clinical relevance of these findings.

In a 2024 prospective RCT, Kumar et al. compared the outcomes of PRP and corticosteroid injections for the treatment of persistent plantar fasciitis. Overall, 70 participants with chronic plantar fasciitis were randomized 1:1 to receive the interventions. Outcomes were assessed via VAS to assess pain, and functional status was assessed using the American Orthopaedic Foot and Ankle Society (AOFAS) score. Baseline scores were similar between the groups, and participants were followed up at 15 days and 1, 3, and 6 months. The results showed significantly greater improvements in VAS and AOFAS scores in the PRP group than the corticosteroid group at all follow-up times. No participants reported any adverse outcomes in either group. The authors concluded that PRP is more effective than corticosteroid injections for long-term pain and functional improvement and should be considered a viable treatment option for chronic plantar fasciitis. This study is limited by a small number of participants and short follow-up. Additional high-quality research with larger numbers of participants and longer follow-up is needed to validate these findings.

A systematic review and meta-analysis of RCTs was performed by Chutumstid et al. (2022) to investigate the efficacy and safety of DPT for treating chronic plantar fasciitis. A comprehensive review of RCTs investigating DPT for chronic plantar fasciitis was done. Two investigators independently screened the titles, abstracts, and full texts and extracted data from eligible studies. The changes in VAS pain score, Foot Function Index (FFI), AOFAS score, and plantar fascia thickness were analyzed. Reports of complications of the procedure were collected. Eight RCTs were included in the meta-analysis, analyzing 444 individuals in total. The subgroup analysis showed that at short-term follow-up (< 6 months), DPT was more effective in reducing VAS pain score than the non–active treatment control group, including exercise and normal saline solution injection. However, no difference in the change of VAS pain score was observed between the DPT and active treatment control group, which included ESWT, steroid injection, and PRP injection. DPT was more effective in reducing FFI, increasing AOFAS score, and reducing plantar fascia thickness at short-term (< 6 months) follow-up than the other comparators. For long-term (≥ 6 months) follow-up, no significant difference in the change in VAS pain score and FFI was observed between the DPT group and the other comparators. No serious complication was reported. The authors concluded that DPT is an effective treatment of chronic plantar fasciitis to reduce pain, improve foot functional score, and decrease plantar fascia thickness at short-term follow-up. Further studies in larger populations are needed to identify the optimal treatment regimen, including dextrose concentration, volume, injection site, injection technique, and the number of injections required. The long-term effects of these treatments also require further examination. This meta-analysis is

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limited by the heterogeneity of the DPT treatment regimen, including the injected solution mixture, concentration, and treatment technique used in some trials and blinded injection used in the others. In addition, the control group varied greatly among studies, including placebo injection, exercise, and multiple active treatment options.

Fei et al. (2021) performed a systematic review and meta-analysis to compare the effectiveness of PRP vs that of steroid injection to relieve pain and improve foot and ankle function in individuals with plantar fasciitis. The study included a total of 12 RCTs involving 653 individuals performed between 2012 and 2019. The primary goals were pain relief and improved function. The VAS in the PRP group was lower than that in the steroid group at 6 months ($p = 0.02$), 1 year ($p = 0.02$), and 1.5 years ($p < 0.00001$) of follow-up. AOFAS scores in the PRP group were higher than those in the steroid group at 1 year ($p = 0.005$) of follow-up. The authors concluded that PRP injection is more effective in relieving pain and improving foot and ankle function than steroid injection at mid-term follow-up. Limitations include a small sample size and short duration of follow-up, high heterogeneity between studies, and subjective outcome measures.

In an updated 2021 Hayes Comparative Effectiveness Review, the effectiveness of PRP for the treatment of conditions of the Achilles tendon and plantar fascia was assessed based on measures of functional improvement and pain relief, along with rates of AEs. The report concluded that while PRP is a minimally invasive treatment that is associated with very few complications, available evidence from randomized trials does not indicate better functional outcomes after Achilles tendon repair (compared with no PRP), and evidence for use of PRP in Achilles tendinitis is limited and inconclusive. For the treatment of plantar fasciitis, PRP may lead to better functional and pain-related outcomes than corticosteroid injection, but evidence for other comparators is limited. The authors concluded that PRP development protocols varied considerably across studies; there was no consensus regarding best practices nor was there clear understanding of which steps and factors (if any) are associated with better outcomes. The annual review identified seven new RCTs. The studies had low-quality evidence and did not change the previous conclusion. Authors Usuelli et al. (2018), Boesen et al. (2017), Gogna et al. (2016), and Jain et al. (2015), previously cited in this policy, are included in this Hayes report.

Shoulder

Desouza and Shetty (2024) performed a systematic review of RCTs comparing PRP with exercise and placebo injections for partial-thickness rotator cuff tears. Twelve studies comprising 762 individuals were included. The primary outcome was pain assessed by VAS score. The secondary outcome was function, assessed using the Constant-Murley score and American Shoulder and Elbow Surgeons (ASES) score. The results showed that at 6 weeks, the PRP group had significantly higher VAS scores than the control group, which extended to 12 months; however, substantial variability was observed among studies. With regard to ASES and Constant-Murley scores, individuals receiving PRP had statistically significant improvement in the short term, but this improvement was not sustained in the long term, in which control groups had better long-term outcomes. The authors concluded that while PRP reduces pain in the short term, functional outcomes did not show significant improvements. The included studies are limited by heterogeneity in PRP preparation and concentration as well as an overall lack of detail regarding lesion size or classification. Future research is needed that reduces heterogeneity and that includes long-term follow-up.

Blanchard et al. (2023) conducted a systematic review on the outcomes of PRP as treatment for adhesive capsulitis objectively using ROM as well as subjective outcomes, including scores on the VAS; DASH; and SPADI. A total of 19 studies were included, 10 of which were RCTs. Overall, 592 individuals received PRP, and 671 received control interventions. Different control groups were included in all articles and included corticosteroid injections, physical therapy, medication management, and saline hydrodissection; however, these were not a requirement for inclusion. The results showed that all studies showed improved ROM and subjective improvement scores with both PRP and control treatments. The authors concluded that PRP is a promising option for patients with adhesive capsulitis. These conclusions are limited by heterogeneity in the type of PRP used, volume of injections, inclusion of anesthetics, and use of activators. Future research should focus on standardization of these confounders as well as longer follow-up times.

