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Use of Platelet-rich Plasma Injections for Treatment in Patients Diagnosed With Achilles Tendinopathy

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USE OF PLATELET-RICH PLASMA INJECTIONS FOR TREATMENT IN PATIENTS DIAGNOSED WITH ACHILLES TENDINOPATHY

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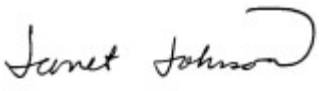
Signature: 

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Abstract

Background: Achilles tendinopathies are common among individuals who are active, usually participating in a sport with a high volume of repetitive motion. Historically, these injuries have been treated with conservative home exercises. If the patient exhausts their conservative treatment options, the next step is typically surgery to repair the tendon (Maffulli, 2015). Recently, platelet-rich plasma (PRP) injections have become more commonly used to treat musculoskeletal injuries and are considered minimally invasive procedures. This allows the patient to return home immediately post injection and return to activity within a few days. However, the research shows mixed results in terms of its effectiveness for treating these conditions.

Purpose: Determine whether platelet rich plasma (PRP) injections are an effective treatment option for individuals diagnosed with Achilles tendinopathy.

Results: Sixteen scholarly articles were analyzed using a matrix format and were evaluated with The John Hopkins Nursing Evidence-Based Practice appraisal tool. Eight of the 16 articles were in favor of using PRP injections to treat Achilles tendinopathies. This was determined using the VISA-A as the primary outcome measure while return to function, tendon thickness and vascularity were common secondary outcomes. Five articles reported PRP injections were not an effective treatment option; three articles concluded they required larger scale studies to make a determination.

Conclusion: PRP injections can be used secondary to traditional treatment of eccentric exercise and other modalities for patients who are looking for a minimally invasive treatment option.

Implications for Research and Practice: The findings of this research does not outline a clear determination for whether or not PRP injections are an effective treatment option for participants diagnosed with Achilles tendinopathy. Further research is needed on “excellent” quality articles with larger numbers of participants and with standardization of the preparation/procedure of the PRP injection.

Keywords: Achilles tendinopathy, platelet-rich plasma, PRP, treatment

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Chapter Ⅰ: Introduction

Over the last few years, platelet rich plasma (PRP) injections have become more commonly used to treat musculoskeletal injuries. United States estimates alone suggest that approximately 86,000 athletes are treated with PRP annually (Wasterlain, 2013). PRP has been used to treat a wide variety of orthopedic conditions, including knee osteoarthritis, lateral and medial epicondylitis, rotator cuff repair, patellar and Achilles tendinopathy, hamstring injuries, and anterior cruciate ligament (ACL) repairs. The research has shown mixed results in terms of its effectiveness for treating these conditions. PRP injections are a form of regenerative medicine. Doctors and researchers have found that the body has the ability to repair itself. Plasma is the liquid portion of the blood and is made up of mostly water and proteins. Platelets are the blood cells in the body that cause blood clots as well as necessary growth healing functions (Wasterlain, 2013). PRP therapy utilizes injections that use the patient's own platelets to accelerate healing in the body. The injection process is started by taking a few tubes of blood from the patient and putting them in the centrifuge to separate and concentrate the platelets. The physician then takes those platelets and injects them back into the patient at the injured site. This releases growth factors that stimulate and increase the number of reparative cells your body produces (Wasterlain, 2013). While research is still limited, there has been debate on whether or not PRP injections are an effective treatment option for Achilles tendinopathy injuries. Some research has shown there are minimal to no benefits, while others state this is a viable treatment option for patients.

Achilles tendinopathy, an overuse injury that occurs from repetitive and intense strain on the Achilles tendon has a prevalence of 9-40% in active individuals (Ackermann, 2012). This

variation is due to the type of activity the individual participates in and the activity level of the individual. Individuals suffering from Achilles tendinopathy will typically have a mild ache in the back of their leg or above their heel after activity. They might also experience tenderness and stiffness either right away in the morning or after long bouts of inactivity.

The traditional treatment for individuals diagnosed with Achilles tendinopathy is eccentric exercises (O'Neill, 2015). These exercises are stretching and strengthening exercises to target the Achilles tendon and the surrounding structures. Eccentric exercise involves a slow elongation of the muscle after a shortening contraction. The most common Achilles tendon eccentric exercise is to have the individual stand on the edge of a stair/ledge rise up on their toes, and then have them slowly lower themselves down, lowering themselves past the point of their toes. This eccentric exercise assists in lengthening the muscle; once the muscle has reached its end range, the lengthening ceases and the tendon undergoes a stretching period prior to a shortening period (O'Neill, 2015). It is critical to the patient's care to effectively manage their Achilles tendinopathy. After six months of conservative treatment, if there is no clinical improvement the next recommendation is surgical intervention (Maffulli, 2015). However, without some management of the injury, roughly 4% of individuals diagnosed with Achilles tendinopathy end up rupturing the tendon (Yasui, 2017). This could lead to a much longer timeframe when the patient would return to normal function.

Statement of Purpose

The purpose of this study is to determine whether platelet rich plasma (PRP) injections are an effective treatment option for individuals diagnosed with chronic Achilles tendinopathy. To determine the effectiveness of treatment options, outcomes assessed will be pain levels and

the amount of time to return to pre-injury level function. Minimal research has been conducted on the effects of PRP injections on Achilles tendinopathy injuries. This could be inhibiting PRP from becoming more widely used in orthopedic practices and could also be deterring insurance companies from seeing the benefits of this treatment option in order to cover the cost of services for patients.

Need for Review

Achilles tendinopathies are common among individuals who are active, usually participating in a sport with a high volume of repetitive motion. Historically, these injuries have been treated with conservative home exercises. If the patient exhausts their conservative treatment options, the next step is typically surgery to repair the tendon (Maffulli, 2015). PRP offers another form of conservative treatment that could potentially decrease pain levels as well as return patients to pre-injury function sooner than a patient's at-home exercise program. PRP injections are considered a minimally invasive procedure, which allows the patient to return home almost immediately post injection and return to activity within a few days. The injected substance is coming directly from the patient's body, which reduces the risk of the body having adverse side effects from an unknown substance being injected. Platelets from the blood, once they are injected into the body, offer healing and reduce inflammation at the injection site. This allows for the patients to be taken off of their anti-inflammatory medications. Long term use of anti inflammatory medication can have adverse health risks. It can cause gastrointestinal bleeding (bleeding in the stomach or elsewhere in the digestive tract), increases the risk of heart attack or stroke, skin reactions such as skin reddening, rash or blisters, or allergic reactions such

as hives, facial swelling, and wheezing (Commissioner, 2015). PRP injections are a more natural way for a muscle, tendon, ligament or joint to begin healing itself.

It is also necessary to review PRP injections in terms of whether or not it is cost effective for the patient. Currently, insurance companies have not seen adequate research stating that PRP injections are effective treatment options. Patients typically will have to pay for these injections out of pocket. This poses the question of whether or not the PRP injections are cost effective when compared to the traditional eccentric home exercise program. Another aspect to consider is the frequency with which patients would need these injections. If the patient is able to have one injection and return to function and then manage their symptoms moving forward, it is potentially a cost-effective treatment. However, if the patient needs to return to the clinic for an injection every 6-9 months, the treatment might not be right for them financially. If the PRP injection is going to reduce recovery time and return people back to function in a timely manner, then the out of pocket cost might be worth it for patients in the long run, and/or insurance companies will see the benefits and begin covering these services.

Significance for Athletic Training

An Athletic Trainer (AT) is an individual who works directly under a supervising physician. They respond to a wide variety of injuries in a multitude of different settings. ATs are well educated in the diagnosis and treatment of musculoskeletal injuries, and in some instances, they are the first people to lay eyes on the injury. An Athletic Trainer's main goals are to effectively and efficiently diagnose an injury and provide the best individualized treatment for the patient/athlete to return to function (Athletic Training, Minn. Stat, 2020). In order for an AT to provide the best care for their patients, they need to understand the benefits and risks of the

treatment plans they are recommending. It's necessary that an AT continue to learn, grow, and adapt with the new techniques of the medical world. However, PRP can take up to 3 months for the effects to take place in the body (Finnoff, 2011). In some instances, PRP injection might not be the most time- effective solution for a patient to return to activity. Athletic trainers need to be able to understand the pros and cons of each available treatment option and help their patients make the best decision for them individually. Overall, this review is intended to provide an understanding for ATs as to what treatment is best for their patients to reduce their pain levels and return them to function as quickly as possible after they have been diagnosed with Achilles tendinopathy.

Chapter Ⅱ: Methods

This chapter describes the processes and methods used to examine articles on the effectiveness of platelet-rich plasma (PRP) injections and eccentric exercise for the treatment of individuals diagnosed with Achilles tendinopathy. The search strategies, inclusion and exclusion criteria, number and type of studies selected, as well as the criteria used for evaluating the studies are discussed in this chapter.

Search Strategies

The majority of the studies found for this Critical Review of the Literature came from using CLICSearch, a database available to members of the Bethel University community. Several other articles were found using PubMed and Scopus. The remainder of the studies were found using the references of previously listed studies with a similar topic of study. Using the CLICSearch, the initial keyword used was “achilles tendinopathy.” This yielded over 6,000 results. In order to narrow the search, I included the keywords, “PRP or platelet-rich plasma,” which lowered the results to 1,100. In order to compare platelet-rich plasma injections and eccentric exercise for the treatment of achilles tendinopathy, the search team “eccentric exercise” was included; this yielded 368 results. CLICSearch allows for the researcher to set certain parameters for the search. The parameter of “peer reviewed” was selected to eliminate as much bias in the articles as possible. The initial search also included only “open access” articles to gain a starting point for the search process. This brought the article count to 132. By changing the dates to include only articles from 2010-2019, only 112 results remained. Lastly, the parameter “humans” was selected, and the parameter “surgery” was excluded. This left 31 remaining

results. The next step was to exclude articles that were irrelevant to the topic. Eighteen articles were used in this Critical Review of Literature.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were determined to locate relevant articles that were recently published in the Critical Review of Literature. In order for an article to be included, it had to have platelet-rich plasma injections and/or eccentric exercise as the treatment of Achilles tendinopathy. The articles also had to have been published within the last decade. All populations were included in this study, specifically all active and inactive individuals. All study designs were considered when reviewing the literature.

Exclusion criteria eliminated articles that were published prior to 2010. Articles that used treatment methods other than platelet-rich plasma injections and/or eccentric exercise for the treatment of Achilles tendinopathy were excluded. Articles with subjects who had ruptured their Achilles tendon (partially or fully) were also excluded. If the articles were not available other than to purchase or they were in another language other than English, they were excluded from this Critical Review of Literature as well.

Number and Types of Articles

Based on the inclusion and exclusion criteria, sixteen articles were chosen. All of the articles were reviewed using the John Hopkins Nursing Appraisal tool. See Appendix B.
The John Hopkins Nursing Evidence-Based Practice appraisal tool was used to determine the quality of each article; the articles were given a score of “High quality,” “Good quality,” or “Fair quality or major flaws.” This appraisal tool clearly explains how to deem the quality of the study. A high-quality study was characterized as being “consistent, generalizable results; sufficient

sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough reference to scientific evidence" (Dearholt, 2012). There was only one "high quality article." A good quality study was characterized as being "reasonably consistent results, sufficient sample size for the study design; some control; and fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes come reference to scientific evidence" (Dearholt, 2012). There were thirteen "good quality" articles. Lastly, the fair-quality study was characterized as being "little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn" (Dearholt, 2012). There were four "fair quality" articles. The level of evidence for each study was also assessed using the John Hopkins Nursing Evidence-Based Practice appraisal tool. The appraisal tool categorized the studies into two sections: A-Single Research Studies and B-Systematic Reviews with or without Meta-Analysis. In part A, three questions were answered:

Question 1: Was there manipulation of an independent variable?

Question 2: Was there a control group?

Question 3: Were the study participants randomly assigned to the intervention and control group?

