Platelet rich plasma (PRP) is an autologous product that has been studied since the 1970s.1 In simple terms, blood is obtained from a patient, placed in a centrifuge and exposed to a system that promotes platelet concentration.2 The platelet rich plasma is considered the separated material that is high in number of platelets.2 It is then applied to the tissue of choice in a form of liquid or gel. Its fame has been attributed to the concentration of autologous growth factors and secretory proteins that are thought to be responsible for enhancing the healing process on a cellular level.1 The thought is that PRP enhances recruitment, proliferation, and differentiation of cells involved in tissue regeneration. As tissue engineering continues to emerge, research is looking at the use of platelet derived growth factors in treatment of different pathologies such as bone repair, pseudoarthritis, wound and ligament healing, tissue repair, degenerative osteoarthritis, and many more.3 More recently, the orthopedic literature has been interested in the role of PRP for muscle and tendon healing and is being talked about frequently in the public.1

The prevalence of anterior cruciate ligament (ACL) ruptures in the United States is estimated at 250,000, making ACL reconstruction one of the most commonly performed procedures.4 ACL reconstruction is typically the treatment of choice in tears that are complete or if they cause knee instability.5 However, the slow graft maturation can result in graft failures and is a major concern in the orthopedic population. This failure brings up a list of issues and has the potential to delay rehabilitation efforts.4 This clinical dilemma has shifted much of PRP attention to ACL healing.2 Studies have focused on healing time, pain, gap healing, and donor site morbidity, but there is lack of consistency in the literature.6 When patellar tendon grafts are used, it typically takes one year after the reconstruction for the remodeling stages to complete. These stages of healing can be correlated to the MRI results as well as from a histolocigal prospective.5 Often times the incongruency of tissues or lack of observatble union is considered a gap. Therefore, this literature review is based on patellar tendon gap area as viewed on MRI in individuals who receive PRP after ACL reconstruction versus those who do not receive PRP after ACL reconstruction.

PICO Question: Do patients who receive platelet rich plasma injections after anterior cruciate ligament reconstruction have a smaller patellar tendon gap area via MRI in comparison to individuals who do not receive PRP injections post-surgery?

 Eight articles that focused on the application of PRP in conjunction with ACL reconstruction were reviewed. Due to the limited amount of research on this topic, there was a large amount of variety in the study purposes as well as the outcome measures utilized. Six articles were randomized control trials1,3-8, one a cohort study2 and one a systemic review9. Seven of the articles were human based1-3,5-9 and one addressed the effects of PRP in canines4. While some of the studies only had two groups (an experimental and control) others spread their participants thin with multiple groups and a variety of interventions. For example, the Silva group had 40 patients and split them into four groups.8 The groups were a control, PRP application at time of surgery, PRP application at time of surgery and again at 2 and 4 weeks, and a group that had PRP activated with thrombin clotalyst and applied at time of surgery.8 The Fallouh article was an interesting one in that the cohort study was done in vivo in a controlled clinical environment and different mediums were applied to the four samples and well-kept through the clinical trial.2 Another of the studies that was assessing the genetic expression chose to utilize canines for the procedure.4 The dogs were euthanized at 2, 6, or 12 weeks post operation for ligament excision and testing. Another novel concept used in this study was that each dog had two knees included in the study, each of which was assigned to a different group.4 As you can see, the design of these studies was not parallel in every aspect. Not only were there differences noted in the allocation of PRP, but the independent and dependent variables differed as well.

 For the most part the independent variable was the application of the PRP substance to the area of interest. However, the method of obtaining and preparing PRP has not yet been well established across the literature. Other factors that were included in the independent variable list were subsequent injections of PRP post-surgery8, inclusion of thrombin catalysts8, and one used different concentrations of PRP2. The Fallouh article also looked at the effects of platelet poor plasma--that is the plasma that is separated during centrifuge but is low in number of platelets.2

 The purpose of this review was to determine the effects on healing at the cellular level. Many of the studies looked at the stage of remodeling5, graft maturation, graft-bone interface healing9, bone gap filling7, and harvest site healing6. Others looked at things like pain, knee function, range of motion, muscle torque, and tibial translation.3,6,7 Lastly, two of the articles reviewed looked at cellular and genetic expression as well as cell viability and collagen content.2,4 The standardized outcome measures used in the eight articles reviewed are as follows: MRI3,5-9, pain visual analog scale3,6,7, and anterior laxity with KT 1000.3,9 Some of the more functional outcome measures used included the Victorian Institute Sport Assessment, International Knee Documentation Committee Objective Questionnaire, Knee Injury and Osteoarthritis Outcome Score, Tegner, Lysholm, and Kujala.3,6,7,9 The more biologically involved studies used specialized systems to obtain lab values and levels of different cellular components.2-4 It can be appreciated when these studies incorporate more than one type of outcome measure as it helps us correlate the findings. Unfortunately, some of the articles reviewed were not as broad in their design and therefore offer minimal results.