Ahmad et al. (2022) performed a systematic review and meta-analyses of rotator cuff repair using PRP to identify whether PRP improves clinical function and rate of tendon retears. The authors carried out a systematic review of previous meta-analyses published on the clinical outcomes of PRP used in the treatment of rotator cuff tears. They performed a comprehensive search of PubMed, MEDLINE, Cochrane, CINAHL, and Embase databases using various combinations of the commercial names of each PRP preparation and "rotator cuff" (with its associated terms), looking specifically at human meta-analysis studies involving the repair of the rotator cuff tendon surgically in the English language. Data validity was assessed and collected on clinical outcomes. Following this, a meta-analysis was undertaken. Thirteen meta-analyses met the inclusion and exclusion criteria. All were considered of similar quality, with an Oxman-Guyatt index of 9 and PRISMA score of more than 24. A total of 1,800 individuals were included, with an average follow-up of 12 to 36 months. Based on review, the use of PRP for arthroscopic rotator cuff tear, when compared with controls, leads to a lower number of retears and improved short-term postoperative scores and functional outcome. The following postoperative scores were reported: Constant, 12; Simple Shoulder Test, 10; ASES, 9; University of California, Los Angeles, 11; Single

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Assessment Numeric Evaluation, 1; VAS, 6; and retears, 13. Subgroup analysis showed that leukocyte content and gel application make no difference in the effectiveness of PRP. VAS score subgroup analysis showed short-term pain relief. The authors concluded that the study shows that PRP is effective in reducing retears after rotator cuff repair and improving functional outcome scores and reducing short-term pain. Limitations to this study include review of meta-analyses with low-level evidence and not individual RCTs. The findings of this review need to be validated by well-designed studies.

Hamid and Sazlina (2021) conducted a systematic review and meta-analysis to assess the clinical effect of PRP injection for rotator cuff tendinopathy. A literature search was conducted using CINAHL, MEDLINE, Scopus, SPORTDiscus, and Web of Science databases to retrieve articles published in peer-reviewed journals until December 2020. RCTs, which compared the clinical effects of PRP injection to the usual care among adults diagnosed with rotator cuff conditions, were reviewed. The main outcomes of interest were changes in shoulder pain symptoms and shoulder functions. All variables were analyzed using random-effects meta-analyses. Eight RCTs were reviewed in this study. The risk of bias for randomization was low for six RCTs, one study had unclear risk, and the other was a high risk. Studies vary on the PRP techniques, including preparation and injections. Moreover, the control intervention also differs. Four studies compared PRP with normal saline injection, while in the remaining four RCTs, the control interventions were rehabilitation program and dry needling. The authors concluded that meta-analysis of selected studies showed that PRP injection is a safe and effective intervention for long-term pain control and shoulder function in patients with rotator cuff disorders. Limitations include variations in PRP intervention and preparation; high heterogeneity was observed across studies. The optimal PRP used for shoulder tendinopathy is yet to be identified. In addition, the funnel plot showed possible publication bias that may be attributed to studies with small sample size and studies with negative results that were not published. Therefore, the outcomes reported in this meta-analysis should be interpreted with caution.

An ECRI Health Technology Assessment (2020) on PRP to aid healing after rotator cuff surgery included one systematic review (n = 781) and two RCTs (n = 87) to compare rotator cuff surgery with PRP and rotator cuff surgery without PRP. Pain and function were assessed. No studies reported on AEs, retreatment rates, or symptom resolution. A single study addressing PRP use after rotator cuff surgery does not support its use. Findings revealed that surgery with PRP reduced incomplete tendon healing (measured via imaging) compared with no PRP. One RCT reported that individuals treated with or without PRP did not differ in shoulder functional status. One RCT reported that Constant scores and pain (VAS) did not differ statistically between surgery with delayed PRP treatment (10 to 14 days post-surgery) and surgery without PRP. The authors concluded that rotator cuff surgery plus PRP yielded small incremental benefits in shoulder function and pain compared with surgery without PRP, but these are too small to be clinically significant. Limitations include small sample size and moderate risk of bias due to the single-center focus.

An updated 2020 Hayes Comparative Effectiveness Review on PRP for the treatment of rotator cuff repairs, tendinopathies, and related conditions identified one good-quality systematic review/meta-analysis with findings from 15 RCTs, along with six additional primary RCTs assessing the use of PRP in arthroscopic rotator cuff repair. Two RCTs were identified that examined PRP injections for the treatment of partial rotator cuff tears or rotator cuff tendinopathy, and two RCTs were identified that examined PRP use with arthroscopic acromioplasty (AA) or needling for calcific tendinitis. Compared with no PRP, the use of PRP in arthroscopic rotator cuff repair may provide short-term benefits for functional improvement and pain reduction, but data were conflicting for this finding, and benefits did not persist long term. Taken together, these findings provide some preliminary evidence that PRP may accelerate recovery from arthroscopic rotator cuff repair in the short term, but PRP treatment does not change long-term functional or pain outcomes. Limited evidence finds no difference in functional improvement with PRP injections for nonarthroscopic treatment of partial rotator cuff tears or tendinopathy, but findings were inconsistent with regard to pain. Finally, limited evidence suggests no difference in functional improvement after AA or needling for rotator cuff tendinopathy, along with no difference in pain relief after AA. The overall quality rating of this body of evidence is considered low to very low. [Authors Ebert et al. (2017), Pandey et al. (2016), Flury et al. (2016), Verhaegen et al. (2016), and Carr et al. (2015), previously cited in this policy, are included in this review]. A 2020 annual review identified two key RCTs. The evidence remains unchanged.

Lateral Epicondylitis

In a 2023 retrospective cohort study, Shaikh et al. compared the clinical efficacy of PRP with that of methylprednisolone injections in patients with lateral epicondylitis. A total of 81 patients were included; 46 received methylprednisolone injections, and 35 received PRP. The primary outcome was improved pain on Numeric Pain Rating score. Secondary outcomes included Quick Disabilities of the Arm, Shoulder, and Hand score, grip strength, and VAS. The results showed no difference in outcomes of the Numeric Pain Rating Scale at the 12-month follow-up, with decreased pain in both groups from 6 to 52 weeks. However, patients receiving steroid injections had significant pain relief at 6 and 12 weeks when compared with the group receiving PRP. No significant differences were observed with regard to the Quick Disabilities of the Arm, Shoulder, and Hand scores and grip strength between the two groups. The authors concluded that no difference between the outcomes of PRP and methylprednisolone injection in the management of lateral epicondylitis

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was observed at 12 months of follow-up and recommend continuing with corticosteroids until higher-quality evidence of superiority is available.