Based on the answers to those questions, the articles were assigned a level. If "yes" was answered for all three questions, the study was considered a randomized control trial (RCT or an experimental study and determined to be a level 1). If "yes" was answered to questions 1 and 2 but "no" was answered to question 3, the study was considered quasi-experimental and given a level 2 grading. Lastly, if "no" was answered to questions 1, 2, and 3, the study was considered non-experimental and given a level 3 grade. In part B, if all the studies were Randomized

Controlled Trials (RCT), they were deemed level 1. If the articles were a combination of RCTs and quasi-experimental, or quasi-experimental only, the article was deemed level 2. Lastly, if the articles were a combination of RCTs, quasi-experimental, and nonexperimental or non-experimental only the article was deemed a level 3. Table 1 provides a clear representation of the level of evidence and quality for each article included in the literature review.

Table 1: Level of Evidence and Quality of Included Articles

Level of Evidence	High Quality	Good Quality	Fair Quality	Total Number of Articles
I	1	6	2	9
II		4		4
III			3	3
Total				16

Criteria for Evaluating the Studies

Each included study was placed into a matrix developed by the Bethel University Graduate Nursing Program. The information integrated in the matrix included citation, design methodology, purpose, sample/setting, design instruments, results and recommendations. In the sample/setting column, subheadings were included to incorporate the “level of evidence” and “quality of the article.” The “level of evidence” and the “quality of the article” were, as stated

above, assessed using the John Hopkins Nursing Evidence-Based appraisal tool. The "Hierarchy of Evidence for Intervention Studies" chart categorizes the levels by research type. The lower numbers on the chart (one or two) are considered to be better quality studies than articles that fall into the four or five categories (Fineout-Overholt et al., 2010). A study is deemed "high quality" if they are able to correlate their findings to another high-quality study, obtain an adequate sample size, have a control group, and are able to blind their participants to the treatment in question. A fair-quality study typically has a small sample size, no control group and is unable to collaborate their findings with other researchers' studies.

Summary

Multiple databases were used to research articles using platelet-rich plasma and/or eccentric exercise as an intervention for the treatment of Achilles tendinopathy. In total, sixteen articles were found once inclusion and exclusion criteria were established. Once the articles were identified, the level of evidence and level of quality were reported on each article.

Chapter III: Literature Review and Analysis

Synthesis of Matrix

In this chapter, the 16 current scholarly articles will be reviewed and analyzed. The aim of this chapter is to use these scholarly articles to answer the research question that was presented in chapter one. The Bethel University Graduate Nursing Program matrix was used to accomplish this goal. The matrix is a chart that aids in the organization of the articles found for the review. The articles were divided and categorized according to their level of evident as determined by the John Hopkins Nursing Evidence-Based Practice appraisal tool. The appraisal tool categorizes the studies into two sections: A-Single Research Studies and B-Systematic Reviews with or without Meta-Analysis. In section A, studies represented are randomized control trials, quasi experimental, retrospective case studies, or pilot studies. In section B, studies represented are systematic reviews, and meta-analyses. This information was also documented in the matrix. In each section, A and B, there were three different levels of evidence, Ⅰ, Ⅱ, and Ⅲ. Articles are presented in order of their level of evidence and summarized alphabetically according to the authors' last names. The matrix and analyzed information can be located in Appendix A.

Synthesis of Major Findings

Level Ⅰ Evidence: Based on the Johns Hopkins Nursing Evidence-Based Practice appraisal tool, there are nine articles that fell into the category of Level Ⅰ evidence. These are a combination of articles from sections A and B of the appraisal tool used. The articles are

summarized below starting with articles in section A with Level Ⅰ evidence, and moving to articles in section B with Level Ⅰ evidence.

Section A:

Boesen, A., Hansen, R., Boesen, M., Malliaras, P., & Langberg, H (2017) conducted a RCT to determine whether eccentric training in combination with high-volume injection (HVI) or platelet-rich plasma (PRP) injections improved outcomes in Achilles tendinopathy. The study included 60 men between the ages of 18 and 59 who had chronic Achilles tendinopathy (>3 months) and followed them for six months. All of the subjects participated in eccentric exercise training with a combination of (1) one HVI injection of steroid, saline, or local anesthetic, (2) four PRP injections each 14 days apart, or (3) placebo (a few drops of saline under the skin). Outcomes assessed were function, symptoms using the Victorian Institute of Sport Assessment-Achilles Questionnaire (VISA-A), tendon thickness and intratendinous vascularity (ultrasonographic imaging and Doppler signal), and muscle function (heel-rise test). The results showed treatment with HVI or PRP in combination with eccentric training in chronic Achilles tendinopathy seems more effective in reducing pain, improving activity level, and reducing tendon thickness and intratendinous vascularity than eccentric training alone. HVI may be more effective in improving outcomes of chronic Achilles tendinopathy than PRP in the short term. This study recommended a larger sample size and a determination of the exact concentration of platelets and growth factors in the PRP injections.

De Vos, Weir and Van Schie (2010) conducted a RCT to examine whether a PRP injection would improve outcome in chronic midportion Achilles tendinopathy. The study was a

randomized, double-blind study in which 54 participants with chronic Achilles tendinopathy participated. All participants went through eccentric exercise with either a PRP or saline injection. There were 27 subjects in each group with complete follow up. The VISA-A questionnaire was used to evaluate pain and activity levels; this was measured at week 6, 12 and 24. The results showed the mean VISA-A score improved significantly after 24 weeks in the PRP group by 21.7 points and in the placebo group by 20.5 points. This was not statistically significant. The conclusion of this study was that patients with chronic Achilles tendinopathy who were treated with eccentric exercises and a PRP injection compared with a saline injection did not result in greater improvement in pain and activity. The study had no specific recommendations for further follow up.

One year later, Jonge, de Vos, and Weir did a follow up on the RCT they performed in 2010. (2011). The aim of their study was to determine the effects of the PRP injection one year post injection. All 54 participants followed up at the one year mark. The primary outcome was the Victorian Institute of Sports Assessment–Achilles (VISA-A) score. Other outcome measures were subjective patient satisfaction (scored as poor, moderate, good, or excellent) and return to sports activity (scored as not active in sports, no return to sports, returning to sport but not in desired sport, returning to desired sport but not at the preinjury level, or returning to preinjury level in the desired sport). Tendon structure was evaluated quantitatively by means of UTC (UTCimaging). Neovascularization was scored using the modified O¨ hberg scoring system. The mean Victorian Institute of Sports Assessment–Achilles score improved in both the platelet-rich plasma group and the placebo group after one year. There was no significant difference in increase between groups. In both groups, 59% of the patients were satisfied with the received

treatment (Jonge et al. 2012). Ultrasonographic tendon structure improved significantly in both groups but was not significantly different between groups. The study concluded that there was no superiority of the PRP injection when compared to the saline injection in chronic Achilles tendinopathy at the one year mark when accompanied by eccentric exercise training. There were no formal recommendations by the authors of this study.

Kearney and Parson (2013) conducted a pilot RCT to evaluate the feasibility of conducting a larger trial to evaluate the difference in VISA-A scores at six months between patients with Achilles tendinopathy treated with a PRP injection compared with an eccentric loading programme. Two groups of patients with midsubstance Achilles tendinopathy were randomised to receive a PRP injection or an eccentric loading programme. A total of 20 patients were randomised, with a mean age of 49 years (35 to 66). The VISA-A was the primary outcome measure and was recorded at baseline, six weeks, three months and six months. The mean VISA-A score for the injection group at the primary endpoint of six months was 76.0 and for the exercise group was 57.4. There was no statistically significant difference between these scores. The conclusion of this study was that it had the ability to conduct a larger scale study to determine the effectiveness of PRP injections when treating Achilles tendinopathy. The results did not reflect any significant findings, but a larger scale study should be done to provide more clarity.

Krogh (2016) performed a RCT with the purpose of examining whether one injection of PRP would improve outcomes more effectively than placebo (saline) after 3 months in patients

with Achilles tendinopathy (AT). A total of 24 participants were randomized into the PRP injection group or the saline (placebo) group. The primary endpoint was improvement in VISA-Ascore at 3 months. Secondary outcomes were pain at rest, pain while walking, pain when the tendon was squeezed, ultrasonographic changes in tendon thickness, and color Doppler activity. The results showed the PRP injection did not result in an improved VISA-A score over a 3-month period in patients with chronic AT compared with placebo. The only secondary outcome demonstrating a statistically significant difference between the groups was change in tendon thickness; this difference indicates that a PRP injection could increase tendon thickness compared with saline injection. The conclusions are limited to the three months after treatment due to the large dropout rate of this study. The recommendation of this study is that a larger sample size be used, and performed on individuals who are not in such a late stage of tendinopathy.

Section B:

Liu et al. (2019) completed a meta-analysis evaluating the current evidence for the efficacy of PRP as a treatment for chronic AT. They obtained all of their sources from PubMed, Embase, Web of Science, and The Cochrane Library databases. Their aim was to find articles on RCTs that compared the efficacy of PRP with that of placebo injections plus eccentric training as treatment for chronic Achilles tendinopathy. The inclusion criteria was a diagnosis of Achilles tendinopathy, an injection of PRP around the tendon, the VISA-A, visual analog scale (VAS), must be a randomized controlled clinical trial and Achilles tendon thickness measurement. The

exclusion criteria was PRP injection combined with surgical intervention, lack of non-PRP controls, incomplete literature or duplicate literature. A total of 650 articles were obtained in the initial search. After completing the screening using the inclusion and exclusion criteria, the authors chose 5 RCTs to be used in this meta-analysis.

Liu et al. (2019) used the 5 RCTs that included 189 patients to complete this meta-analysis. The VISA-A was the primary outcome indicator used for each of the RCTs. There was no significant difference found in the improvement of the individuals when followed up with at the 6, 12 and 24 weeks mark. However, the VISA-A score of the PRP group was significantly higher than that of the control group 6 weeks after treatment. In two of the studies, patients were followed up with at the one year mark. In those studies there was no significant difference between the PRP and the placebo groups. The author concluded that PRP is a treatment option for chronic Achilles tendinopathy, but in order to verify the results of this study, the authors recommended a large number of well-designed, homogeneous RCT studies.

Madhi et al. (2020) conducted a systematic review to determine the efficacy of PRP as a treatment option for individuals with chronic AT. . They obtained their articles using the following electronic databases: PubMed, EMBASE, Cochrane collaborate, Google scholar, the Web of Science and Cochrane Library. The quality of each study was evaluated using the Oxford CEBM tool to assess the articles for validity, relevance, and applicability of the results. A total number of 288 studies were found, and only 11 met the inclusion criteria. The inclusion criteria was studies with designs of RCTs retrospective or prospective cohort studies, a diagnosis of an

Achilles tendon disorder, and studies reporting at least one of the following outcomes: Time to recover (or play), recurrences, patient-reported outcomes (PROMs), pain scales, adverse events, or VISA score. Exclusion criteria were articles that were case series or case reports.

Madhi et al. (2020) included 5 RCTs , 4 prospective and 2 retrospective cohort studies in this systematic review. These studies were chosen by the authors after they examined the studies for the inclusion and exclusion criteria. From these 11 studies, 203 patients underwent PRP injection with ultrasound guidance for treatment of Achilles tendinopathy. The primary outcome used to assess the effectiveness of the PRP injection was the VISA-A questionnaire as well as an ultrasound scan for the assessment of the tendon thickness pre- and post-treatment. Patient means baseline VISA-A score was 41.2 which improved to 70.12 after treatment, the mean difference between VISA-A score was 28.9 points which were substantial compared to other non-operative care approaches. Many of the retrospective studies suggested an advantage of using PRP, the higher level of evidence studies do not support a significant efficacy. The studies in this systematic review did have multiple limitations. Some of the studies have been cohort-controlled and non-randomised, and the randomised controlled trials were small sample sizes. This study specifically recommends that future research should include larger sample sizes to produce more consistent results.