 For example, Seijas only looked at MRI stages of remodeling. He found that at 4 months and 6 months, post operatively, the PRP group had significantly higher ratings; however, at 12 months there was no significant difference (p=0.354).5 Since they found a trend of positive influence, it would have been useful if they had incorporated other clinical outcomes in their research. On the other hand, Cervellin utilized three outcome measures (MRI, VAS, and VISA) and only found the pain scales on the VISA to be significantly improved in the PRP group.7 They did find that 85% of PRP group had satisfactory bone filling compared to only 60% of the control group. However, this was not enough to be significant.7 This brings up another situation in that the sample size may not be substantial enough to show dramatic influence. de Almeidam found significant changes in pain on day 1 and gap area at 6 months post op. However, they found no significant differences in cross sectional area of the graft, height of the graft, functional improvement, or torque produced.6

 Unfortunately not all studies had significant findings. Valenti nor Silva found any differences between application of PRP and controls. Silva is the study that has been mentioned previously that looked at four different scenarios and there were no difference between any of the groups (control, PRP at time of surgery, PRP at time of surgery plus subsequent injections at weeks 2 and 4, and a PRP application that was combined with a thrombin catalyst).8 They, like Seijas, only used MRI as an outcome measure and they only had 10 subjects in each group. The systematic review found that four out of seven studies that focused on graft maturation had significantly better outcomes in the PRP groups; four out of five studies that focused on tunnel healing found no significant differences; and of the three studies that included clinical outcomes, none found significant differences.9

 So why if the literature is so scattered are the researchers still trying. Many of the more biologically focused studies are reporting hopeful conclusions. Fallouh’s in vivo study found that PRP application significantly increased the concentrations of growth factors and collagen.2 PRP also showed high type III collagen gene expression, even when compared to platelet poor plasma.2 Xie’s study on canines found remarkable results focused around the gene expressions of different growth factors.4 They went on to explain the potential that PRP may have on ACL healing. Their conclusions suggest that PRP may promote neovascularization, ACL graft remodeling, re-innervation, nervous tissue regeneration, and may be a key mediator in angiogenesis.4

 When comparing the more functional articles, you notice that pain seems to be one of the most affected in at least two of those reviewed here.6,7 These two studies were blinded, so that limits the amount of placebo effect to some degree.6,7 When we look across the studies at healing rates, de Almeidam had an improved gap area at 6 months post op, Seijas found higher stages of remodeling at 4 and 6 months, but not at 12, and the Level III systematic review found 57% of articles to be significant in terms of graft maturation and 20% of studies to be significant when assessing tunnel healing.5,6,9 However, each study uses a different method of obtaining and delivering PRP as well as different measurements that are taken post-operatively. For example, Seijas uses an intensity comparison method done by a blinded radiologist and de Almeidam used a computerized measuring tool to assess gap area.5,6 Overall, the goals of these studies are aiming in the same direction and using a very similar generalized approach, however the differences within each may be the leading factor of inconsistent findings.

 The similarities within the human operative articles are evident, but vague at the same time. The studies used the same surgical team with each patient group and many of them had similar inclusion and exclusion criteria.3,5-8 The most noted exclusion criteria that came up 100% of the time was if the subject had a previous knee injury or surgery prior to this ACL disruption. Each study also required their participants to follow the same protocol. However, the protocols were not the same across the board.3,5-8 One may notice that the list of similarities across the literature is sparse and that a big playing factor in this literature review is the high number of differences between studies.

 As mentioned before, one of the most evident differences within the literature is the method of obtaining PRP and its application as well as outcome measurements used post-operatively. Each of the studies used a different specialized system to obtain PRP and the concentrations varied among the groups. Valenti3, de Almeidam6, and Cervellin7 all used a gel form of PRP, while the others5,8 did not. After the PRP was obtained, the application of the material is also noted to be inconsistent across the board. The location of application spanned from the tendon defect6, the graft strands8, the harvest sites7, the suprapatellar joint after portal suture5, and a combination of covering the ligament graft and within the tunnel after suture3. The difference in outcome measures used has been discussed and while some of these are assessing the same things, the literature does not have a standardized time of assessment. The measurements were taken at 1 day3, 3 months8, 4 months5, 6 months3,5, and 12 months5,7. When reviewing the more biological studies, you notice their time frame is much shorter. Fallouh measured outcomes at 24 hours, 48 hours, 4 days, and 7 days.2 Xie euthanized the dogs and excised ligaments for cellular composition studies at 2, 6, and 12 weeks.4 One may think that this would be beneficial as we could understand the changes over time, but the inconsistency limits the reliability of findings.