Masiello et al. (2023) conducted a systematic review and meta-analysis evaluating USG injections of PRP as conservative treatment of tendinopathies. A total of 33 RCTs (2,025 individuals) met the inclusion criteria: eight in lateral epicondylitis, five in plantar fasciitis, five in Achilles tendinopathy, seven in rotator cuff tendinopathy, three in patellar tendinopathy, and five in carpal tunnel syndrome. PRP, given as a single injection (20 trials) or multiple injections (13 trials), was compared with USG injection of steroids, saline, autologous whole blood, local anesthetic, dry needling, prolotherapy, bone marrow mesenchymal stem cells, or noninjective interventions. The outcomes more commonly reported included pain and functional measures, subgrouped as in the short term (< 3 months from the intervention), medium term (3 to 6 months), or long term (≥ 12 months). No clear between-group differences in these outcomes were observed in individuals with lateral epicondylitis; plantar fasciitis; or Achilles, rotator cuff, or patellar tendinopathy. In individuals with carpal tunnel syndrome, VAS scores for pain at 3 and 6 months and Boston Carpal Tunnel Questionnaire severity scores at 1, 3, and 6 months were lower in PRP recipients than in controls. The certainty of evidence of all these comparisons was graded as low or very low due to risk of bias, imprecision, and/or inconsistency. Pain at the injection site was more common among PRP recipients than controls receiving other USG injections. In individuals with tendinopathies, a trend toward pain reduction and functional improvement from baseline was observed after USG PRP injection, but in the majority of the comparisons, the effect size was comparable to that observed in control groups. The authors concluded that evidence to routinely recommend USG PRP injections is insufficient. Further well-designed, large, randomized trials are needed to better define potential indications for long-term benefits of, and optimal treatment protocols for PRP as a conservative treatment in orthopedics.

A systematic review and meta-analysis by Niemiec et al. (2022) were performed to evaluate the effectiveness of PRP in lateral epicondylitis treatment using MCID values as a reference and to investigate if leukocyte content can influence the effectiveness of the therapy. Following the PRISMA guidelines, the authors searched the MEDLINE and Scopus databases for studies on lateral epicondylitis and PRP therapy that used the following PROMs: VAS for pain; DASH; PRTEE; and Mayo Clinic Performance Index (MAYO). The weighted arithmetic means for the PROMs were calculated at baseline (week 0) and follow-up weeks 4, 8, 12, 24, 52, and 104. The MDs in outcomes (ΔVAS, ΔDASH, ΔPRTEE, and ΔMAYO) were compared with the MCID values at each follow-up point. In addition, the effectiveness of LR-PRP vs that of LP-PRP was also compared. The Student *t* test was used in all analyses. A total of 26 studies were included in the analysis. After PRP injection, all PROM scores improved with time. The scores improved significantly from baseline to each follow-up time ($p < 0.0001$), with the exception of the PRTEE (no significant difference at follow-up weeks 12 and 52). The MD in scores from baseline exceeded the respective MCIDs from weeks 4 to 104 for the VAS and DASH, from weeks 4 to 52 for the MAYO, and from weeks 8 to 52 for the PRTEE. The MCID for each of the PROMs was exceeded at almost every observation period in both the LR-PRP and the LP-PRP systems. Based on comparisons with the MCID values of commonly used outcome scores, the authors concluded that PRP seems to be an effective form of treatment for lateral epicondylitis. Both the LR-PRP and the LP-PRP systems were effective in the context of meeting the MCID. Limitations include varying parameters in the studies used for this analysis, including protocol; type of PRP preparation; preparation technique and administration; postinjection management, including rehabilitation; characteristics of the individuals; and baseline clinical conditions. There is also a high risk of heterogeneity among the compared clinical studies. The available evidence is limited, with overall poor-quality methodology and design and diversity in reporting outcome measures. Therefore, no conclusions can be made regarding the relative efficacy, effectiveness, or safety of treatment.

An ECRI Clinical Evidence Assessment on PRP for lateral epicondylitis included two systematic reviews that included 25 RCTs and five additional RCTs (n = 2,033) to compare PRP with alternative treatments (e.g., saline, corticosteroid injections) or placebo. Pain, function, and AEs were assessed. Findings revealed that saline injection, PRP injection, and steroid injections all provided comparable pain relief and functional improvement up to 3 months post treatment. However, by 3 months, PRP provided better pain relief than steroid injection. PRP combined with surgery revealed improved pain in both groups up to 1 year post treatment. However, at 24 weeks post treatment, PRP provided better pain control than physical therapy. Transient postinjection pain was the most reported adverse reaction, and no serious AEs were observed. The authors concluded that evidence is inconclusive, with mixed results for PRP as treatment for lateral epicondylitis. Limitations include wide variations in how PRP is prepared and used as well as varied characteristics of individuals and symptoms of lateral epicondylitis (ECRI, 2021).

In a 2021 Comparative Effectiveness Review by Hayes, which was updated in January 2022, prolotherapy using PRP was identified as a minimally invasive treatment option for patients with persistent lateral epicondylitis that is unresponsive to other conservative measures. Current evidence suggests that PRP may yield some long-term benefits that are not apparent before 6 months, particularly when compared with corticosteroid injection. Once PRP preparations are standardized and best practices are established, trials can identify which factors are associated with better outcomes,

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yielding more effective PRP preparations and patient selection criteria. Author Schöffl et al. (2017), previously cited in this policy, is included in this review.