Nauwelaers, Van Oost and Peers (2020) conducted a systematic review to establish the existing evidence of PRP injections for chronic midsubstance Achilles tendinopathy on the functional outcome, with a risk of bias assessment of each included study. Systematic guidelines

were used to perform their search for articles using the following databases: Embase, the Cochrane Library and Pubmed. Inclusion criteria included only clinical trials comparing PRP injections with a placebo, additional to eccentric exercise training for individuals diagnosed with midsubstance Achilles tendinopathy. Exclusion criteria included: no placebo group, animal studies, articles without full text availability, Achilles tendon rupture, incomplete literature and if the article was not in English. The initial search yielded 367 articles. After narrowing the search based on the inclusion and exclusion criteria, the authors decided on only 4 articles that were used for this systematic review.

Nauwelaers, Van Oost and Peers (2020) systematic review used four RCTs with 170 participants. The primary outcome was VISA-A score at 3, 6 and 12 months post-injection. However, only two of the four studies reported any follow up at the one year mark. As a secondary measure, tendon structure was assessed under ultrasound. VISA-A scores at 3, 6 and 12 months show no significant difference between the PRP group and placebo group. Three of the four studies used imaging to address the tendon structure under ultrasound. One study reported significant reduction in tendon thickness and vascularity using PRP, one described an increased tendon thickness, and the third reported no difference in tendon structure. The conclusion of this study was that PRP injection offers no additional value to eccentric exercise training for the treatment of Achilles tendinopathy. Their recommendation is for larger high quality randomised controlled trials to be done to appreciate the effectiveness of PRP injections

better. They also recommend more research be done to understand whether PRP injections' goals are to improve tendon structure or pain.

Zhang et al. (2018) conducted a meta analysis with the intention of gathering all RCTs pertaining to PRP and its effectiveness for treatment of Achilles tendinopathy. The three questions they posed were: does PRP plus eccentric strength training result in (1) greater improvements in VISA-A scores; (2) differences in tendon thickness; or (3) differences in color Doppler activity compared with placebo (saline) injections plus eccentric strength training in patients with chronic Achilles tendinopathy? A search for peer reviewed articles was done using PubMed, Web of Science (SCI-E/SSCI/A&HCI), and EMBASE. Exclusion criteria included studies related to tendon tears rather than tendinopathy; assessed muscle injuries, were duplicates, related to ligament injuries, had surgical interventions, or did not use PRP. The studies used were analyzed for the following: control type, treatment type and technique. All trials that were used in the meta-analysis compared PRP injection and eccentric training with saline injection and eccentric training for chronic Achilles tendinopathy.

Zhang et al. (2018) identified 146 studies in their initial search of the literature. After review of the studies, the authors kept 4 RCTs to include in their meta-analysis. The main evaluation tool for each study was the VISA-A questionnaire, while three other studies also evaluated tendon thickness change. Color Doppler activity and other functional measures such as pain and return to sports activity were also measured. The study found there was no difference between the PRP and saline groups regarding the primary outcome of the VISA-A questionnaire.

They also noted that there was no difference between the PRP and saline groups in terms of ultrasonographic evaluation of tendon thickness; the mean difference between the PRP and saline groups in tendon thickness change was 0.2 mm. There was also no difference between the PRP and saline groups in terms of color Doppler activity. Pain levels and return to sport had mixed results between the RCTs in the meta-analysis. The authors concluded larger randomized trials are needed to confirm these results, but until or unless a clear benefit has been demonstrated in favor of the new treatment, they cannot recommend it for general use.

Level Ⅱ Evidence: Based on the Johns Hopkins Nursing Evidence-Based Practice appraisal tool, there were four articles that fell into the category of Level Ⅱ evidence. These are a combination of articles from sections A and B of the appraisal tool used. The articles are summarized below starting with articles in section A with Level Ⅱ evidence, and moving to articles in section B with Level Ⅱ evidence.

Section A:

Filardo et al. (2014) conducted a quasi experimental study to evaluate the therapeutic effects of repeated injections of PRP, administered to promote the healing of chronic Achilles tendinopathy. 27 patients (22 men, five women) were enrolled in the study. Seven of the patients had bilateral chronic Achilles tendinopathy, so 34 tendons were evaluated in this study. Inclusion criteria were: history (>three months) of exercise-associated pain, pain or tenderness on palpation and imaging findings (MRI or Ultrasound) of degenerative changes in the Achilles' tendon. The VISA-A score improved significantly. In detail, the baseline score of 49.9 increased

to 62.9 at two months, with a further improvement at six months, and remained stable at four and a half years. 89% of the patients returned to sport and 93% of the patients were satisfied and would repeat the treatment if needed (Filardo, 2014). The treatment failed in three patients, one of which was a bilateral case. One patient was treated with corticosteroid injection before the 6 months' evaluation, thus eliminating the participant from further follow up. The other two patients sought surgical intervention, roughly one year after the PRP treatment. The main findings of the study are that patients treated with repeated PRP injections for Achilles tendinopathy obtained overall good results. Clinical improvement was significantly slower in patients with a higher pretreatment symptom level, and the return to sport was more difficult in patients with a longer history of symptoms. The authors recognized the current study has major limitations, such as the lack of a randomised control group and imaging evaluation. Further recommendations would be to repeat this in a RCT with a larger sample size.

Mautner et al. (2013) performed a retrospective cross sectional survey on 180 individuals who received ultrasound-guided PRP injections for tendinopathy refractory to conventional treatments. The aim of the study was to determine whether ultrasound-guided PRP injections are an effective treatment for chronic tendinopathies. The inclusion criteria for the study was subjects men or women between the ages of 18 and 75 years old who have been diagnosed with tendinopathy for longer than six months. The individuals also needed to have tried conventional treatment and have not had any resolution. Conventional treatment included: oral medications, physiotherapeutic modalities and eccentric exercise. Exclusion criteria included sensory or

neurologic complaints affecting the specified region, coagulation disorder, platelet disorder, pregnancy, or a major systemic illness such as diabetes mellitus, rheumatoid arthritis, fibromyalgia, autoimmune disorder, or any other condition that required strict antiplatelet or anticoagulation therapy.

The results of the study done by Mautner et al. (2013) showed that 82% of participants recorded a moderate-to-complete resolution of symptoms. Of the 180 participants, 27 of them were individuals diagnosed with Achilles tendinopathy specifically. 100% of the participants who received the ultrasound-guided injection in the Achilles tendon reported moderate to complete resolution of symptoms. The perceived change in the visual analog scale (VAS) was -5.2; resulting in an average reduction of pain of 75%. However, there was no significant difference found in the estimated change in VAS between the patients who answered the survey at 1 year or less after the PRP procedure and those who answered more than 1 year after the procedure. From a functional standpoint, 68% of patients reported no pain while performing activities and minimal to no pain before or after activities. 85% of patients were satisfied with the procedure, 13% were dissatisfied, and 2% were indifferent. The study noted their limitations being a small response rate in the survey study (only 55%); there was no standardization to the rehabilitation protocols and recall bias based on the nature of the retrospective study design. The authors concluded PRP has a positive effect in patients diagnosed with refractory tendinopathy. However, more rigorous studies are needed to confirm these findings.

Ferrero et al. (2012) used a quasi experimental design study to evaluate the effectiveness of ultrasound (US)-guided autologous PRP injections in patellar and Achilles tendinopathy. The study included 30 Achilles tendons and 28 patellar tendons. Individuals in the Achilles tendon group ranged in age from 20 to 61 years old. All participants were physically active, competing in competitive or amateur sports. The inclusion criteria was: presence of patellar or Achilles tendinopathy, pain during palpation of the tendon and during physical activity for at least three months, and ultrasound or MRI evidence of tendon degeneration. All participants had undergone some form of other treatment that had been unsuccessful. The exclusion criteria was: systemic disease, antiplatelet therapy in progress, intake of NSAIDs less than five days before the procedure, hemoglobin <11 g/dl and platelets <150.000/mmc. The participants underwent a pre-treatment examination where they filled out the VISA-A or VISA-P. These results were used as a baseline to be compared to after the PRP injection. Each participant underwent two PRP injections roughly three weeks apart. In all patients, clinical evaluation was performed using VISA-P or VISA-A questionnaires. US evaluation included patellar or Achilles tendon thickness, presence/absence of hypoechoic areas and vascularity on power Doppler 20 days and six months after the second PRP administration. At the 6-month follow-up, patients were also asked about their overall satisfaction with the treatment using a semiquantitative scale (poor, good, excellent). For the Achilles tendon participants, the 20-day follow up was completed for all tendons. Only 23 tendons (19 patients) were followed up with at the six month time. The VISA-A score showed minimal (non-significant) improvement compared to baseline was observed at the 20-day

follow-up and a significant improvement at the six month follow-up. Tendon thickness was not significantly reduced at the 20-day follow-up compared to baseline. However, at the six month follow-up this reduction was statistically significant. Participants who followed up on their Achilles tendon injection at the six month mark rated their overall satisfaction with the treatment as: excellent for 10 tendons, good for 11 tendons and poor in nine tendons. The authors of this study concluded that the use of PRP treatment for Achilles tendinopathy is feasible as a minimally invasive treatment option. The authors also recommend further RCTs performed on a larger sample size be done to confirm and validate their results.

Section B:

Vannini et al. (2013) performed a systematic review on platelet-rich plasma (PRP) injections for foot and ankle pathologies. Their aim was to systematically review the literature available on the clinical application of PRP for the treatment of foot and ankle pathologies, as well as to understand its best indication for clinical use. This article was included in the review of the literature due to this systematic review including PRP injections for the Achilles tendon injections as part of the foot and ankle pathology. Research was performed using PubMed. The inclusion criteria included: (1) papers in the English language, (2) dealing with the clinical application of PRP for the treatment of orthopedic-related conditions affecting the foot and ankle district, (3) with a I to IV level of evidence, and (4) reporting clinical results. The exclusion criteria were reviews in vitro and animal studies, and studies that included non orthopedic conditions. The initial search yielded 194 papers. After careful review of the inclusion and

exclusion criteria, the authors decided 14 papers were considered eligible for inclusion. The authors then analyzed the references of the 14 papers, and three more papers were included. At the end of the process, 17 papers fulfilled the selection criteria.

Of the 17 papers discussed in this systematic review, five of them looked at PRP injections and their effectiveness for treating Achilles tendinopathy. Those studies included 1 RCT and 4 case series. All four case series studies showed similar results in that the VISA-A scores of the patients who received PRP injections accompanied by eccentric exercise training improved over time (each study follow-up bench mark was slightly different). All four studies also found significant decrease in pain with concomitant functional recovery. However, the only randomized double-blind controlled trial that reported no significant difference between PRP and placebo directly contrasts with those results. At this time, the authors recognize the limitations of their systematic review to be lack of randomized controlled trials (for all foot and ankle pathologies; not specifically Achilles tendinopathy in regards to PRP injections), and lack of a true understanding of PRP. At this time there is no clear clinical indication for whether or not PRP injections should be used to treat foot and ankle pathologies (including Achilles tendinopathy) and further research must be done.

Level Ⅲ ***Evidence:*** Based on the Johns Hopkins Nursing Evidence-Based Practice appraisal tool, there were three articles that fell into the category of Level Ⅲ evidence. These are a combination of articles from sections A and B of the appraisal tool used. The articles are

summarized below starting with articles in section A with Level Ⅲ evidence, and moving to articles in section B with Level Ⅲ evidence.

Section A:

Murawski et al. (2014) performed a retrospective preliminary analysis to evaluate a series of patients undergoing a single platelet-rich plasma (PRP) injection for the treatment of chronic midsubstance Achilles tendinopathy, in whom conservative treatment had failed. The study included 32 patients who underwent a single PRP injection. The patient returned to the clinic at two weeks, six weeks, three months and six months. The Foot and Ankle Outcome Score (FAOS) questionnaire and Short Form 12 (SF-12) general health questionnaire were used to determine effectiveness of the injection. The FAOS and SF-12 were answered by the patients at the pre-injection evaluation as well as the six month follow up post injection. At the six month follow up, 78% or 25 patients reported they were asymptomatic and were able to return to sport and daily activity. The FAOS outcome score improved significantly from 51 points prior to the injection to 87 points at final follow-up. The SF-12 score also improved from 68 points preinjection to 91 points at follow-up and was statistically significant. The remaining 22% or 7 patients reported no improvement at the six month follow up, and ultimately went on to have surgical intervention of the Achilles tendon. This study acknowledged their limitations to be: lack of control group, limited follow up time, no cytological analyses of the PRP aliquots injected, and inconsistent physical therapy protocols. Despite the limitations, the authors concluded that with 78% of patients reporting improvement of pain and functional status, PRP

can be considered as a therapeutic option for the conservative management of Achilles tendinopathy.