There are other differences within these studies that exist. Some of the papers claimed that meniscus repairs or extractions were made depending on injury, and chondral defects were left alone.3,7 This is a situation that may be poorly standardized depending on the opinion of the surgeon. These influences may also cause a change in rehabilitative efforts and potential outcome measures. Only one article mentioned exclusion criteria that involve comorbidities that may not be optimal for PRP application such as neoplasms or hyperuricaemia.5

 As one sifts through these materials, it is noticed a solid conclusion is difficult, if not impossible, to agree on. The systematic review published in 2011 is the most well rounded study focused on PRP application to ACL reconstruction and states that PRP may have beneficial effects on graft maturation and improve union by 20-30%.9 de Almeidam agrees with this statement, suggesting that PRP could improve tissue healing at the patellar tendon harvest site.6 Seijas also found positive results at 4 and 6 months post PRP application with surgery.5 However, Valenti and Silva found no significant results and state that the stability of the graft must be provided by a fixation device at 3 months post-op and that the available data to this point is insufficient to make predictions regarding clinical implication and utility.3,8

 While the results may not be consistent, two concepts that are emphasized in the literature may be enough to keep the research going. de Almeidam and Cervellin both found that PRP significantly reduces pain in postoperative patients.6,7 Minimizing pain has great potential for both the patient and the therapist. With reduced pain levels our efforts may be more focused on returning to functional ability and less focused on pain reduction techniques. The second major finding in the literature is focused on the cellular components and genetic changes. Fallouh found two growth factors that had increased levels after PRP application that could be significant enough to induce biological effects.2 Then Xie found a combination of genetic changes in the canine study that have the potential to enhance neovascularization, remodeling, protein synthesis, revascularization and reinnervation.4

 As stated previously, there are many gaps in the literature that will need to be addressed prior to making steadfast decisions concerning PRP application. Some examples of changes that need to take place before we are given more solid evidence include standardizing the obtaining procedure of PRP, the concentration used, the timing of application, location of application, and outcome measures used. With these missing links, I cannot confidently say that I have answered the originally stated PICO question.

 Fortunately, the information gathered can be used in the clinical setting. By having a foundation of knowledge on the procedure and techniques, clinicians can have educated and well-versed conversations with patients and physicians. With this information we can educate our patients on the postulations and current findings. As research continues to develop, this information may take us to more aggressive therapy. If healing rate can in fact be more successful and established at a faster rate, we may have the opportunity to return our patients to sport or pre-operative status much more quickly.

 As we move toward the conclusion of the curriculum, I intend to focus my capstone project on platelet rich plasma and it’s overall effects. I will expand on the knowledge and literature that I have reviewed here and include treatments for tendon, muscle, and cartilage injuries. I will also take the opportunity to elaborate more on the background and preparation of PRP as well as the clinical application. Lastly, I will focus on the regulation of PRP in sports. I intend to deliver this information in a luncheon presentation that will be open for all students and faculty within the Division of Physical Therapy at the University of North Carolina.

Reference:

1. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: From basic science to clinical applications. *Am J Sports Med*. 2009;37(11):2259-2272. doi: 10.1177/0363546509349921; 10.1177/0363546509349921.

2. Fallouh L, Nakagawa K, Sasho T, et al. **Effects of autologous platelet-rich plasma on cell viability and collagen synthesis in injured human anterior cruciate ligament. . american volume. 2010-12-15;92:2909-16.**. *Journal of bone and joint surgery*. 2010;92:2909-2916.

3. Valenti Nin J, Gasque G, Azcarate A, Beola J, Gonzalez M. **Has platelet-rich plasma any role in anterior cruciate ligament allograft healing?**. *Arthroscopy*. 2009;25:1206-1213.

4. Xie X, Zhao S, Wu H, et al. **Platelet-rich plasma enhances autograft revascularization and reinnervation in a dog model of anterior cruciate ligament reconstruction**. *The Journal of surgical research*. 2013;183:214-222.

5. Seijas R, Ares O, Catala J, Alvarez-Diaz P, Cusco X, Cugat R. **Magnetic resonance imaging evaluation of patellar tendon graft remodelling after anterior cruciate ligament reconstruction with or without platelet-rich plasma**. *Journal of Orthopaedic Surgery*. 2013;21(1).

6. de Almeidam A, Demange M, Sobrado M, Rodrigues M, Pedrinelli A, Hernandez A. **Patellar tendon healing with platelet-rich plasma: A prospective randomized controlled trial**. *Am J Sports Med*. 2012;40(6):1282-1288.

7. Cervellin M, Girolamo L, Bait C, Denti M, Volpi P. **Autologous platelet-rich plasma gel to reduce donor-site morbidity after patellar tendon graft harvesting for anterior cruciate ligament reconstruction: A randomized, controlled clinical study**. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2012;20:114-120.

8. Silva A, Sampaio R. **Anatomic ACL reconstruction: Does the platelet-rich plasma accelerate tendon healing?**. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2009;17:676-682.

9. Vavken P, Sadoghi P, Murray M. **The effect of platelet concentrates on graft maturation and graft-bone interface healing in anterior cruciate ligament reconstruction in human patients: A systematic review of controlled trials**. *Arthroscopy*. 2011;27:1573-1583.