In 2017, Merolla and colleagues conducted a prospective, comparative, randomized study to compare the efficacy of autologous PRP injections and arthroscopic lateral release in treating chronic lateral epicondylitis. A total of 101 participants received arthroscopic release (n = 50) or USG PRP injections (n = 51). Outcomes were assessed using the VAS for pain, PRTEE, and a calibrated hand dynamometer for grip strength. Follow-up assessment intervals were at weeks 2, 4, 8, 12, and 24 and at 1 and 2 years for the PRP group. While unable to be assessed at weeks 2 and 4 due to immobilization and rehabilitation, the arthroscopy group was evaluated at the same intervals. Both groups experienced significant improvement in all measures. The PRP group experienced significantly improved grip strength at week 8; all other significant differences were in favor of arthroscopy. Consumption of rescue pain medication was not significantly different between the groups. The authors concluded that while both procedures were safe and well accepted, arthroscopic release ensured better long-term outcomes than PRP injection. The findings are limited by a lack of comparison to a placebo injection and active intervention in the non-PRP group.

Foot Injuries

In 2024, Basciani et al. conducted a systematic review and meta-analysis to evaluate the effects of additional procedures on arthroscopic ankle microperforations for osteochondral lesions (OCLs). Ten studies comprising 464 individuals undergoing microperforation were included. Of the total number of individuals, 276 underwent microperforation combined with other therapies that included PRP, HA, and bone marrow concentrate. The results showed benefit with all surgical procedures, with or without additional therapies. With regard to the additional therapies, the results showed no significant difference in VAS and AOFAS scores when comparing arthroscopic microperforation and arthroscopic microperforation plus HA. Slightly better AOFAS scores were observed in the PRP group, but this was not statistically significant. The authors concluded that arthroscopic microperforations with the additional therapies of HA, PRP, and bone marrow concentrate result in improved postoperative outcomes regarding return to daily activities and improvement in symptoms; however, these were not significant. Further studies with larger numbers of participants are needed to validate these findings.

Görmeli and colleagues (2015) conducted a prospective, blinded RCT to compare the effects of HA and PRP as adjunct therapies after arthroscopic microfracture in OCLs of the talus. Participants with talar OCLs in their ankle joints (n = 40) were treated with arthroscopic debridement and a microfracture technique. Thirteen randomly selected participants received PRP, 14 participants received HA, and the remaining 13 participants received saline as a control group. The participants were assessed using AOFAS and VAS scores after a 15-month follow-up. Post operation, all the groups had significantly increased AOFAS scores and decreased VAS scores compared with their preoperative results. The AOFAS scores were significantly increased in the PRP group vs the HA and control groups, although the increased AOFAS scores in the HA group vs the control group were also significant. Similar to the AOFAS scores, the decrease in the VAS scores was significantly lower in the PRP group vs the HA and control groups. The HA group had significantly lower VAS scores than the control group. The authors concluded that both PRP and HA injections improved the clinical outcomes in participants who underwent surgery for talar OCLs in the midterm period and can be used as adjunct therapies for these participants. Because a single dose of PRP provided better results, they recommended PRP as the primary adjunct treatment option in the talar OCL postoperative period. Limitations to this study include small sample size, a short follow-up period, and no masking of the participants to the intervention, which could have introduced biases.

Low Back Pain

Zhang et al. (2024) performed a network meta-analysis of four RCTs comprising 154 individuals that evaluated the clinical efficacy of PRP compared with that in control groups that included corticosteroid and lidocaine injections and RF treatment for chronic LBP. Outcomes were assessed using the VAS and Oswestry Disability Index (ODI). Follow-up time ranged from 4 to 52 weeks. The results showed that VAS scores for all interventions resulted in significant pain reduction at 4 weeks, and it was not statistically significant between the individuals receiving PRP and corticosteroid or lidocaine. These results were the same at 3 and 6 months. A significant difference between individuals injected with PRP and RF at 3 months that did not continue to the 6-month follow-up was observed. With regard to ODI, all groups had significant improvements in disability indices compared with before injection at all follow-up points; however, none were statistically significant, except the PRP compared with RF at 3 months and PRP vs corticosteroid at 6 months. The authors concluded that corticosteroid injections showed better short-term improvement after 4 weeks. PRP injections and RF improvement effects matched, but at least 6 months of follow-up showed that PRP injections were better in terms of improvement of disability indices. This article is limited by a small number of relevant studies and participants, and large, well-designed studies that include optimal preparation and quantity of PRP are needed to validate these findings.

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Singh et al. (2023) conducted a double-blinded RCT aimed to evaluate the effect of autologous PRP on LBP in participants with LBP due to prolapsed intervertebral disk (IVDP). A total of 42 participants with IVDP were randomized either to the autologous PRP (n = 21) group or control (epidural local anesthetics with steroids; n = 21) group. Change in pain was assessed using the numeric rating scale (NRS). Impact of treatment was assessed using the Global Perceived Effect scale. All the participants were followed up for 6 months. Data were compared using the chi-square independent sample *t* test and Mann-Whitney U test. The two groups were similar in their demographic and clinical profiles. The baseline mean NRS ±SD was 6.91 ±0.94 in the PRP group and 7.38 ±1.16 in the control group (p = 0.099). At 6 months, the mean NRS ±SD was 1.43 ±0.75 in the PRP group compared with 5.43 ±0.75 in the control group (p < 0.001). The Global Perceived Effect scale score was also found to be significantly higher in the PRP group than the control group in the final assessment (p < 0.001). During the course of the study, the PRP group had a consistent decline in NRS, whereas the control group had an initial decline followed by a consistent increase in NRS. The authors concluded that PRP provided sustained relief from LBP due to IVDP and that it can be recommended as a safe and promising alternative to epidural local anesthetics and steroids. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population. In addition, the short-term follow-up did not allow for assessment of intermediate- and long-term outcomes. Further investigation is needed before the clinical usefulness of this procedure is proven.

Singjie et al. (2023, included in the Zhang 2024 systematic review above) conducted a systematic review and meta-analysis to determine the efficacy of PRP treatment for individuals with chronic LBP. Comprehensive database searches were performed in four databases. This study was conducted and reported based on the PRISMA guidelines and registered to PROSPERO. The authors included and examined RCTs that looked into research that used PRP for individuals with chronic LBP. Outcomes of interest included clinical enhancement of pain, which is demonstrated in pain scores. Following initial screening, three studies were included, comprising 138 individuals with chronic LBP. After 1, 3, and 6 months post injection, a substantial reduction in the pain score difference between the PRP and control groups was observed, demonstrating PRP's superiority over the control group in the treatment of chronic LBP. The authors concluded that PRP injection enhances chronic LBP in the first, third, and sixth months after injection compared with controls. A limitation of this analysis is the small number of samples among the included studies. Further research with RCTs is needed to validate these findings.