Monto (2012) conducted a case series using 30 patients to determine its potential long-term efficacy in treating chronic cases of Achilles tendinopathy in which traditional nonoperative management has failed. All 30 patients had undergone a minimum of six months of standard nonoperative treatment including rest, physical therapy, silicone heel lifts, CAM walker bracing, cast immobilization, night splinting, and non-steroidal medication. The patients had an average duration of symptoms of eight months prior to the PRP injection. The American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot scoring data and physical examinations were completed on all patients immediately prior to PRP treatment. They were then repeated at the one, two, three, six, twelve and twenty-four month marks following the PRP injection. Patients also repeated MRI or ultrasound imaging studies to be compared to the pretreatment findings. Pre injection AOFAS scores averaged 34, and 22 of 26 patients who played sports were unable to participate due to their condition. Ten of the 22 employed patients were also unable to work because of the severity of their symptoms. All patients completed either an MRI (18 patients) or ultrasound imaging (12 patients) prior to the PRP injection. Of the MRI patients, all exhibited signs of significant Achilles swelling, four had tendon calcifications, and six displayed partial Achilles tendon tears. The Ultrasound studies showed all patients had Achilles swelling and only four demonstrated partial Achilles tears. All patients in this study were also instructed in a home based eccentrically based exercise program but the majority of patients were

noncompliant in doing this regularly. The results showed 27 of 30 were satisfied with the results of the PRP treatment at six months. At the 24-month follow up, 28 of 30 patients were satisfied. Two patients were clinically dissatisfied with their results at the six month follow up due to persistent pain and left the study. Those two patients went on to have surgical repair of the Achilles tendon. The author concluded that PRP can safely and effectively be used to treat severe chronic Achilles tendinitis in patients who have failed to respond to traditional nonoperative management techniques.

Section B:

DiMatteo, Filardo, and Marcacci (2014) conducted a systematic review to analyze the available clinical evidence concerning the application of PRP in the treatment of patellar and Achilles tendinopathy. The inclusion criteria was: clinical reports of any level of evidence, written in the English language, on the use of PRP to treat Achilles and patellar tendinopathy and had no time limitation. The exclusion criteria was: case reports, articles written in other languages and reviews and articles that did not report clinical results. Twenty-two articles were used in this systematic review. Nine articles were focused solely on patellar tendinopathy, nine were focused solely on Achilles tendinopathy and four articles reported data on both patellar and Achilles tendinopathies. Twelve articles were used to assess the effectiveness of PRP injections for Achilles tendinopathy. In regards to those articles, the results were mixed. Only one of the studies was a randomized controlled trial and it showed no significant improvement in the VISA-A scores of the patients who had the PRP injection compared to the control group

(placebo injection). However,the remaining 11 articles were case series, and each one of those found significant improvement, in a variety of timeframes for the effectiveness of PRP injections when used to treat Achilles tendinopathy. The authors of this systematic review concluded this particular study is not conclusive when assessing whether or not PRP is an effective treatment for individuals with Achilles tendinopathy.

Critique of Strengths and Weaknesses

The appraisal of the 16 articles above listed various strengths and weaknesses. One key strength to the articles evaluated is that 13 of those articles used the VISA-A as their primary outcome measure. The VISA-A has been determined as the gold standard outcome measurement for assessing pain and function of the Achilles tendon. However, the questions are geared toward a sport specific population. Many of these studies did not specify the activity levels of the participants prior to giving them the VISA-A as the assessment tool. The same evaluation tool allowed for consistency when assessing the effectiveness of PRP injections on chronic Achilles tendinopathy. The major weakness of the articles as a whole was lack of adequate sample size. The largest sample size was reported in Mautner et. al (2013) with 180 participants. However, this study was a retrospective, cross-sectional survey with lack of a control group. Another weakness to this review of the literature was the lack ofRCTs. There were only five RCTs, one of which was a pilot study. More studies with larger sample sizes would help findings be of greater significance.

Summary

Sixteen research articles were critically reviewed to determine whether platelet rich plasma (PRP) is an effective treatment option for the treatment of chronic Achilles tendinopathy. All articles were categorized into a Level of Evidence of Ⅰ, II, Ⅲ according to The Johns Hopkins Nursing Evidence-Based Practice appraisal tool. The articles were assessed for quality and represented levels of fair, good, and excellent again according to The John Hopkins Nursing Evidence-Based Practice appraisal tool. Five of the sixteen articles acknowledged that PRP injections are an effective treatment option for chronic Achilles tendinopathy. Six of the sixteen articles determined that PRP injections are not effective for the treatment of Achilles tendinopathy. Five of the sixteen articles were unsure of the results, and recommended larger randomized controlled trials be done with adequate sample sizes to confirm or deny the findings.

Chapter Ⅳ: Discussion, Implications & Conclusions

The purpose of this review is to determine if PRP injections are effective treatment options for chronic Achilles tendinopathy. After a critical analysis was conducted, 16 articles were reviewed in chapter three. Chapter four will address the question presented, discuss the trends and gaps within the literature, analyze the literature in terms of implications in athletic training, and provide recommendations for further research.

Literature Synthesis

The main focus of this Critical Review of the Literature was to answer the question, "Is platelet rich plasma an effective treatment option for individuals diagnosed with chronic Achilles tendinopathy?" Sixteen articles were reviewed to answer this question. The following paragraphs will separate all 16 articles into three different categories: (1) PRP injections are effective for the treatment of Achilles tendinopathy, (2) PRP injections are not effective for the treatment of Achilles tendinopathy, and (3) no conclusions can be drawn regarding whether or not PRP is effective for the treatment of Achilles tendinopathy.

Eight of the 16 articles used in this Review of the Literature concluded that PRP injections were an acceptable and minimally invasive treatment option for Achilles tendinopathy. Boesen et al. (2017) was the only article of "high quality" while the following four articles were considered of "good" quality: Ferrero et al. (2012), Mautner et al. (2013), Filardo et al. (2014) and Liu et al. (2019). Of these four articles, Liu et al. was the only Meta-Analysis which analyzed five RCTs. The VISA-A was the primary outcome of all five RCTs. Of those five RCTs, four followed up with the participants at six weeks, and five of the articles followed up with participants at 6, 12 and 24 weeks. The results stated that there was no significant difference

found in improvement; however, the PRP group's VISA-A score was significantly higher than the control group at the six-week mark. Liu et al. (2012) also found that the thickness of the Achilles tendon was significantly thinner after the PRP injection. This can be an objective measure as to why participants feel relief of symptoms of their Achilles tendinopathy. Mautner et al. (2013) had the largest sample of Achilles tendons used in their study at 180 Achilles tendons. This was a retrospective, cross sectional survey to determine participant satisfaction after receiving a PRP injection to treat chronic tendinopathies. Prior to PRP injections, 180 participants underwent physical therapy that included eccentric exercise. Of the 180 participants, 27 of them were patients diagnosed with Achilles tendinopathy who all reported moderate to complete resolution of symptoms. The study, as a whole, reported that 82% of patients experienced significant improvement in symptoms and 68% of participants reported no pain while performing activities and minimal to no pain before or after activities. Ferrero et al. (2012) was the last article in the "good" category; this was a quasi-experimental study which looked at 30 Achilles tendons.

The remaining three articles which were supportive of using PRP injections to treat Achilles tendinopathy were Di Matteo et al. (2014), Monto (2012) and Murawski (2014); these articles fell into the "fair" category when ranking quality. Filardo et al. (2014), Ferrero et al. (2012), Monto (2012), and Murawski (2014) were all very similar in their findings. At the sixth month follow up, patients were reporting a decrease in symptoms, a return to sport and physical activity, as well as reduction of tendon thickness and increased intratendinous vascularity. Di Matteo et al. (2014) was a systematic review that included one RCT and 11 case series. Their results were favorable to using PRP injections for the treatment of chronic Achilles tendinopathy.

However, the favorable results came from the case series, and the RCT actually did not support their conclusion.

Five of the 16 articles concluded that their results did not support the treatment of PRP injections for individuals diagnosed with Achilles tendinopathy. There were no articles in the "high quality" category, and four were categorized as "good". De Vos et al. (2010) performed a RCT in which 54 participants were divided into two groups. Twenty-seven participants underwent the PRP injection while 27 received a placebo injection into the Achilles tendon. At the six-month follow up, the VISA-A scores were not significantly different than the control group. Jonge et al. (2011) followed up on the same participant pool at the one-year mark following their injections. He found that both the PRP group and the placebo group had improved VISA-A scores; however, there was no significant difference between the two groups. The other two "good" quality articles were systematic reviews by Vannini et al. (2013) and Nauwelaers et al. (2020). Vannini et al. (2013) looked at 17 studies, although only nine studies evaluated the efficacy of PRP in the Achilles tendon; the other studies pertained to other foot and ankle pathologies. Nauwelaers et al. (2020) only reviewed four RCT, two of which were De Vos et al. (2010) and Jonge et al. (2011). Their results were similar in that they could not recommend the use of PRP injections for the treatment of Achilles tendinopathy. The study conducted by Zhang et al. (2018) was classified in the "fair" category and concluded PRP injections with eccentric training did not improve VISA-A scores, reduce tendon thickness, or reduce color Doppler activity in patients with chronic Achilles tendinopathy compared with saline injection. Larger randomized trials are needed to confirm these results, but until or unless a clear benefit has been demonstrated in favor of the new treatment, we cannot recommend it for general use.

Lastly, there were three articles of the 16 that could not draw a specific conclusion for whether or not PRP injections were effective for the treatment of Achilles tendinopathy. Those studies included no "high" quality studies, two of "good" quality (Krogh (2016), and Madhi et al. (2020)), and one "fair" quality article (Kearney 2013). Madhi et. al (2020), a systematic review of literature, analyzed five randomised control trials, four prospective studies, and two retrospective cohort studies. Although the results were inconclusive, many of the retrospective studies suggested an advantage of using PRP; however, the higher level of evidence studies do not support a significant efficacy. They recommended more RCTs with larger sample sizes be conducted in order to confirm the results of the retrospective studies. Krogh (2016), a RCT with 24 patients, found no statistical significance in the difference in the primary outcome of the VISA-A scores, but did find statistically significant secondary outcomes of color Doppler activity and tendon thickness. They also reported a large drop-out rate after the three-month mark and could not make long term comparisons. Lastly, Kearney et al. (2013), a pilot RCT, looked at 20 patients and found no statistical significance between the PRP group and the exercise only group from the primary endpoint of six months. This, however, was an expected outcome based on the nature of the pilot study, but demonstrated the methodology is feasible to perform a larger RCT.

Current Trends and Gaps in Literature

During this Critical Review of the Literature, multiple trends and gaps were identified. First, the number of RCTs conducted to determine the effectiveness of PRP injections for the treatment of chronic Achilles tendinopathy is very limited. In this review, only four articles were RCTs, and one other was a RCT pilot. As the gold standard for research, this shows there is a lot

of potential for bias among the other studies that are currently available. Di Matteo et al. (2014) performed a systematic review of the literature regarding the effectiveness of PRP on Achilles tendinopathy. They found that 12 papers met the inclusion criteria; however, only one trial was a double-blind RCT, whereas the others were all case series. Second, the sample sizes of the studies found were small. Some of the studies which had larger sample sizes did not focus solely on Achilles tendinopathy. For example, Vannini et al. (2013), a systematic review, took 17 studies and reviewed the effectiveness of PRP injections on foot and ankle pathologies. Only nine of those studies dealt with Achilles tendinopathy.

In addition to the lack of RCT and small sample size, the standardization for the PRP injections varied in each study. For example, two of the RCT had vastly different procedures for administering the PRP injection. De Vos et al. (2010) collected 54 mL of blood from each of the participants. The blood was then mixed with 6 mL of citrate to prevent clotting in the centrifuge. The mixed sample was placed in the centrifuge and ran for 15 minutes. To match the pH of PRP with the pH of the tendon tissue, the researchers added 0.3 mL of 8.4% sodium bicarbonate buffer to the mixture. One milliliter of PRP was collected and analyzed for possible contamination. They used a 22-gauge needle to inject 2 mL of a local anesthetic and 4 mL of the PRP sample. The procedure was performed under ultrasound guidance to ensure proper placement of the PRP. Post procedure, the participants were asked to be non-weight bearing for four weeks and began a 12-week eccentric exercise program. Boesen et. al (2017)'s purpose was to determine whether eccentric training, in combination with high-volume injection (HVI) or PRP injections, would improve outcomes of participants with Achilles tendinopathy. Their participants were divided into three groups: HVI, PRP or placebo. The participants in the PRP

group had only 10 mL of blood drawn. The blood was spun in the centrifuge for five minutes and approximately 4 mL of PRP sample was obtained. A 21-gauge needle was used under ultrasound guidance to direct the injection. However, placement of the injection was dependent on the most symptomatic area based on patient feedback and palpation. No local anesthetic was used, and the procedure itself was performed four times with the first injection at baseline and with 2-week intervals between each injection. Participants were able to bear weight immediately after the injections and began a 12-week eccentric exercise program. The remaining studies also had variations of how the PRP was prepared and injected. This can cause discrepancy in results, altering whether or not PRP injections were, in fact, effective for the treatment of chronic Achilles tendinopathy.

Implications for Athletic Training

Implications for athletic training, based on the findings of this Critical Review of the Literature, include discussing and educating patients and healthcare providers about the potential but also the uncertainty of the use of PRP injections for the treatment of chronic Achilles tendinopathy. When discussing various treatment options for chronic Achilles tendinopathy, it is critical to consider the research that has already been completed. This will allow for the patient and the healthcare provider to choose a treatment option best suited for the patient. Athletic trainers serve as advocates for their patients as well as licensed delegates of the physicians. This allows them to have informational conversations with both parties to ensure the providers are giving the best care and patients are receiving the best care. The findings of this review offer a starting point for further research regarding the efficacy of PRP injections and the treatment of chronic Achilles tendinopathy. With more research, it is hopeful a more comprehensive

understanding of PRP can be developed. This would potentially lead to more evidence and better practice standards in hopes that insurance companies would then cover PRP injections as treatment options (Jones, 2018). Achilles tendinopathy is one of the most frequent ankle/foot overuse injuries, and is characterized by a combination of pain, swelling, and impaired performance (Li, 2016). The current gold standard treatment is eccentric exercise training (O'Neill, 2015). However, not all individuals respond to that form a treatment. As more people are affected each year, now is the time to continue the growing research on PRP injections and determine whether or not they can be used safely and effectively for the treatment of chronic Achilles tendinopathy.

Conclusion

The findings of this review did not completely validate that PRP injections are an effective treatment option for individuals diagnosed with chronic Achilles tendinopathy. To come to this conclusion, 16 articles were reviewed using the Bethel University Graduate Nursing Program matrix format and were further evaluated with use of the John Hopkins Nursing Evidence-Based appraisal tool. Eight articles were in favor of using PRP injections to treat chronic Achilles tendinopathies, five articles reported PRP injections were not an effective treatment option, and three articles concluded they required larger scale studies to make a determination. Overall, the critical review of the literature provides vastly different evidence on the effectiveness of PRP injections for treatment of chronic Achilles tendinopathy. Future research should focus on completing large sample size RCTs with standardization of the preparation/procedure of the PRP injection. With that information, PRP injections can be used

secondary to traditional treatment of eccentric exercise and other modalities for patients who are looking for a minimally invasive treatment option.

References

Ackermann, P. W., & Renström, P. (2012). Tendinopathy in sport. Sports health, 4(3), 193–201. https://doi.org/10.1177/1941738112440957

Athletic Training, Minn. Stat. § 148.7806 (2020). https://www.revisor.mn.gov/statutes/cite/148.7806

Boesen, A., Hansen, R., Boesen, M., Malliaras, P., & Langberg, H. (2017). Effect of High-Volume Injection, Platelet-Rich Plasma, and Sham Treatment in Chronic Midportion Achilles Tendinopathy: A Randomized Double-Blinded Prospective Study. *The American Journal of Sports Medicine*, *45*(9), 2034–2043. https://doi.org/10.1177/0363546517702862

Commissioner, O. of the. (2015, September 24). *The Benefits and Risks of Pain Relievers: Q & A on NSAIDs*. U.S. Food and Drug Administration. https://www.fda.gov/consumers/consumer-updates/benefits-and-risks-pain-relievers-q-nsaids-sharon-hertz-md.

Dearholt, S. L., & Dang, D. (2012). Research Evidence Appraisal Tool. In *Johns Hopkins nursing evidence-based practice models and guidelines* (pp. 238–240). Sigma Theta Tau International.

Di Matteo, B., Filardo, G., Kon, E., & Marcacci, M. (2014). Platelet-rich plasma: evidence for the treatment of patellar and Achilles tendinopathy—a systematic review. *Musculoskeletal Surgery*, *99*(1), 1–9. https://doi.org/10.1007/s12306-014-0340-1

de Vos RJ, Weir A, van Schie HTM, et al. Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy: A Randomized Controlled Trial. *JAMA*. 2010;303(2):144–149. doi:10.1001/jama.2009.1986

Ferrero, G., Fabbro, E., Orlandi, D., Martini, C., Lacelli, F., Serafini, G., Silvestri, E., & Sconfienza, L. M. (2012). Ultrasound-guided injection of platelet-rich plasma in chronic Achilles and patellar tendinopathy. *Journal of ultrasound*, *15*(4), 260–266. https://doi.org/10.1016/j.jus.2012.09.006

Filardo, G., Kon, E., Di Matteo, B., Di Martino, A., Tesei, G., Pelotti, P., Cenacchi, A., & Marcacci, M. (2014). Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: results at 4 years. *Blood transfusion = Trasfusione del sangue*, *12*(4), 533–540. https://doi.org/10.2450/2014.0289-13

Fineout-Overholt, E. , Melnyk, B. , Stillwell, S. B. & Williamson, K. M. (2010). Evidence-based practice step by step: Critical appraisal of the evidence: Part I. *American Journal of Nursing*, 110(7), 47-52. doi: 10.1097/01.NAJ.0000383935.22721.9c.

Finnoff, J. T., Fowler, S. P., Lai, J. K., Santrach, P. J., Willis, E. A., Sayeed, Y. A., & Smith, J. (2011). Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. *PM & R : the journal of injury, function, and rehabilitation*, *3*(10), 900–911.

Jones, I. A., Togashi, R. C., & Vangsness, C. T. (2018). The Economics and Regulation of PRP in the Evolving Field of Orthopedic Biologics. Current Reviews in Musculoskeletal Medicine, 11(4), 558–565. doi: 10.1007/s12178-018-9514-z

Jonge, S. D., Vos, R. J., Weir, A., Schie, H. T., Bierma-Zeinstra, S. M., Verhaar, J. A., . . . Tol, J. L. (2011). One-Year Follow-up of Platelet-Rich Plasma Treatment in Chronic Achilles Tendinopathy. *The American Journal of Sports Medicine, 39*(8), 1623-1630. doi:10.1177/0363546511404877

Kearney, R. S., Parsons, N., & Costa, M. L. (2013). Achilles tendinopathy management: A pilot randomised controlled trial comparing platelet-rich plasma injection with an eccentric loading programme. *Bone & joint research*, *2*(10), 227–232. https://doi.org/10.1302/2046-3758.210.2000200

Krogh, E. (2016). Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline: A Randomized, Blinded, Placebo-Controlled Trial. The American Journal of Sports Medicine, 44(8), 1990–1997. https://doi.org/10.1177/0363546516647958

Li, H. Y., & Hua, Y. H. (2016). Achilles Tendinopathy: Current Concepts about the Basic Science and Clinical Treatments. *BioMed research international*, *2016*, 6492597. https://doi.org/10.1155/2016/6492597

Liu, C. J., Yu, K. L., Bai, J. B., Tian, D. H., & Liu, G. L. (2019). Platelet-rich plasma injection for the treatment of chronic Achilles tendinopathy: A meta-analysis. *Medicine*, *98*(16), e15278. https://doi.org/10.1097/MD.0000000000015278

Madhi, M. I., Yausep, O. E., Khamdan, K., & Trigkilidas, D. (2020). The use of PRP in treatment of Achilles Tendinopathy: A systematic review of literature. Study design: Systematic review of literature. *Annals of medicine and surgery (2012)*, *55*, 320–326. https://doi.org/10.1016/j.amsu.2020.04.042

Maffulli, N., Via, A. G., & Oliva, F. (2015). Chronic Achilles Tendon Disorders: Tendinopathy and Chronic Rupture. *Clinics in sports medicine*, *34*(4), 607–624. https://doi.org/10.1016/j.csm.2015.06.010

Mautner, K., Colberg, R. E., Malanga, G., Borg-Stein, J. P., Harmon, K. G., Dharamsi, A. S., Chu, S., & Homer, P. (2013). Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, retrospective review. *PM & R : the journal of injury, function, and rehabilitation*, *5*(3), 169–175. https://doi.org/10.1016/j.pmrj.2012.12.010

Monto, R. (2012). Platelet Rich Plasma Treatment for Chronic Achilles Tendinosis. *Foot & Ankle International*, *33*(5), 379–385. https://doi.org/10.3113/FAI.2012.0379

Murawski, S. (2014). A Single Platelet-Rich Plasma Injection for Chronic Midsubstance Achilles Tendinopathy: A Retrospective Preliminary Analysis. *Foot and Ankle Specialist*, *7*(5), 372–376. https://doi.org/10.1177/1938640014532129

Nauwelaers, A. K., Van Oost, L., & Peers, K. (2020). Evidence for the use of PRP in chronic midsubstance Achilles tendinopathy: A systematic review with meta-analysis. *Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons*, S1268-7731(20)30163-6. Advance online publication. https://doi.org/10.1016/j.fas.2020.07.009

O'Neill, S., Watson, P. J., & Barry, S. (2015). Why are Eccentric Exercises Effective for Achilles Tendinopathy?. International journal of sports physical therapy, 10(4), 552–562.