A prospective, double-blinded RCT was conducted by Won et al. (2022, included in the Zhang 2024 systematic review above) to evaluate the efficacy of PRP injection and prolotherapy in participants with chronic LBP. This RCT was conducted over a period of 3 years for participant enrollment and follow-up. Overall, 34 participants with chronic, nonspecific LBP (duration of at least 3 months) refractory to conventional management were randomized to PRP injection and lidocaine injection. Participants were treated with weekly PRP or lidocaine injections at the lumbopelvic ligaments for two weeks and then weekly prolotherapy with 15% glucose for two weeks and followed up for 6 months. The VAS, ODI, and Roland-Morris Disability Questionnaire were evaluated at the initial visit, four weeks, three months, and six months: 0.2 (95% CI, -1.15 to 0.74), 0.0 (95% CI, -1.41 to 1.46), and 0.7 (95% CI -0.54 to 1.97). Four participants did not complete this trial. Three were in the PRP injection group, and one was in the lidocaine injection group. Results of the study revealed that the pain intensity was decreased with PRP injections at 6 months compared with lidocaine injections; the between-group difference was 0.9 (95% CI, 0.10-1.75; p = 0.027). All participants had a decreased pain and disability index at 4 weeks, 3 months, and 6 months, but no differences between groups were observed, except for the VAS at 6 months. The baseline parameters revealed no differences in both groups. The authors concluded that in chronic, nonspecific LBP, the PRP injection in combination with prolotherapy is an effective intervention, and either lidocaine or PRP injection reduced disability. In addition, the authors stated that injection at the lumbopelvic ligaments using PRP and prolotherapy is also an effective treatment for pain. Limitations include a small sample size (34 participants) and short duration of follow-up (6 months).

Zhang et al. (2022) conducted a prospective clinical study aimed at evaluating the effectiveness of autologous PRP on discogenic LBP at 48 weeks post injection in participants who received a single intradiscal injection. All participants received a single intradiscal injection of PRP in a prospective trial. Pain scores, lumbar function, and AEs were assessed at 1 week, 4 weeks, 8 weeks, 12 weeks, 24 weeks, and 48 weeks post injection and compared with the preinjection values (0 weeks). Data were analyzed from 31 participants, with a 94% follow-up rate. Compared with prior to injection, pain and lumbar function were improved, and differences (p < 0.05) over the 48-week follow-up were observed. Overall, 22 participants (71%) were classified as successes after the intradiscal injection of PRP. One participant received surgery at 2 weeks post injection due to intervertebral discitis. The authors concluded that intradiscal injection of PRP can relieve pain sensation and improve lumbar function in patients with discogenic LBP over a 48-week follow-up period. This study has several limitations. First, the sample size was relatively small, and a control group was not used. Second, there is a lack of composition data of PRP on cell count, including platelets, red cells, and white blood cells, as well as biological analysis of various growth factors. Finally, there is no routine radiological assessment of the morphological changes of the disk treated with PRP during follow-up, preferably with MRI analysis. Further RCTs are needed to assess the effects of this injection therapy.

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Zielinksi et al. (2022) performed a prospective, multicenter, randomized, double-blinded, placebo-controlled study to evaluate the efficacy of PRP for the treatment of lumbar discogenic pain. Overall, 26 (12 men, 14 women) human participants, who were aged 25 to 71 years with a diagnosis of chronic lumbar discogenic pain, were randomly assigned to active (PRP) or control (saline) groups in a ratio of two active to one control. Baseline and follow-up ODI and Numeric Pain Rating Scale questionnaires were obtained to track participant outcomes at 8 weeks post operation. Within-group assessment showed a clinically significant improvement in 17% of PRP participants and clinical decline in 5% (one participant) in the active group. Clinical improvement was seen in 13% of placebo group participants, and no placebo participants had clinical decline secondary to the procedure. The authors concluded that this study posits necessary caution for researchers who wish to administer PRP for therapeutic benefit and may ultimately point to necessary redirection of interventional research for discogenic pain populations. Limitations include a small sample size (26 participants) and short duration of follow-up (8 weeks). Additional limitations include a range of factors, including differences in participant demographics, outcome-measure sensitivity, and misalignment of statistical analyses. Further investigation is needed before the clinical usefulness of this procedure is proven.

A randomized study by Wu et al. (2017) compared efficacy and safety between autologous PRP and local anesthetic /corticosteroid intra-articular injection for the treatment of lumbar facet joint syndrome. Overall, 46 participants were randomized into group A (intra-articular injection with PRP) and group B (intra-articular injection with local anesthetic/corticosteroid). Outcomes were assessed via the VAS, Roland-Morris Disability Questionnaire, ODI, and modified MacNab criteria for pain relief and applications of posttreatment drugs; assessments were performed prior to injection, at 1 week, and at 1, 2, 3, and 6 months post injection. No significant difference between groups was observed at baseline. Compared with prior to treatment, both group A and group B demonstrated statistical improvements in the pain VAS score at rest or during flexion, Roland-Morris Disability Questionnaire, and ODI. For group B, subjective satisfaction based on the modified MacNab criteria and objective success rate were highest (80% and 85%) after 1 month but only 50% and 20%, respectively, after 6 months. However, for group A, they increased over time. No treatment-related complications were reported by either group. The authors concluded that both autologous PRP and local anesthetic/corticosteroid for intra-articular injection are effective, easy, and safe enough in the treatment of lumbar facet joint syndrome. However, autologous PRP was considered superior due to longer duration of efficacy. Limitations to this study include a short follow-up period and small sample size.