Vannini, F., Di Matteo, B., Filardo, G., Kon, E., Marcacci, M., & Giannini, S. (2014). Platelet-rich plasma for foot and ankle pathologies: a systematic review. *Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons*, *20*(1), 2–9. https://doi.org/10.1016/j.fas.2013.08.001

Wasterlain, A. S., Braun, H. J., Harris, A. H., Kim, H. J., & Dragoo, J. L. (2013). The systemic effects of platelet-rich plasma injection. *The American journal of sports medicine*, *41*(1), 186–193. https://doi.org/10.1177/0363546512466383

Yasui, Y., Tonogai, I., Rosenbaum, A. J., Shimozono, Y., Kawano, H., & Kennedy, J. G. (2017). The Risk of Achilles Tendon Rupture in the Patients with Achilles Tendinopathy: Healthcare Database Analysis in the United States. *BioMed research international*, *2017*, 7021862. https://doi.org/10.1155/2017/7021862

Zhang, Y. J., Xu, S. Z., Gu, P. C., Du, J. Y., Cai, Y. Z., Zhang, C., & Lin, X. J. (2018). Is

Platelet-rich Plasma Injection Effective for Chronic Achilles Tendinopathy? A Meta-analysis. *Clinical orthopaedics and related research*, *476*(8), 1633–1641. https://doi.org/10.1007/s11999.0000000000000258

Appendices

Appendix A: Literature Review Matrix

Level I *Evidence; Section A*

Source: Boesen, A., Hansen, R., Boesen, M., Malliaras, P., & Langberg, H. (2017). Effect of High-Volume Injection, Platelet-Rich Plasma, and Sham Treatment in Chronic Midportion Achilles Tendinopathy: A Randomized Double-Blinded Prospective Study. *The American Journal of Sports Medicine*, *45*(9), 2034–2043. https://doi.org/10.1177/0363546517702862			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Randomized controlled trial **Purpose:** To determine whether eccentric training in combination with high-volume injection (HVI) or platelet-rich plasma (PRP) injections improves outcomes in AT. **Method:** All participants performed eccentric training combined with either (1) one HVI (steroid, saline, and local anesthetic), (2) four PRP injections each 14 days apart, or (3) placebo (a few drops of saline under the skin). Randomization was stratified for age, function, and symptom severity (Victorian Institute of Sports Assessment–Achilles [VISA-A]).	A total of 60 men (age, 18-59 years) with chronic (>3 months) AT were included and followed for 6 months (n = 57). John Hopkins Evidence Appraisal Level: 1 Quality: A	Outcomes included function and symptoms (VISA-A), self-reported tendon pain during activity (visual analog pain scale [VAS]), tendon thickness and intratendinous vascularity (ultrasonographic imaging and Doppler signal), and muscle function (heel-rise test). Outcomes were assessed at baseline and at 6, 12, and 24 weeks of follow-up.	Treatment with HVI or PRP in combination with eccentric training in chronic AT seems more effective in reducing pain, improving activity level, and reducing tendon thickness and intratendinous vascularity than eccentric training alone. HVI may be more effective in improving outcomes of chronic AT than PRP in the short term
Recommendations: Larger sample size, determine the exact concentration of platelets and growth factors in the PRP			

Source: de Vos RJ, Weir A, van Schie HTM, et al. Platelet-Rich Plasma Injection for Chronic Achilles Tendinopathy: A Randomized Controlled Trial. *JAMA*. 2010;303(2):144–149. doi:10.1001/jama.2009.1986			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Randomized Control Trial **Purpose:** To examine whether a PRP injection would improve outcome in chronic	54 randomized patients aged 18 to 70 years with chronic	All patients completed a questionnaire consisting of standardized outcome	The mean VISA-A score improved significantly after 24

midportion Achilles tendinopathy **Method:** Stratified, block-randomized, double-blind, placebo-controlled trial. The PRP treatment was disseminated as a potentially successful treatment for tendinopathies. According to the study protocol, the primary analysis was performed after 24 weeks of follow-up. After 24 weeks, blinding was disclosed for the primary researcher. Results at 52 weeks will be used as a secondary outcome to describe the long-term results in a future analysis.	tendinopathy 2 to 7 cm above the Achilles tendon insertion John Hopkins Evidence Appraisal Level: 1 Quality: B	measures at baseline and after 6, 12, and 24 weeks. The primary outcome measure VISA-A questionnaire. Secondary outcome measures were subjective patient satisfaction, return to sports, and adherence of the eccentric exercises.	weeks in the PRP group by 21.7 points (95% confidence interval [CI], 13.0-30.5) and in the placebo group by 20.5 points (95% CI, 11.6-29.4). The increase was not significantly different between both groups
Recommendations: No recommendations were given			

Source: Jonge, S. D., Vos, R. J., Weir, A., Schie, H. T., Bierma-Zeinstra, S. M., Verhaar, J. A., . . . Tol, J. L. (2011). One-Year Follow-up of Platelet-Rich Plasma Treatment in Chronic Achilles Tendinopathy. *The American Journal of Sports Medicine, 39*(8), 1623-1630. doi:10.1177/0363546511404877

Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
A Double-Blind Randomized Placebo-Controlled Trial **Purpose:** To study the effects of a platelet-rich plasma injection in patients with chronic midportion Achilles tendinopathy at 1-year follow-up **Method:** participants were randomized to receive either a blinded injection containing platelet-rich plasma or saline (placebo group) in addition to an eccentric training program. The main outcome was the validated Victorian Institute of Sports Assessment–Achilles score. Patient satisfaction was recorded and ultrasound examination performed at baseline and follow-up.	54 patients aged 18-70 years diagnosed with chronic tendinopathy John Hopkins Evidence Appraisal Level: 1 Quality: B	The primary outcome was the VISA-A score. Other outcome measures were subjective patient satisfaction (scored as moderate, poor, good, or excellent) and return to sports activity (scored as not active in sports, no return to sports, returning to sport but not in desired sport, returning to desired sport but not at the preinjury level, or returning to preinjury level in the desired sport). Tendon structure was evaluated quantitatively by means of UTC (UTCimaging, Stein, the Netherlands). Neovascularization was scored using the modified O¨ hberg scoring system.	The mean Victorian Institute of Sports Assessment–Achilles score improved in both the platelet-rich plasma group and the placebo group after 1 year. There was no significant difference in increase between both groups (adjusted between-group difference, 5.5; 95% confidence interval, –4.9 to 15.8, P = .292). In both groups, 59% of the patients were satisfied with the received treatment. Ultrasonographic tendon structure improved significantly in both groups but was not significantly different between groups (adjusted between-group difference, 1.2%; 95% confidence interval, –4.1 to 6.6, P = .647).

Recommendations: No recommendations were given

Source: Kearney, R. S., Parsons, N., & Costa, M. L. (2013). Achilles tendinopathy management: A pilot randomised controlled trial comparing platelet-rich plasma injection with an eccentric loading programme. *Bone & joint research*, *2*(10), 227–232. https://doi.org/10.1302/2046-3758.210.2000200			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
A pilot randomised controlled trial **Purpose:** To conduct a pilot randomised controlled trial to evaluate the feasibility of conducting a larger trial to evaluate the difference in Victorian Institute of Sports Assessment-Achilles (VISA-A) scores at six months between patients with Achilles tendinopathy treated with a platelet-rich plasma (PRP) injection compared with an eccentric loading programme. **Method:** Two groups of patients with mid-substance Achilles tendinopathy were randomised to receive a PRP injection or an eccentric loading programme. A total of 20 patients were randomised, with a mean age of 49 years (35 to 66). All outcome measures were recorded at baseline, six weeks, three months and six months.	20 participants who were assessed at a United Kingdom teaching hospital John Hopkins Evidence Appraisal Level: 1 Quality: C	All patients were assessed at standard clinical follow-up at six weeks, three months and six months. At these timepoints the VISA-A questionnaire was administered, which was the primary outcome measure.	The mean VISA-A score for the injection group at the primary endpoint of six months was 76.0 (95% confidence interval (CI) 58.3 to 93.7) and for the exercise group was 57.4 (95% CI 38.1 to 76.7). There was no statistically significant difference between these scores (p = 0.171)
Recommendations: The results of this pilot trial would enable conclusions to be drawn regarding the feasibility of completing a full study to evaluate the clinical effectiveness of PRP injections.			

Source: Krogh, E. (2016). Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline: A Randomized, Blinded, Placebo-Controlled Trial. The American Journal of Sports Medicine, 44(8), 1990–1997. https://doi.org/10.1177/0363546516647958			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**

RCT **Purpose:** To examine whether 1 injection of platelet-rich plasma (PRP) would improve outcomes more effectively than placebo (saline) after 3 months in patients with AT. **Method:** A total of 24 patients with chronic AT (median disease duration, 33 months) were randomized (1:1) to receive either a blinded injection of PRP (n = 12) or saline (n = 12).	24 patients John Hopkins Evidence Appraisal Level: 1 Quality: B	The primary endpoint was improvement in Victorian Institute of Sports Assessment–Achilles (VISA-A) score at 3 months. Secondary outcomes were pain at rest, pain while walking, pain when the tendon was squeezed, ultrasonographic changes in tendon thickness, and color Doppler activity.	PRP injection did not result in an improved VISA-A score over a 3-month period in patients with chronic AT compared with placebo. The only secondary outcome demonstrating a statistically significant difference between the groups was change in tendon thickness; this difference indicates that a PRP injection could increase tendon thickness compared with saline injection. The conclusions are limited to the 3 months after treatment owing to the large dropout rate.
Recommendations: A larger study population could demonstrate statistically significant differences that were not revealed in our study.			

Level I *Evidence; Section B*

Source: Liu, C. J., Yu, K. L., Bai, J. B., Tian, D. H., & Liu, G. L. (2019). Platelet-rich plasma injection for the treatment of chronic Achilles tendinopathy: A meta-analysis. *Medicine*, *98*(16), e15278. https://doi.org/10.1097/MD.0000000000015278

Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Meta-Analysis **Purpose:** evaluated the current evidence for the efficacy of PRP as a treatment for chronic Achilles Tendinopathy (AT). **Method:** The PubMed, Embase, Web of Science, and The Cochrane Library databases were searched for articles on randomized controlled trials (RCTs) that compared the efficacy of PRP with that of placebo injections plus eccentric training as treatment for AT.	5 RCTs were used in this Meta-Analysis John Hopkins Evidence Appraisal Level: 1 Quality: B	Outcome measurements included the Victorian Institute of Sports Assessment-Achilles (VISA-A), visual analog scale (VAS) and Achilles tendon thickness. Statistical analysis was performed. Two independent reviewers (CJL and JBB) evaluated the quality of the included studies by using the ROB tool provided by the Cochrane collaboration. The mean difference and 95% CI were calculated and analysed as the effect amounts in accordance with the ankle function scores of each study treatment group and control group. If multiple ankle joint function scores were used in the study, the priority sequence of VISA-A, VAS, and Achilles tendon thickness was calculated in case of	PRP injection around the Achilles tendon is an option for the treatment of chronic AT, but has limited evidence.

		complete data. Data extraction, transformation and analysis methods were performed in reference to the Cochrane system evaluation manual.	
Recommendations: These results still require verification by a large number of well designed, heterogeneous RCT studies			

Source: Madhi, M. I., Yausep, O. E., Khamdan, K., & Trigkilidas, D. (2020). The use of PRP in treatment of Achilles Tendinopathy: A systematic review of literature. Study design: Systematic review of literature. *Annals of medicine and surgery (2012)*, *55*, 320–326. https://doi.org/10.1016/j.amsu.2020.04.042

Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Systematic Review **Purpose:** to ascertain the efficacy of Platelet Rich Plasma (PRP) as a treatment option in chronic Achilles tendinopathy. **Method:** PRISMA reporting item for systematic review has been used to conduct the selection, Electronic databases included PubMed, EMBASE, Cochrane collaboration, Google scholar, the web of science and Cochrane Library were searched for all RCT, prospective and retrospective studies conducted between January 2010 to February 2019.	5 Randomised control trials, 4 prospective and 2 retrospective cohort studies were included in this systematic review. A total number of 406 patients were treated for non-insertional Achilles tendinopathy of which 230 patients had PRP local injection under Ultrasound guide. John Hopkins Evidence Appraisal Level: 1 Quality: B	The primary outcome was the VISA-A score and Ultrasound scan assessment of the tendon thickness pre- and post-treatment. Oxford CEBM tool was used to assess the articles for validity, relevance and applicability of the results. All studies were of high quality and varied slightly in terms of the blinding methods implemented.	Many of the retrospective studies suggested an advantage of using PRP, the higher level of evidence studies do not support a significant efficacy. This systematic review showed very promising results from the use of Platelet Rich Plasma demonstrated by a significant improvement in the VISA-A score
Recommendations: More RCTs with large sample size to determine treatment effectiveness			

Source: Nauwelaers, A. K., Van Oost, L., & Peers, K. (2020). Evidence for the use of PRP in chronic midsubstance Achilles tendinopathy: A systematic review with meta-analysis. *Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons*, S1268-7731(20)30163-6. Advance online publication. https://doi.org/10.1016/j.fas.2020.07.009

Design Methodology/Purpose	Sample/Setting	Design Instruments	Results
Systematic review with meta analysis **Purpose:** establish the existing evidence of PRP injections for chronic midsubstance AT on the functional outcome, with a risk of bias assessment of each included study. **Method:** According to the PRISMA guidelines systematic searches were performed in Embase, the Cochrane library and Pubmed on June 12, 2020 for relevant literature. Only clinical trials comparing PRP injections with placebo, additional to an eccentric training program, in midsubstance AT were included. The primary outcome was Victorian Institute of Sport Assessment - Achilles (VISA-A) score at 3, 6 and 12 months post-injection. Risk of bias was assessed using the Cochrane risk-of-bias tool for randomized trials (Rob 2). As secondary outcome we assessed reported changes in tendon structure after PRP injections.	Clinical; 4 RCTs, 170 patients John Hopkins Evidence Appraisal Level: 1 Quality: B	comparison: saline injection or placebo, outcome: VISA-A and study design: clinical trials.	A total of 367 studies were identified with the initial database search. Finally, four randomized controlled trials (RCTs) met inclusion criteria for systematic review and meta-analysis with data of 170 patients available for pooling. Results showed no difference in clinical outcome between the PRP and placebo group at different points in time using the VISA-A score as outcome parameter (3 months 0.23 (CI -0.45, 0.91); 6 months 0.83 (CI -0.26, 1.92); 12 months 0.83 (CI -0.77, 2.44)).
Recommendations: PRP has no clear additional value in management of chronic midsubstance Achilles tendinopathy and therefore should not be used as a first-line treatment option.			