Singla and colleagues (2017) conducted a Prospective Randomized Open Blinded End-Point (PROBE) study to assess the efficacy and safety of PRP compared with those of methylprednisolone in USG sacroiliac joint (SIJ) injection for LBP. Participants (n = 40) with chronic LBP and SIJ pathology were randomly allocated into two groups. Group S received 1.5 mL of methylprednisolone (40 mg/mL) and 1.5 mL of 2% lidocaine with 0.5 mL of saline, while Group p received 3 mL of leukocyte-free PRP with 0.5 mL of calcium chloride into USG SIJ injection. VAS scores, Modified Oswestry Disability Questionnaire scores, 12-Item Short Form Survey scores, and complications (if any) were evaluated at 2, 4, 6, and 12 weeks. Intensity of pain was significantly lower in Group p at 6 and 12 weeks than Group S. The efficacy of steroid injection was reduced to only 25% at 3 months in Group S, while it was 90% in Group P. Participants receiving PRP also showed a reduction of VAS of ≥ 50% from baseline when other factors were controlled. The Modified Oswestry Disability Questionnaire and 12-Item Short Form Survey scores were improved initially for up to 4 weeks but deteriorated further at 3 months in Group S, while both the scores improved gradually in Group p for the entire follow-up period. Authors concluded that PRP injection is an effective treatment modality in LBP involving the SIJ. Limitations include a small study group size and short follow-up period.

A prospective, double-blinded RCT was conducted by Tuakli-Wosornu et al. (2016) to determine whether single injections of autologous PRP into symptomatic degenerative intervertebral disks will improve participant-reported pain and function. Adults (n = 46) with chronic (≥ 6 months), moderate to severe lumbar discogenic pain that was unresponsive to conservative treatment were randomized to receive intradiscal PRP (n = 29) or contrast agent (n = 18). Main outcome measures included the Functional Rating Index, NRS for pain, pain and physical function domains of the 36-Item Short Form Survey, and modified North American Spine Society Outcome Questionnaire. Data on pain, physical function, and participant satisfaction were collected at 1 week, 4 weeks, 8 weeks, 6 months, and 1 year. Participants in the control group who did not improve at 8 weeks were offered the option to receive PRP and subsequently followed up. Over 8 weeks of follow-up, statistically significant improvements were observed in participants who received intradiscal PRP, with regard to pain, function, and participant satisfaction, compared with controls. No AEs of disk space infection, neurological injury, or progressive herniation were reported following the injection of PRP. The authors concluded that intradiscal PRP injection resulted in significant improvements in function, pain, and participant satisfaction scores over 8 weeks compared with controls. Those who received PRP maintained significant improvements in functional scores through at least 1 year of follow-up. The study limitation cited is the very limited follow-up time of only 8 weeks for the randomized portion of the study and differential exclusion of participants after randomization. The authors concluded that although these results are promising, further studies are needed to define the subset of patients most likely to respond to biological intradiscal treatment and the ideal cellular characteristics of the intradiscal PRP injectate.

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Wounds

A Hayes Technology Assessment Report on PRP for wound treatment in diabetic foot ulcers (DFUs) was performed. For use of autologous PRP as an adjunct to conventional wound therapy (CWT) to treat adults who have hard-to-heal DFUs that have not responded to prolonged standalone CWT, a C rating was assigned. An overall low-quality body of evidence comprises 12 RCTs and two prospective cohort studies and suggests that PRP is safe and has the potential to improve wound healing compared with standalone CWT in patients with DFUs that have not healed adequately with CWT. Despite the abundance of well-designed studies, conclusions of statistical analyses were inconsistent across the evidence base, and pooled interstudy ranges of key efficacy outcomes varied widely. Furthermore, 13 of the 14 studies used different PRP preparation protocols, and three methods of PRP application were investigated. Three of the reviewed studies included individuals with concomitant peripheral artery disease (PAD) and evaluated how concurrent disease impacted the efficacy and safety of PRP compared with individuals who had DFUs and no PAD, suggesting that the existence of PAD impedes healing. The heterogeneity across studies leaves substantial uncertainty regarding which PRP protocols are most effective and which patient populations are most likely to benefit from PRP therapy (Hayes, 2022, updated 2024). Author Deng et al. (2022), previously cited in this policy, is included in this review.

Boztug et al. (2021) conducted a prospective RCT to evaluate the effect of PRP on participants' pain scores, wound healing, and quality of life in the process of treatment for pilonidal sinus (PS) disease. Participants who were over 18 years old and had chronic PS disease between March 2018 and January 2019 were enrolled and randomly divided into three groups. Open surgery and moist dressings were applied to participants in group A (n = 18). Open surgery followed by PRP application was performed on participants in group B (n = 22). Group C (n = 9) underwent curettage of the sinus cavity followed by application of PRP. In this prospective RCT study, participants completed questionnaires (including the Nottingham Health Profile, 36-Item Short Form Survey, and clinical information) before and after surgery. Demographics, preoperative characteristics, healing parameters, and quality-of-life scores were evaluated and calculated before and after surgery. The cavity volume and wound healing time were compared among the groups on postoperative days 0, 2, 3, 4, and 21. Each participant was followed up throughout the process of wound healing, and follow-up was continued afterward to monitor the participants for recurrence. Due to the nature of the treatment that group C received, this group achieved shorter healing times and smaller cavity volume than the other groups. In contrast, the recovery time per unit of cavity volume was faster in group B than in the other groups. Overall postoperative pain scores were lower for both PRP groups (open surgery, group B; minimally invasive surgery, group C) than for group A ($p < 0.001$) and showed different time courses among the groups. The authors concluded that in the treatment of PS disease, PRP application improves postoperative recovery in that it speeds patients' return to daily activities, reduces their pain scores, and increases their quality of life. This study has limitations, including a small sample size. Group C had fewer participants than either of the other groups, as the authors stopped allocating participants to group C due to the high rate of postoperative abscess formation. The absence of a minimally invasive non–PRP-treated control for group C is another limitation. Also, participant follow-up times varied between 6 and 18 months. These limitations make it difficult to decide whether these conclusions can be generalized to a larger population.

An RCT was performed by Nolan et al. (2021) to determine if the local administration of fat grafts with PRP increases wound healing in DFUs at a histological level compared with standard care. A three-armed RCT was undertaken and included 18 participants with DFUs: fat grafting; fat grafting with PRP; and routine podiatry care. Biopsies were obtained at weeks 0, 1, and 4 and underwent quantitative histology/immunohistochemistry (H&E, CD31, and Ki67). Treatment with fat and PRP increased mean microvessel density at 1 week to 1,645 (SD, 96) microvessels/mm^2 (+ 32%-45% to other arms; $p = 0.035$). PRP appeared to increase vascularity surrounding fat grafts, and histology suggested that PRP may enhance fat graft survival. No clinical difference was observed between arms. The authors concluded that this study demonstrates that PRP with fat grafts increased neovascularization and graft survival in DFUs. However, the histology was not correlated with wound healing time. Future studies should consider using apoptosis markers and fluorescent labeling to ascertain if enhanced fat graft survival is due to proliferation or reduced apoptosis. The trial registration number is NCT03085550. The approach used to measure fat graft survival (visual comparison of the density of adipocytes) had limitations compared with other approaches, such as apoptosis markers or fluorescent labeling. In addition, another limitation is that increased microvessel density was observed at week 1; however, it is not clear which cell type is responsible for this. Additional limitations include small sample size (18 participants) and a short duration of follow-up (4 weeks).