Source: Zhang, Y. J., Xu, S. Z., Gu, P. C., Du, J. Y., Cai, Y. Z., Zhang, C., & Lin, X. J. (2018). Is Platelet-rich Plasma Injection Effective for Chronic Achilles Tendinopathy? A Meta-analysis. *Clinical orthopaedics and related research*, *476*(8), 1633–1641. https://doi.org/10.1007/s11999.0000000000000258

Design Methodology/Purpose	Sample/Setting	Design Instruments	Results
Meta-Analysis **Purpose:** to gather the Randomized control trials (RCT) done regarding PRP treatment on achilles	4 Level 1 RCT trials with 170 participants used in the quantitative synthesis	The primary endpoint was improvement in the VISA-A score, which ranges from 0 to 100 points with higher scores	PRP injection with eccentric training did not improve VISA-A scores, reduce tendon thickness, or reduce

tendinopathy and determine whether or not the research says PRP is an effective treatment option **Method:** A search of peer-reviewed articles was conducted to identify all RCTs using PRP injection with eccentric training for chronic Achilles tendinopathy in the electronic databases of PubMed, Web of Science (SCI-E/SSCI/A&HCI), and EMBASE from January 1981 to August 2017. Two reviewers assessed study quality using the Cochrane Collaboration risk-of-bias tool. The primary endpoint was improvement in the VISA-A score	John Hopkins Evidence Appraisal Level: 1 Quality: C	representing increased activity and less pain. The VISA-A score is a validated questionnaire, specifically designed for evaluating outcome in Achilles tendinopathy. Secondary outcomes were tendon thickness, color Doppler activity, and other functional measures (such as pain and return to sports activity).	color Doppler activity in patients with chronic Achilles tendinopathy compared with saline injection. Larger randomized trials are needed to confirm these results, but until or unless a clear benefit has been demonstrated in favor of the new treatment, we cannot recommend it for general use.
Recommendations: Larger randomized trials are needed to confirm these results			

Level Ⅱ *Evidence; Section A*

Source: Filardo, G., Kon, E., Di Matteo, B., Di Martino, A., Tesei, G., Pelotti, P., Cenacchi, A., & Marcacci, M. (2014). Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: results at 4 years. *Blood transfusion = Trasfusione del sangue*, *12*(4), 533–540. https://doi.org/10.2450/2014.0289-13			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Quasi-experimental **Purpose:** document the mid-term results obtained after treating recalcitrant Achilles tendinopathy with injections of high concentrate, leucocyte-rich PRP **Method:** Twenty-seven patients (mean age: 44.6 years; 22 men and 5 women) affected by chronic mid-portion Achilles tendinopathy (7 bilateral, for a total of 34 tendons), refractory to previous treatments, were enrolled. Patients were treated with three	Clinical; 27 patients enrolled--34 Achilles tendons assessed (7 patients had bilateral AT) John Hopkins Evidence Appraisal Level: 2 Quality: B	Blanzina, VISA-A, EQ-VAS for general health, and Tegner scores	The VISA-A score showed a significant improvement: the baseline score of 49.9±18.1 increased to 62.9±19.8 at 2 months ($p=0.002$), with a further improvement at 6 months (84.3±17.1, $p<0.0005$), and stable results at 4.5 years (90.0±13.9). The EQ-VAS score also showed a similar positive trend. An evaluation of the activity level confirmed these findings, showing a significant improvement in

ultrasound-guided intra-tendinous injections of PRP at 2-week intervals. Patients were prospectively evaluated at baseline, and then at 2, 6, and up to a mean of 54.1 months of follow-up (minimum 30 months)			the Tegner score over time (p=0.017 for the final evaluation). The longer duration of symptoms before treatment was associated with a slower return to sport (p=0.041).
Recommendations: PRP injections produced good overall results for the treatment of chronic recalcitrant Achilles tendinopathy with a stable outcome up to a medium-term follow-up. Longer symptom duration was related with a more difficult return to sporting activity.			

Source: Mautner, K., Colberg, R. E., Malanga, G., Borg-Stein, J. P., Harmon, K. G., Dharamsi, A. S., Chu, S., & Homer, P. (2013). Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, retrospective review. *PM & R : the journal of injury, function, and rehabilitation*, *5*(3), 169–175. https://doi.org/10.1016/j.pmrj.2012.12.010			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
A retrospective, cross-sectional survey **Purpose:** To determine whether ultrasound-guided platelet-rich plasma (PRP) injec- tions are an effective treatment for chronic tendinopathies. **Method:** The tendinopathy had to be reconfirmed at the time of the procedure with ultrasound evaluation of the tendon after the aforementioned criteria were met. Patients must have received one or more ultrasound-guided PRP injections no less than 6 months before the time of contact for the survey. In addition, the procedure must have followed a defined protocol for preparation and delivery of the PRP that included 2 patient identifiers, aseptic technique, blood draw volume from 20-60 mL depending on the amount of final PRP product	Four academic sports medicine centers from across the United States. A total of 180 men and women between the ages of 18 and 75 years who received ultrasound-guided PRP injections for tendinopathy refractory to conventional treatments. John Hopkins Evidence Appraisal Level: 2 Quality: B	Survey on satisfaction and functional outcome.Perceived improvement in symptoms at least 6 months after treatment, perceived change in visual analog scale score, assessment of functional pain, and overall satisfaction.	Overall, 82% of patients indicated moderate to complete improvement in symptoms. The most common injection sites were the lateral epicondyle, Achilles, and patellar tendons. In this retrospective study, in which we evaluated administration of PRP for chronic tendinopathy, we found that the majority of patients reported a moderate (50%) improvement in pain symptoms. The Achilles tendon group had the best response, with all patients having at least moderate improvement and 96% of patients reporting mostly to complete improvement. This finding was promising for patients with recalcitrant Achilles tendinopathy because the authors of one systematic

needed to inject into a specific tendon, PRP preparation according to manufacturer- recommendations, no activator added, and ultrasound guidance for the injection. Finally, the patients must have completed a rehabilitation program that included eccentric exercises no earlier than 4 weeks after the procedure. The primary outcome measurement (improvement in symptoms) was analyzed by calculating a global average for all tendons, average improvement for each of the most commonly treated tendon groups, and average improvement according to the number of injections received. The perceived change in VAS was analyzed using a t-test for statistical significance. Averages also were calculated for functional pain after PRP and overall satisfaction with the procedure.			review noted that 24%-45.5% of patients with Achilles tendinopathy eventually consider surgery
Recommendations: PRP should be reserved for recalcitrant cases that do not respond to conservative treatments, including eccentric exercises.			

Source: Ferrero, G., Fabbro, E., Orlandi, D., Martini, C., Lacelli, F., Serafini, G., Silvestri, E., & Sconfienza, L. M. (2012). Ultrasound-guided injection of platelet-rich plasma in chronic Achilles and patellar tendinopathy. *Journal of ultrasound*, *15*(4), 260–266. https://doi.org/10.1016/j.jus.2012.09.006			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
quasi-experimental **Purpose:** evaluate the effectiveness of ultrasound (US)-guided autologous PRP injections in patellar and Achilles tendinopathy. **Method:** Autologous PRP was injected under US-guidance into the Achilles and patellar tendons (30	30 Achilles tendons in 24 patients (16 men, 8 women) were prospectively evaluated John Hopkins Evidence Appraisal Level: 2	VISA-A, Doppler to assess tendon thickness	20 days after PRP injection the patients presented a non-significant improvement of clinical symptoms. At the 6-month follow-up VISA score increased from a mean value of 57–75.5 ($p < .01$). US evaluation revealed a reduction of hypoechoic areas in 26 tendons ($p < .01$)

Achilles tendons, 28 patellar tendons) in 48 prospectively selected patients (30 males, 18 females, mean age 38 ± 16 years, range 20–61 years). All patients were previously evaluated according to the Victoria Institute of Sport Assessment (VISA) scale, which assessed pain and activity level, and they all underwent US of the tendon before treatment and at follow-up after 20 days and 6 months. Statistical analysis was performed with Chi-square and Wilcoxon tests.	Quality: B		associated with a widespread improvement of fibrillar echotexture of the tendon and reduced hypervascularity at power Doppler. At the 6-month follow-up, overall satisfaction was rated by patients in whom Achilles tendon was treated as positive in 21 tendons (70%; excellent = 10/30 tendons; good = 11/30 tendons) and poor in 9 tendons (30%).
Recommendations: The present study shows that US-guided treatment of jumper's knee and Achilles tendinopathy using PRP is feasible as it is an effective and minimally invasive treatment option. Further randomized controlled studies performed on a larger sample size are warranted to confirm these preliminary results.			

Level Ⅱ *Evidence; Section B*

Source: Vannini, F., Di Matteo, B., Filardo, G., Kon, E., Marcacci, M., & Giannini, S. (2014). Platelet-rich plasma for foot and ankle pathologies: a systematic review. *Foot and ankle surgery : official journal of the European Society of Foot and Ankle Surgeons*, *20*(1), 2–9. https://doi.org/10.1016/j.fas.2013.08.001			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
A systematic Review **Purpose:** The aim of this article is to systematically review all the literature available on the clinical application of PRP for the treatment of foot and ankle pathologies, to understand its potential and best indications for clinical use. **Method:** A systematic search of the PubMed database was performed. Research criteria were the following: (1) papers in the English language, (2) dealing with the clinical application of PRP for the	17 studies John Hopkins Evidence Appraisal Level: 2 Quality: B	Achilles tendinopathy section only: Victorian Institute of Sport Assessment-Achilles tendon (VISA-A) questionnaire, and registering patient satisfaction and return to sport, Foot and Ankle Ability Measure (FAAM), Foot and Ankle Ability Measure Sport (FAAM-S) and Short Form Health Survey (SF-8), AOFAS score (depending on the study)	A total of 17 studies fulfilled the inclusion criteria. Nine papers dealt with Achilles tendon management, 2 articles with plantar fasciitis, 3 papers with talar osteochondral lesions, 2 with PRP application in total ankle replacement, and 1 article with PRP in foot and ankle fusions. The overall evaluation of the results reported does not clearly demonstrate the potential of PRP treatment in any of the specific fields of application.

treatment of orthopedic-related conditions affecting the foot and ankle district, (3) with I to IV level of evidence, and (4) reporting clinical results.			
Recommendations: it is important to underline that, at the present moment, it is impossible to define a clear indication for the use of this biological product, neither as a conservative approach nor as a biological enhancer during surgical procedures. The reasons for this lack of clinical evidence might be both the nature of PRP itself and the quality of the studies published up to the present date.			