A Hayes Health Technology Assessment report focused on the efficacy and safety of PRP for treatment of venous leg ulcers (VLUs). Individuals enrolled in the reviewed studies were adult men and women who had VLUs that had not responded adequately to conventional treatment, with an average VLU duration range from 3 months to 6 years. The studies included were eight RCTs and one comparative cohort study that evaluated PRP for treatment of VLUs. PRP was administered as either a gel, topical liquid, or injected liquid in conjunction with standard wound care and compared with standard wound care alone. Findings from seven studies suggested that PRP may significantly improve healing of VLUs, one study found no benefit, and the other study did not perform between-group statistical analyses. Six studies reported

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that no complications occurred. Two studies reported the following complications: cellulitis prompting antibiotic treatment (8%), superficial minute ulceration (4%), and pain (unidentified number of individuals). No deaths related to PRP treatment were identified. There was variation in protocols for preparation and administration of PRP, small treatment groups, heterogeneous study populations, and variability in the number of PRP treatment sessions. The authors concluded that the results of the reviewed studies suggested that PRP is reasonably safe for treatment of VLUs. Additional RCTs with large study populations and appropriate controls to avoid potential bias of results are needed to confirm that PRP improves VLU healing and to determine the optimal method for administration of PRP (Hayes, 2021; updated 2023). [Authors Escamilla Cardenosa et al. (2017) and Moneib et al. (2018), previously cited in this policy, are included in this review].

An ECRI Clinical Evidence Assessment on PRP for DFUs reported on 1,323 individuals. ECRI documented that PRP for DFUs reveals that "evidence is somewhat favorable"; however, given the inclusive evidence, routine use of these products is not recommended. This report focuses on how the safety and effectiveness of wound care that includes PRP therapy compares with those of standard wound care without PRP for treating DFUs. Moderate-strength evidence from a systematic review with meta-analysis of RCTs found that PRP therapy added to wound care for DFUs increased complete wound closure; low-strength evidence found that PRP shortened the time to complete wound closure and reduced wound area and wound depth compared with wound care with no PRP therapy. For outcomes of hospitalization rates, amputation, pain reduction, wound infection, recurrence, serious AEs, and deaths, no significant differences were found between groups treated with or without PRP. Three additional RCTs (not in the systematic review) reported either improved outcomes with PRP or no difference in outcomes. Thirteen RCTs and one observational study were meta-analyzed, and despite numerous limitations to the individual included studies, the SOE was low to moderate for DFU and outcomes in individuals, enabling conclusions, albeit with some level of uncertainty. Results of three additional RCTs were generally consistent with the systematic review findings for the outcomes assessed. Several factors limit the strength of these findings: lack of standard reporting of PRP preparation and application and selection of individuals and follow-up differences. Approximately 40% of RCTs did not report on AEs; reporting was inconsistent among those that did. Results may not be generalizable because studies were primarily single center and conducted in several different countries. Additional RCTs (preferably multicenter) are needed that use standard PRP protocols and standard reporting on key outcomes (ECRI 2021).

An ECRI Clinical Evidence Assessment on PRP therapy for chronic VLUs indicates that "evidence is inconclusive: too few data on outcomes of interest." This report focuses on whether standard wound care that includes PRP therapy is safe and more effective than standard wound care without PRP for chronic VLUs. Wound care that includes PRP therapy appears to be safe; however, evidence from a systematic review with meta-analysis and two additional single-center RCTs is insufficient to determine PRP therapy's effects on VLU wound healing. Results from the systematic review and two additional small RCTs regarding the potential benefits of adding PRP therapy to standard care are mixed. Findings from studies in the systematic review and additional RCTs were limited by lack of blinding and a standard procedure for producing PRP as well as differences in platelet concentrations, frequency of PRP application, and follow-up times. Also, results may not be generalizable because studies were primarily single center and conducted in several different countries. Additional RCTs (preferably multicenter) are needed that use standard PRP protocols and standard reporting on key outcomes. The authors did not identify any guidelines that discuss PRP therapy for chronic VLUs [ECRI 2021; Author Escamilla Cardenosa et al. (2017), previously cited in this policy, is included in this review].

Qu et al. (2020) completed a systematic review and meta-analysis to evaluate the efficacy of autologous PRP in individuals with lower extremity diabetic ulcers (DUs), lower extremity venous ulcers (VUs), and pressure ulcers (PUs). A total of 27 (22 randomized and five comparative observational) studies with 1,796 individuals were included in the review: DUs, 15; VUs, 11; and PUs, 2. Follow-up post treatment ranged from no follow-up to 11 months. PRP therapy increased healing and complete wound closure in lower extremity DUs compared with treatment without PRP (relative risk, 1.20; 97% CI, 1.09-1.32; moderate SOE). PRP therapy also shortened the time to complete wound closure and reduced wound area and depth (low SOE). No significant changes in terms of wound infection, amputation, wound recurrence, or hospitalization were observed. Evidence related to VUs and PUs was insufficient to estimate the effect on critical outcomes. No statistically significant difference in death, total AEs, or serious AEs was observed between PRP and management without PRP. The authors concluded that autologous PRP, based on moderate SOE, increases complete wound closure/healing, and low SOE shortens healing time and reduces wound size in patients with lower extremity DUs. The evidence is insufficient regarding VUs and PUs. Limitations include a lack of standard reporting of PRP formulation techniques, PRP concentration, formulation and volume used, lower extremity DU off-loading procedures and periprocedural restrictions, and patient recruiting methods. In addition, the available data are relatively weak and inconclusive and derived primarily from uncontrolled or poorly controlled studies with significant methodological flaws.

A systematic review was performed by Miron et al. (2017) to analyze studies using platelet-rich fibrin (PRF) for soft tissue regeneration, augmentation, and/or wound healing. Overall, 31 clinical studies were included; a total of eight reported the

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effects of PRF in an RCT, with five additional studies (13 total) reporting appropriate controls. In total, 58% of clinical studies reported positive wound healing events associated with the use of PRF. Overall, 27 of the 31 studies (87%) supported the use of PRF for soft tissue regeneration and wound healing for a variety of procedures in medicine and dentistry. The findings of the RCT were conflicting, with a number of studies showing no benefit of PRP. While the authors concluded that the currently available literature supports soft tissue regeneration after soft tissue regenerative procedures using PRF, they stated that appropriate controls with which to conduct comparative analyses are lacking. The authors note that it is imperative that the next wave of research using PRF as an adjunct to soft tissue regenerative therapies designs appropriate studies with necessary controls to further evaluate the regenerative potential of PRF for soft tissue wound healing.

In a meta-analysis, Martinez-Zapata et al. (2016) examined whether autologous PRP promotes the healing of chronic wounds. Ten RCTs that compared autologous PRP with placebo or alternative treatments for any type of chronic wound in adults were included (n = 442). Four RCTs recruited individuals with a range of chronic wounds; three RCTs recruited individuals with VLUs, and three RCTs studied foot ulcers in individuals with diabetes. The median length of treatment was 12 weeks. The authors concluded that the results were inconclusive as to whether autologous PRP improves the healing of chronic wounds generally compared with standard treatment. Autologous PRP may increase the healing of foot ulcers in individuals with diabetes compared with standard care, but it is unclear if autologous PRP has an effect on other types of chronic wounds. Three studies reported wound complications such as infection or dermatitis, but results showed no difference in the risk of AEs in individuals treated with PRP or standard care. These findings are based on low-quality evidence due to the small number of studies and individuals included and the poor methodological quality of the studies.

Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

A 2022 AAOS clinical practice guideline on management of OA of the knee states that PRP may reduce pain and improve function in patients with symptomatic OA of the knee. This recommendation is based on evidence from one or more low-quality studies, with consistent findings or evidence from a single moderate-quality study recommending for or against the intervention. The AAOS recommends that future research in this area should include detailed OA characterization, including subgroup analyses and osteoarthrosis severity stratification (AAOS, 2021).

A 2020 AAOS clinical practice guideline on management of glenohumeral joint OA is based on a systematic review of published studies. Evidence of the use of PRP in the treatment of OA of the glenohumeral joint is lacking, and this treatment cannot be recommended. The AAOS concluded that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA (AAOS, 2020).

A 2019 AAOS clinical practice guideline on the management of rotator cuff injuries makes the following recommendations:

- Limited evidence does not support the routine use of PRP for the treatment of rotator cuff tendinopathy or partial tears
- Strong evidence does not support biological augmentation of rotator cuff repair with platelet-derived products on improving patient-reported outcomes; however, limited evidence supports the use of liquid PRP in the context of decreasing retear rates
- Lack of supporting evidence does not support the routine use of PRP in the nonoperative management of full-thickness rotator cuff tears (AAOS, 2019)

American Association of Hip and Knee Surgeons

The American Association of Hip and Knee Surgeons 2019 position statement on biologics for advanced hip and knee arthritis stated, “It is our position that biologic therapies, including stem cell and PRP injections, cannot currently be recommended for the treatment of advanced hip or knee arthritis. With unproven benefits, high out-of-pocket costs for patients, and clear safety concerns, we do not support the routine clinical use of these therapies. While we do recognize the potential benefit of biologic therapies, we encourage rigorous, well-designed clinical trials to establish the safety, efficacy, and cost-effectiveness of these potential treatments prior to widespread adoption” (Browne et al., 2019).

American College of Rheumatology

A 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of OA of the hand, hip, and knee made the following recommendations:

- Prolotherapy is conditionally recommended against in patients with knee and/or hip OA
- PRP treatment is strongly recommended against in patients with knee and/or hip OA (Kolasinski et al., 2019)

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American Society of Interventional Pain Physicians (ASIPP)

A 2019 ASIPP guideline on the responsible, safe, and effective use of biologics in the management of LBP stated that after review of evidence, there is Level III (fair) evidence for intradiscal injections of PRP, whereas the evidence is considered Level IV (limited) for lumbar facet joint, lumbar epidural, and SIJ injections of PRP. The guideline also states that regenerative therapy may be provided independently or in conjunction with other modalities of treatment, including a structured exercise program, physical therapy, and behavioral therapy, along with the appropriate conventional medical therapy as necessary. Appropriate precautions should be taken into consideration and followed prior to performing biological therapy, including the awareness of the multiple guidelines from the US Food and Drug Administration, potential limitations in the use of biological therapy, and the appropriate requirements for compliance with the US Food and Drug Administration.

National Institute for Health and Care Excellence (NICE)

NICE's 2019 interventional procedures guidance on PRP injections for KOA states that the technology raises no major safety concerns; however, the evidence on efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Further research should be in the form of RCTs with medium- to long-term -follow-up, including validated measures of knee function and patient-reported outcomes.

In a diabetic inpatient clinical guideline, NICE recommends that autologous PRP gel should not be offered as treatment for diabetic foot problems, unless part of a clinical trial (2016, updated 2019).

Veterans Affairs/Department of Defense (VA/DoD)

The VA/DoD 2020 clinical practice guideline for the nonsurgical management of hip OA and KOA made the following statement: "There is insufficient evidence to recommend for or against platelet-rich plasma injections for the treatment of osteoarthritis of the hip or knee." The quality of evidence reviewed was very low, given the serious inconsistency and imprecision with study designs, lack of standardization (e.g., dose, frequency, preparation technique), and outcome measures.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Prolotherapy and platelet-rich plasma therapy are procedures and, therefore, not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of these procedures may be subject to FDA regulation.

For additional information, search product codes KSS, ORG, or JQC at the following website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed October 9, 2025)

The agents used in the reviewed studies, such as dextrose and lidocaine, are approved for injection by the FDA but are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off label.

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Policy History/Revision Information

Date	Summary of Changes
01/01/2026	**Template Update** • Created shared policy version to support application to Oxford plan membership **Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy versions 2025T0498BB and SURGERY 060.26

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

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