Level Ⅲ *Evidence; Section A*

Source: Murawski, S. (2014). A Single Platelet-Rich Plasma Injection for Chronic Midsubstance Achilles Tendinopathy: A Retrospective Preliminary Analysis. *Foot and Ankle Specialist*, *7*(5), 372–376. https://doi.org/10.1177/1938640014532129			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
A Retrospective Preliminary Analysis **Purpose:** evaluate a series of patients undergoing a single platelet-rich plasma (PRP) injection for the treatment of chronic midsubstance Achilles tendinopathy, in whom conservative treatment had failed. **Method:** Thirty-two patients underwent a single PRP injection for the treatment of chronic midsubstance Achilles tendinopathy and were evaluated at a 6-month final follow-up using the Foot and Ankle Outcome Score and Short Form 12 general health questionnaire. Magnetic resonance imaging was performed on all patients prior to and 6 months after injection.	32 patients--mean age of 41 years old John Hopkins Evidence Appraisal Level: 3 Quality: C	Foot and Ankle Outcome Score and Short Form 12 general health questionnaire; as well as the patients' ability to return to athletic activity.	Twenty-five of 32 patients (78%) reported that they were asymptomatic at the 6-month follow-up visit and were able to participate in their respective sports and daily activities. The remaining 7 patients (22%) who reported symptoms that did not improve after 6 months ultimately required surgery. Four patients went on to have an Achilles tendoscopy, while the other 3 had an open debridement via a tendon splitting approach. A retrospective evaluation of patients receiving a single PRP injection for chronic midsubstance Achilles tendinopathy revealed that 78% had experienced clinical improvement and had avoided surgical intervention at 6-month follow-up.
Recommendations: No recommendations were given by the authors			

Source: Monto, R. (2012). Platelet Rich Plasma Treatment for Chronic Achilles Tendinosis. *Foot & Ankle International*, *33*(5), 379–385. https://doi.org/10.3113/FAI.2012.0379			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
Case Series **Purpose:** to determine its potential long-term efficacy in treating chronic cases of Achilles tendinosis resistant to traditional nonoperative management **Method:** Thirty patients with chronic Achilles tendinosis who did not respond to a minimum of 6 months of traditional nonoperative treatment modalities were treated with a single ultrasound guided injection of PRP	30 patients--clinical setting John Hopkins Evidence Appraisal Level: 3 Quality: C	AOFAS scoring was completed for all patients pretreatment and at 0, 1, 2, 3, 6, 12, and 24 months post-treatment. MRI and/or ultrasound studies were completed for all patients pre-treatment and at 6 months post-treatment.	The average AOFAS score increased from 34 (range, 20 to 60) to 92 (range, 87 to 100) by 3 months after PRP treatment and remained elevated at 88 (range, 76 to 100) at 24 months post-treatment. Pretreatment imaging abnormalities present in the Achilles tendon on MRI and ultrasound studies resolved in 27 of 29 patients at 6 months post-treatment. Clinical success was achieved in 28 of 30 patients.
Recommendations: No formal recommendations listed			

Level Ⅲ *Evidence; Section B*

Source: Di Matteo, B., Filardo, G., Kon, E., & Marcacci, M. (2014). Platelet-rich plasma: evidence for the treatment of patellar and Achilles tendinopathy—a systematic review. *Musculoskeletal Surgery*, *99*(1), 1–9. https://doi.org/10.1007/s12306-014-0340-1			
Design Methodology/Purpose	**Sample/Setting**	**Design Instruments**	**Results**
A Systematic Review **Purpose:** review systematically the available clinical evidence concerning the application of PRP in the treatment of patellar and Achilles tendinopathy **Method:** Articles were found using PubMed. First, the articles were screened by title and abstract. The	Twelve papers in total met the inclusion criteria and were analyzed. Only one trial was a double-blind RCT, whereas the others were all case series.	VISA-A questionnaire	The double-blind RCT was published by de Vos et al. in 2010 and was followed by a second paper dealing with the same patients evaluated at longer follow-up (1 year). The authors compared PRP versus saline injections in patients affected by chronic mid-portion Achilles tendinopathy for more than 2 months. Fifty-four patients, aged from 18 to 70

following inclusion criteria for relevant articles were used during the initial screening of titles and abstracts: clinical reports of any level of evidence, written in the English language, with no time limitation, on the use of PRP to treat conservatively Achilles and patellar tendinopathy. Studies reporting the application of PRP as a biological augmentation during patellar and Achilles surgical repair were excluded from analysis. Other exclusion criteria were as follows: case reports, articles written in other languages and reviews. In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Moreover, articles not reporting clinical results were excluded.	John Hopkins Evidence Appraisal Level: 3 Quality: C		years, were included and treated by a single injection by needling technique of either 4 mL of non-activated PRP or 4 mL of saline solution. After the injection, patients were assigned to a standardized rehabilitation program based on eccentric exercises. Prospective evaluations were performed for up to 24 weeks using the VISA-A questionnaire, patient satisfaction and return to sport. The results showed improvements in both treatment groups without any significant inter-group difference in any parameter considered. In a later article, the authors reported the results at 1 year of follow-up where they confirmed no difference in clinical outcome or in time to return to sport.
Recommendations: The most controversial debate concerns Achilles tendinopathy, since the only double-blind RCT showed negative results for PRP, whereas the remaining trials (all case series) reported overall positive outcomes even at mid-/long-term evaluation. In conclusion, the clinical data available, although not univocal, suggest considering PRP as an option for the management of both patellar and Achilles tendinopathies.			

Appendix B: Quality Assessment

Johns Hopkins Nursing Evidence-Based Practice

Appendix E
Research Evidence Appraisal Tool

Evidence level and quality rating:	
Article title:	Number:
Author(s):	Publication date:
Journal:	
Setting:	Sample (composition and size):

Does this evidence address my EBP question?

☐ Yes
☐ No-*Do not proceed with appraisal of this evidence*

Is this study:

☐ **QuaNtitative** (collection, analysis, and reporting of numerical data)
Measurable data (how many; how much; or how often) used to formulate facts, uncover patterns in research, and generalize results from a larger sample population; provides observed effects of a program, problem, or condition, measured precisely, rather than through researcher interpretation of data. Common methods are surveys, face-to-face structured interviews, observations, and reviews of records or documents. Statistical tests are used in data analysis.

➡ Go to ***Section I: QuaNtitative***

☐ **QuaLitative** (collection, analysis, and reporting of narrative data)
Rich narrative documents are used for uncovering themes; describes a problem or condition from the point of view of those experiencing it. Common methods are focus groups, individual interviews (unstructured or semi structured), and participation/observations. Sample sizes are small and are determined when data saturation is achieved. Data saturation is reached when the researcher identifies that no new themes emerge and redundancy is occurring. Synthesis is used in data analysis. Often a starting point for studies when little research exists; may use results to design empirical studies. The researcher describes, analyzes, and interprets reports, descriptions, and observations from participants.

➡ Go to ***Section II: QuaLitative***

☐ **Mixed methods** (results reported both numerically and narratively)
Both quaNtitative and quaLitative methods are used in the study design. Using both approaches, in combination, provides a better understanding of research problems than using either approach alone. Sample sizes vary based on methods used. Data collection involves collecting and analyzing both quaNtitative and quaLitative data in a single study or series of studies. Interpretation is continual and can influence stages in the research process.

➡ Go to ***Section III: Mixed Methods***

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Appendix E
Research Evidence Appraisal Tool

Section I: QuaNtitative		
Level of Evidence (Study Design)		
A Is this a report of a single research study?	□ Yes	□No **Go to B**
1. Was there manipulation of an independent variable?	□ Yes	□ No
2. Was there a control group?	□ Yes	□ No
3. Were study participants randomly assigned to the intervention and control groups?	□ Yes	□ No
If **Yes to questions 1, 2, and 3,** this is a randomized controlled trial (RCT) or experimental study.		**LEVEL I**
If **Yes to questions 1 and 2 and No to question 3** or **Yes to question 1 and No to questions 2 and 3,** this is quasi-experimental. *(Some degree of investigator control, some manipulation of an independent variable, lacks random assignment to groups, and may have a control group).*		**LEVEL II**
If **No to questions 1, 2, and 3,** this is nonexperimental. *(No manipulation of independent variable; can be descriptive, comparative, or correlational; often uses secondary data).*		**LEVEL III**
Study Findings That Help Answer the EBP Question		
Skip to the **Appraisal of QuaNtitative Research Studies** section		

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Appendix E
Research Evidence Appraisal Tool

Section I: QuaNtitative (continued)		
B Is this a summary of multiple sources of research evidence?	☐ Yes *Continue*	☐ No **Use Appendix F**
1. Does it employ a comprehensive search strategy and rigorous appraisal method? *If this study includes research, nonresearch, and experiential evidence, it is an integrative review (see Appendix F).*	☐ Yes *Continue*	☐ No **Use Appendix F**
2. For systematic reviews and systematic reviews with meta-analysis (see descriptions below):		
a. Are all studies included RCTs?		**LEVEL I**
b. Are the studies a combination of RCTs and quasi-experimental, or quasi-experimental only?		**LEVEL II**
c. Are the studies a combination of RCTs, quasi-experimental, and nonexperimental, or non- experimental only?		**LEVEL III**
A **systematic review** employs a search strategy and a rigorous appraisal method, but does not generate an effect size. A **meta-analysis**, or systematic review with meta-analysis, combines and analyzes results from studies to generate a new statistic: the effect size.		
Study Findings That Help Answer the EBP Question		
Skip to the **Appraisal of Systematic Review** (With or Without a Meta-Analysis) section		

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Appendix E
Research Evidence Appraisal Tool

Appraisal of QuaNtitative Research Studies			
Does the researcher identify what is known and not known about the problem and how the study will address any gaps in knowledge?	☐ Yes	☐ No	
Was the purpose of the study clearly presented?	☐ Yes	☐ No	
Was the literature review current (most sources within the past five years or a seminal study)?	☐ Yes	☐ No	
Was sample size sufficient based on study design and rationale?	☐ Yes	☐ No	
If there is a control group: • Were the characteristics and/or demographics similar in both the control and intervention groups?	☐ Yes	☐ No	N/A
• If multiple settings were used, were the settings similar?	☐ Yes	☐ No	N/A
• Were all groups equally treated except for the intervention group(s)?	☐ Yes	☐ No	N/A
Are data collection methods described clearly?	☐ Yes	☐ No	
Were the instruments reliable (Cronbach's α[alpha] $\geq$ 0.70)?	☐ Yes	☐ No	N/A
Was instrument validity discussed?	☐ Yes	☐ No	N/A
If surveys or questionnaires were used, was the response rate $\geq$ 25%?	☐ Yes	☐ No	N/A
Were the results presented clearly?	☐ Yes	☐ No	
If tables were presented, was the narrative consistent with the table content?	☐ Yes	☐ No	N/A
Were study limitations identified and addressed?	☐ Yes	☐ No	
Were conclusions based on results?	☐ Yes	☐ No	
Complete the Quality Rating for QuaNtitative Studies section			

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Appendix E
Research Evidence Appraisal Tool

Appraisal of Systematic Review (With or Without Meta-Analysis)		
Were the variables of interest clearly identified?	☐ Yes	☐ No
Was the search comprehensive and reproducible? • Key search terms stated	☐ Yes	☐ No
• Multiple databases searched and identified	☐ Yes	☐ No
• Inclusion and exclusion criteria stated	☐ Yes	☐ No
Was there a flow diagram that included the number of studies eliminated at each level of review?	☐ Yes	☐ No
Were details of included studies presented (design, sample, methods, results, outcomes, strengths, and limitations)?	☐ Yes	☐ No
Were methods for appraising the strength of evidence (level and quality) described?	☐ Yes	☐ No
Were conclusions based on results?	☐ Yes	☐ No
• Results were interpreted	☐ Yes	☐ No
• Conclusions flowed logically from the interpretation and systematic review question	☐ Yes	☐ No
Did the systematic review include a section addressing limitations **and** how they were addressed?	☐ Yes	☐ No
Complete the Quality Rating for QuaNtitative Studies section (below)		

Quality Rating for QuaNtitative Studies

Circle the appropriate quality rating below:

A High quality: Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough reference to scientific evidence.

B Good quality: Reasonably consistent results; sufficient sample size for the study design; some control, and fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence.

C Low quality or major flaws: Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn.