DIAGNOSTIC ULTRASOUND ASSESSMENT OF FEMORAL CARTILAGE HEALTH IN INDIVIDUALS WITH PATELLOFEMORAL PAIN

by

Hyunjae Jeon

A dissertation submitted to the faculty of
The University of North Carolina at Charlotte
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in
Biology

Charlotte

2021

Approved by:

_____
Dr. Abbey Thomas Fenwick

_____
Dr. Luke Donovan

_____
Dr. Adam Reitzel

_____
Dr. Andrew Truman

_____
Dr. Jeanette Bennett

ABSTRACT

HYUNJAE JEON. Diagnostic ultrasound assessment of femoral cartilage health in individuals with patellofemoral pain. (Under the direction of ABBEY THOMAS FENWICK)

Patients with patellofemoral pain (PFP) experience pain during or after physical activities. Recent evidence suggests PFP is not only a painful symptom which hinders daily activity but also a potential marker for future development of patellofemoral osteoarthritis (PFOA). Ultimately, PFP may also lead to tibiofemoral osteoarthritis (TFOA), which is recognized as a knee osteoarthritis. Traditionally, lower extremity strengthening exercises successfully alleviate pain for patients with PFP. However, strengthening exercises are not effective in modifying certain movement patterns associated with PFP development and progression. Researchers found feedback motion retraining to be an effective mode of intervention to alter movement patterns. However, there is no research synthesizing the efficacy of feedback motion retraining for patients with PFP. Therefore, in Chapter 2, we assessed the efficacy of feedback motion retraining by summarizing relevant scientific evidence. Diagnostic ultrasound (US) is a cost-effective imaging tool to assess morphology of soft tissue, but it is rarely used for evaluating cartilage health in individuals with PFP. But, diagnostic US may be a useful clinical tool for understanding the progression from PFP to PFOA. Therefore, our aims were to evaluate femoral cartilage health in patients with PFP. In Chapter 3, we compared the deformative characteristics of femoral cartilage following varied forms of loading conditions between individuals with and without PFP by assessing US image cross-sectional area and echo intensity. In Chapter 4, we compared the image quality grade

between individuals with and without PFP to understand whether individuals with PFP are demonstrating worse cartilage health that may not be captured using traditional evaluation methods. We identified significant correlations between patient-reported outcomes and echo intensity following loading conditions. We also identified statistically significant differences of femoral cartilage image quality between individuals with and without PFP which indicates increased risk of osteoarthritis in individuals with PFP.

ACKNOWLEDGEMENTS

This project wouldn’t have been possible without guidance and support of Dr. Abbey Thomas. I sincerely appreciate you for the mentorship and humane support when I was in trouble. I would also like to thank Dr. Luke Donovan, who gave tremendous support in developing critical thinking capacity. I would like to thank the fellow graduate students: Danielle Torp and Sean Krysak for their help working in the lab and mental assists. Lastly, I would like to acknowledge my parents for their limitless support and friends for their emotional help during the graduate studies.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACL	anterior cruciate ligament
PFP	patellofemoral pain
PFOA	patellofemoral osteoarthritis
TFOA	tibiofemoral osteoarthritis
OA	osteoarthritis
US	ultrasound
MRI	magnetic resonance imaging
CSA	cross-sectional area
EI	echo intensity
PRO	patient-reported outcome
VAS	visual analog scale
AKPS	anterior knee pain scale
KOOS	knee injury and osteoarthritis score
KOOSPF	knee injury and osteoarthritis score for patellofemoral pain and osteoarthritis

CHAPTER 1: INTRODUCTION

1.1 Background and Significance

Patellofemoral pain (PFP) is a painful retropatellar and peripatellar pathology. It is the most commonly reported musculoskeletal disorder among physically active individuals, especially young adults.[1] Specifically, it affects up to 23% of the general population[2] and its prevalence is likely to increase as the population ages.[3] Activities that load the patellofemoral joint, such as stair ambulation, jumping, and prolonged running and squatting typically aggravate the pain.[1] PFP is often perceived as innocuous by patients and as a result more than 82% of patients with PFP do not seek medical attention or treatment.[4] Despite the subtle characteristics of PFP, the long-term prognosis is poor.[5] For majority of patients with PFP, the initial pain persists, the disorder progresses to a chronic condition,[3-7] and PFP eventually develops into serious knee pain or patellofemoral osteoarthritis (PFOA) if not adequately resolved.[8-10]

There is an ongoing scientific debate regarding the etiology of the PFP. However, the general consensus is that PFP is a multifactorial pathology, including anatomical,[11,12] biomechanical,[13] motor neuronal,[14] and psychological factors.[15] Abnormal biomechanics, specifically dynamic knee valgus—a combination of increased hip adduction and internal rotation—during weight bearing movements, are considered a modifiable cause of PFP.[16,17] Researchers found patients with PFP demonstrate increased hip adduction and internal rotation during daily movements[18] and this was found to have a correlation with hip abductor and external rotator muscle weakness.[19] Notably, abnormal hip kinematics contribute to aberrant patellofemoral joint reaction force (PFJRF). The PFJRF is the resultant compressive force applied on the PF joint.[20] PFJRF can vary from 1.3 times

body weight (BW) up to 7.8 times BW depending on the movement.[21] The aforementioned dynamic knee valgus position increases the lateral facet and decreases medial facet PFJRF by altering the location of contact between the patella and femur, precipitating PFP development and articular cartilage degeneration. Additional factors may also increase PFJRF on the lateral facet including pathologic lateral soft-tissue restraints[22] and muscular firing timing imbalance between vastii muscles.[23,24] This provides a foundation that movement quality (aberrant biomechanics) may contribute to the severity of PFP symptoms and should be considered in the treatment for improving the symptoms to mitigate the progression to PFOA.

There are various rehabilitative strategies to address pain and improve function.[25] The premise of these interventions is to change biomechanics to normalize the joint compression and improve lower extremity muscle strength. The current evidence supports the effectiveness of lower extremity musculature strengthening exercises and movement modification in managing knee joint pain and improving function.[26] However, despite its effectiveness in pain management, current strengthening interventions fail to alter biomechanics.[27] Modifying movements using feedback is gaining more attention in treating PFP since recent series of investigations on gait retraining suggest that feedback on faulty biomechanics is necessary to improve biomechanics in the long-term.[28-30]

Osteoarthritis (OA) is the most common form of arthritis and the knee is the most commonly affected joint.[31] Despite the weight-bearing nature of the tibiofemoral (TF) joint, radiographic PFOA is more common; however, combined TF-PF OA is the most prevalent.[32] Isolated PFOA is considered to contribute to the development of tibiofemoral OA (TFOA) from altered TF and PF joint mechanics.[32,33] Therefore, it is plausible to

conclude that isolated chronic PFP is a precursor for PFOA, and PFOA contributes to TFOA, which eventually progress into TF-PF OA.

Radiographic evidence of osteophyte formation and joint space narrowing on plain radiographs remain the gold standard for diagnosing OA.[34] However, 32% of patients with painful, symptomatic OA have a normal cartilage surface according to the radiographic analysis.[35] Moreover, joints without advanced symptom of OA do not usually show signs of cartilage thinning making it hard to diagnose patients with PFOA or TFOA using plain radiograph. Thus, despite its usefulness in detecting bony structural anomaly of the knee joint, plain radiography is limited in its ability to provide information on overall cartilage health. Magnetic resonance imaging (MRI) has also been used to measure changes in soft tissues, including cartilage, in patients with PFP and PFOA. MRI studies demonstrate 14% less cartilage thickness in individuals with PFP,[36] Hoffa's fat pad edema and impingement, and chondromalacia patella, the latter two of which are implicated in causing the pain associated with PFP.[37] While useful, MRI is a costly and time-consuming alternative to plain radiography.

Diagnostic ultrasound (US) is a valid imaging tool[38,39] that may aid in assessing femoral cartilage thickness before radiography would detect changes in joint integrity and at a lower cost than MRI. More clinicians are considering adopting US in the evaluation of the joint health since it provides a real-time image of soft tissues and is cost-efficient. Still, there is a limited amount of research that utilized US in the evaluation of knee joint health especially in individuals with PFP. Images obtained from US can provide not only the quantitative measures for the femoral cartilage thickness and water content[40,41] but also allow for a qualitative evaluation of the sharpness of image quality that may be able

to explain the signs of early osteoarthritic changes in the cartilage.[42] Therefore, there is a need for research comprehensively evaluating knee joint health in individuals suffering PFP using US in quantitatively and with image quality.

1.2 Specific Aims

Specific Aim 1: To assess the effectiveness of movement retraining in individuals with PFP. This was accomplished by comparing research which provided feedback movement retraining in individuals with PFP.

Objective:

To review current evidence to understand if the feedback motion retraining improves kinematics, pain, and self-reported function in patients with PFP.

Specific Aim 2: To quantitatively compare cartilage health between individuals with and without PFP.

Objective:

1. To quantify the deformative behavior of femoral cartilage following loading conditions in individuals with PFP.
2. To determine the association between femoral cartilage cross-sectional area and echo intensity alteration following loading conditions with clinical measures of patient-reported outcomes and pain.

Hypotheses:

I hypothesized that individuals with PFP would show less deformative characteristics of femoral cartilage compared to pain-free individuals following loading conditions.

Additionally, I hypothesized that percent-change of quantitative US measures would be associated with patient-reported outcomes and pain.

Specific Aim 3: To compare image quality to understand quality of cartilage surface between individuals with and without PFP.

Objective:

1. To compare femoral cartilage US image quality between individuals with and without PFP.
2. To establish intra-and inter-assessor reliability of the femoral cartilage image quality grading scheme.

Hypotheses:

I hypothesized that individuals with PFP would show worse US image quality based on US grading scheme. I hypothesized that assessors would be able to establish strong intra- and inter-assessor reliability.

CHAPTER 2: EFFICACY OF FEEDBACK ON RUNNING GAIT RETRAINING IN PATIENTS WITH PATELLOFEMORAL PAIN: A CRITICALLY APPRAISED TOPIC

Accepted author manuscript version reprinted, by permission, from [International Journal of Athletic Therapy and Training, 2019, 24 (1): 9-14, https://doi.org/10.1123/ijatt.2017-0082. © Human Kinetics, Inc.

2.1 Introduction

Healthcare providers frequently encounter patients with patellofemoral pain (PFP), a non-traumatic and non-abnormal structural pathology which is localized in the retropatellar region.[1] PFP accounts for up to 17% of visits to general practice physicians for knee pain.[2] In recreational athletes, the prevalence may be closer to 25%, with individuals participating in running and jumping related activities most commonly affected.[1,3] Patients with PFP often experience limitations of daily and physical activities.[4] Athletes with prolonged symptoms of PFP may experience decreased performance and early cessation of their athletic careers.[4] Recent evidence suggests that PFP in young adults is a precursor to subsequent patellofemoral osteoarthritis.[5]

A systematic review established numerous risk factors of PFP, including dysfunction of knee extensor and/or hip abductor musculature, increased Q-angle, abnormal vastii reflex timing, patellar compression or tilting, and increased ground reaction forces during landing.[6] In combination with these risk factors, dynamic knee valgus during various movements may increase patellofemoral pressure and result in development of PFP.[1,7,8] To correct dynamic valgus, researchers incorporated hip abductor musculature strengthening exercises such as side lying hip abduction, clamshell,

and resistive band exercises into treatments.[8] Most of these investigations resulted in pain alleviation and improved self-reported function, but biomechanics were not improved.[9]

Due to the ineffectiveness of the hip strengthening exercise in altering biomechanics, researchers and clinicians have begun incorporating feedback of biomechanical movement patterns into PFP rehabilitation.[10] This feedback is often either verbal or visual. Notably, a single, verbal feedback session has demonstrated immediate reductions in vertical ground reaction force during landing.[11] Visual feedback is often provided via mirrors or videotape and has demonstrated improvements in dynamic valgus.[12] Collectively, these studies suggest that using feedback during motion retraining is a beneficial addition to PFP rehabilitation treatment. This critically appraised topic (CAT) serves to review the current evidence regarding the effectiveness of feedback motion retraining on pain, function and running kinematics in patients with PFP. Running was selected because PFP is a common injury among runners.[13] This will help healthcare providers to make evidence based decisions regarding whether or not to use feedback gait retraining in treating PFP.

2.2 Focused Clinical Question

Can feedback motion retraining improve kinematics, pain and self-reported function in patients with PFP?

2.3 Methods

Search Strategy

A database search was conducted in July of 2017. The search terms used were:

- Patient/client group: Patellofemoral Pain
- Intervention: Feedback Motion Retraining, Augmented Feedback

- Outcome: Kinematics, Function

Sources of Evidence Searched

- CINAHL
- Medline
- Pubmed
- Google Scholar

Inclusion Criteria

- Strength of Recommendation Taxonomy (SORT) Level 3 evidence or higher
- Studies that identify PFP criteria
- Studies that describe feedback motion retraining

Exclusion Criteria

- Studies that did not perform motion analysis in lower extremities
- Studies used feedback motion retraining in combination with other treatments
- Articles published prior to 2010
- Pilot study

Evidence Quality Assessment

- Studies included were assessed with Physiotherapy Evidence Database (PEDro) scale for randomized controlled design (RCT) and strengthening the reporting of observational studies in epidemiology (STROBE) statement for non-RCT studies. All studies were evaluated using SORT. All assessments were performed by a single author (HJ).

2.4 Results

Summary of Search, Evidence Appraised, and Key Findings

- The search of the literature was to find studies that investigated the effectiveness of feedback running gait retraining on biomechanical, pain and self-reported function in patients with PFP. All four studies used 2-week feedback gait retraining in movement pattern modification in patients with PFP that also displayed faulty movement patterns.
- The initial search process resulted in 21 possible studies for inclusion and total of four relevant articles met the inclusion criteria (Figure 1).
- All four studies used 2 week feedback gait retraining in movement pattern modification in patients with PFP. One study[14] used a computer-programmed visual feedback and three studies used a combination of mirror, script and verbal feedback (Table 2).[15-17]
- All studies[14-17] analyzed lower extremity kinematics and reported pain during running and three studies additionally reported changes of self-reported function.[14-16] 1 month follow-up was performed in all included studies and extra 3 month follow-up was reported in two studies.[15,16]
- Hip adduction angle and contralateral pelvic drop was significantly reduced in three studies[14,15] and knee abduction angle[17] was improved immediately after the conclusion of the 2 week feedback training. Pain reduction retained at 1 and 3 months and kinematic improvement was also reported in three studies.[14,15,17]

Results of Evidence Quality Assessment

Only one study[17] utilized random allocation by random numbers generator which distributed participants into experimental and control groups. However, neither participants nor the investigator performing the intervention were blinded. Two studies[14,15] were pre-test/post-test studies that did not include a control group. One

study[16] was a case report of two participants from previous research.[15] Our search process did not solely focus on randomized controlled trials since there was lack of literature with a randomized controlled trial design. According to those reasons, PEDro score was 8/10, STROBE scores were 15/20, 17/20 and 10/20, and SORT ranged from 1 to 3 (Table 1).

2.5 Discussion

Clinical Bottom Line

There is sufficient evidence to support the use of feedback motion retraining in PFP rehabilitation. Three included studies[14-16] found a significant reduction in hip adduction angle ($p<0.05$),[14,15] contralateral pelvic drop ($p=0.001$),[15,16] internal hip abduction moment ($p=0.008$),[15] and vertical loading impact ($p<0.05$)[14] after intervention. Additionally, knee abduction angle and ankle plantarflexion improved after the gait retraining.[15,17] Lastly, significant pain reduction[14-17] and improvement of self-reported function[14-16] was observed throughout the included studies, with Willy et al. observing very large effect sizes (pain: $d= 7.61$, $p<0.05$; function: $d=3.81$, $p<0.05$).[15]

Strength of Recommendation

SORT appraisal for the included articles resulted in scores ranging from level 1 to 3 (Table 1). The level 1 evidence[17] to support the use of feedback motion retraining was chosen because of its consistency and good quality patient-oriented evidence. The level 2 evidence was selected because one of the studies[15] used an identical feedback method to the level 3 study and the other study used a unique mode of visual feedback.[14] The level 3 evidence[16] was included since it included expanded outcome measures that were not included in the identical level 2 study.[15] A single randomized controlled trial[17] was

included and scored 8/10 on the PEDro scale with the only points lost being due to lack of blinding. According to the STROBE assessment, two articles[14,15] were rated as high quality (≥14/20) and one[16] was rated as having a high risk of bias (≤13/20). Collectively, the included evidence received a grade of B since the findings were consistent among included studies despite utilization of weak research designs. These studies suggest that providing feedback of movement patterns during gait retraining to patients with PFP is necessary to improve gait kinematics, pain and self-reported function.

2.6 Implications for Practice

PFP is a chronic condition resulting in retropatellar knee pain often exacerbated by faulty biomechanics, including increased hip adduction.[18] The included studies identified consistent improvements in these aberrant gait kinematics after 8 sessions (15-30 minutes each) of feedback gait retraining. Providing programmed visual[14] and combination of mirror, script and supplemental verbal feedback[15-17] during motion retraining not only improved biomechanics but also improved pain and self-reported function in all included studies. Therefore, incorporation of the aforementioned modes of feedback to decrease hip adduction, internal rotation, knee valgus, and contralateral pelvic drop and increase ankle plantarflexion and range of motion appears beneficial to patients with PFP especially who displayed faulty movement patterns.

The feedback protocols examined were similar among included studies (Table 2). Specifically, all included research used 8 training sessions during a 2-week period and reduced the amount of feedback during the last 4 sessions. Also, all included researches targeted PFP patients who displayed faulty movement patterns. Noehren et al.[14] utilized real-time visual feedback of participants' hip adduction angles during stance phase as a

graph generated from 3D motion capture software. Participants observed their hip adduction angles during running and were instructed to keep the angle within one standard deviation of mean hip adduction angles obtained from healthy individuals. Participants were also instructed to contract their gluteal muscles and run with their knees pointing straight ahead; however, no additional verbal cues were provided when participants demonstrated any biomechanical errors during running.[14] Willy et al.[15] combined visual and verbal feedback during gait retraining. Participants were first shown video of their baseline movement so they could see their aberrant biomechanics. For the feedback portion, participants ran with a mirror in front of them so they could see their biomechanics in real-time. They were provided the same instructions as in the Noehren et al[14] study prior to the start of each feedback session, which was to keep their knees apart and patella facing forward. Additional verbal feedback was provided once the faulty biomechanics were noticed. Roper et al.[17] used the same mirror feedback as Willy et al.[15], but provided different verbal instructions to encourage participants to run with a forefoot striking pattern since the purpose of the study was to alter the rearfoot strike pattern. Similar to Willy et al[15], verbal feedback was given if movement error was detected. Feedback methods of included studies altered faulty kinematics which were risk factors for PFP could have potentially contributed to the reduction of pain and improvement of function.[19]

Feedback of proper movement patterns is not unique to the PFP population. Biomechanical feedback to correct faulty movements is widely used to reduce the risk of sustaining other knee injuries, including anterior cruciate ligament (ACL) injuries. In fact, based on the success of feedback at improving jump-landing biomechanics,[20-22,23]

the use of feedback on proper movement technique is a key recommendation on the prevention of ACL injury.[24] Further, feedback has been deemed beneficial in patients after ACL reconstruction to improve biomechanics.[25] Collectively, these studies suggest the benefit of feedback to improve biomechanics across lower extremity injuries.

Both the immediate benefits and retention (1 and 3 months post-training) of the treatment were studied.[14-17] Noehren et al.[14] reported reduced pain (mean difference(MD)=4.3, p=0.001) and improved self-reported function (MD=11.4, p=0.008) immediately after the interventions. Immediate improvements in running mechanics were also observed across studies. Specifically, Willy et al. reported hip adduction angle improvement ($p<0.001$, d=2.91) during running immediately after the intervention. One month after termination of the feedback interventions, patients continued to experience improvements. Hip adduction angle during running increased by 1.1° at the 1-month follow-up; however, this change was associated with a small effect size (d=0.37) since the magnitude of change was minimal compared to the initial improvement between baseline and immediate post-training.[15] Both Noehren et al.[14] and Roper et al.[17] reported that patients continued to experience reduced knee pain, knee abduction, and vertical loading with concurrent increased ankle range of motion at 1-month follow up with Roper reporting a large effect size ($\eta^2 = 0.43$). Finally, reductions in pain (d=7.61) and improvements in lower extremity function (d=3.81) were also reported 3-months post-training.[15] Examining other interventions for patients with PFP suggests similar retention of improvements. Specifically, hip and knee strengthening exercises are widely adopted in the treatment of PFP and are effective in improving patient reported outcomes through 1 year follow-up.[26]

Participants who underwent mirror gait retraining showed the greatest improvements with large effect sizes (pain: d=7.61, function: d=3.81) and residual effect for 3 months.[15] Importantly, all participants included in these feedback studies presented with faulty movement patterns prior to gait retraining. Targeting individuals who present with faulty biomechanics appears critical to intervention success as these individuals have more room to improve their biomechanics than persons not presenting with excessive hip adduction.[27]

Future research should investigate the optimal treatment duration, dosage of feedback, and instructions provided. Instructions provided are important to consider given that the most recent and best quality evidence included presently demonstrated that instructing patients to modify their foot strike pattern improved both hip and knee biomechanics, which is of great importance to patients with PFP.[17] Additionally, future studies should determine if including lower extremity strengthening exercises, which are popular during traditional rehabilitation, into these feedback interventions will yield a greater magnitude of training effect and longer residual benefits. Finally, research should include control groups to ensure the treatment effect is not simply due to time or random chance. The conclusions drawn from this investigation will expire in 2021 and should be revisited by that time point.

2.7 References

1. Petersen W, Rembitzki I, Liebau C. Patellofemoral pain in athletes. *Open Access J Sports Med.* 2017;8:143-154.
2. Crossley KM, Stefanik JJ, Selfe J, et al. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: Terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures. *Br J Sports Med.* 2016;50(14):839-843.
3. Barber Foss KD, Myer GD, Chen SS, Hewett TE. Expected prevalence from the differential diagnosis of anterior knee pain in adolescent female athletes during preparticipation screening. *Journal of athletic training.* 2012;47(5):519-524.
4. Glaviano NR, Baellow A, Saliba S. Physical activity levels in individuals with and without patellofemoral pain. *Phys Ther Sport.* 2017;27:12-16.
5. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord.* 2010;11:201.
6. Waryasz GR, McDermott AY. Patellofemoral pain syndrome (PFPS): a systematic review of anatomy and potential risk factors. *Dyn Med.* 2008;7:9.
7. Dierks TA, Manal KT, Hamill J, Davis IS. Proximal and distal influences on hip and knee kinematics in runners with patellofemoral pain during a prolonged run. *J Orthop Sports Phys Ther.* 2008;38(8):448-456.

8. Ferber R, Kendall KD, Farr L. Changes in knee biomechanics after a hip-abductor strengthening protocol for runners with patellofemoral pain syndrome. *Journal of athletic training.* 2011;46(2):142-149.

9. Thomson C, Krouwel O, Kuisma R, Hebron C. The outcome of hip exercise in patellofemoral pain: A systematic review. *Man Ther.* 2016;26:1-30.

10. Neal BS, Barton CJ, Gallie R, O'Halloran P, Morrissey D. Runners with patellofemoral pain have altered biomechanics which targeted interventions can modify: A systematic review and meta-analysis. *Gait Posture.* 2016;45:69-82.

11. Milner CE, Fairbrother JT, Srivatsan A, Zhang S. Simple verbal instruction improves knee biomechanics during landing in female athletes. *The Knee.* 2012;19(4):399-403.

12. Munro A, Herrington L. The effect of videotape augmented feedback on drop jump landing strategy: Implications for anterior cruciate ligament and patellofemoral joint injury prevention. *The Knee.* 2014;21(5):891-895.

13. Taunton JE, Ryan MB, Clement DB, McKenzie DC, Lloyd-Smith DR, Zumbo BD. A retrospective case-control analysis of 2002 running injuries. *Br J Sports Med.* 2002;36(2):95-101.

14. Noehren B, Scholz J, Davis I. The effect of real-time gait retraining on hip kinematics, pain and function in subjects with patellofemoral pain syndrome. *Br J Sports Med.* 2011;45(9):691-696.

15. Willy RW, Scholz JP, Davis IS. Mirror gait retraining for the treatment of patellofemoral pain in female runners. *Clin Biomech (Bristol, Avon).* 2012;27(10):1045-1051.

16. Willy RW, Davis IS. Varied response to mirror gait retraining of gluteus medius control, hip kinematics, pain, and function in 2 female runners with patellofemoral pain. *J Orthop Sports Phys Ther.* 2013;43(12):864-874.

17. Roper JL, Harding EM, Doerfler D, et al. The effects of gait retraining in runners with patellofemoral pain: A randomized trial. *Clin Biomech (Bristol, Avon).* 2016;35:14-22.

18. Powers CM. The influence of abnormal hip mechanics on knee injury: a biomechanical perspective. *J Orthop Sports Phys Ther.* 2010;40(2):42-51.

19. Powers CM, Witvrouw E, Davis IS, Crossley KM. Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: part 3. *Br J Sports Med.* 2017;51(24):1713-1723.

20. Ericksen HM, Thomas AC, Gribble PA, Doebel SC, Pietrosimone BG. Immediate effects of real-time feedback on jump-landing kinematics. *J Orthop Sports Phys Ther.* 2015;45(2):112-118.

21. Mandelbaum BR, Silvers HJ, Watanabe DS, et al. Effectiveness of a neuromuscular and proprioceptive training program in preventing anterior cruciate ligament injuries in female athletes: 2-year follow-up. *Am J Sports Med.* 2005;33(7):1003-1010.

22. Etnoyer J, Cortes N, Ringleb SI, Van Lunen BL, Onate JA. Instruction and jump-landing kinematics in college-aged female athletes over time. *Journal of athletic training.* 2013;48(2):161-171.

23. Hewett TE, Myer GD, Ford KR. Reducing knee and anterior cruciate ligament injuries among female athletes: a systematic review of neuromuscular training interventions. *J Knee Surg.* 2005;18(1):82-88.

24. Padua DA, DiStefano LJ, Hewett TE, et al. National Athletic Trainers' Association Position Statement: Prevention of Anterior Cruciate Ligament Injury. *Journal of Athletic Training Journal of Athletic Training.* 2018;53(1):5-19.

25. Gokeler A, Benjaminse A, Welling W, Alferink M, Eppinga P, Otten B. The effects of attentional focus on jump performance and knee joint kinematics in patients after ACL reconstruction. *Phys Ther Sport.* 2015;16(2):114-120.

26. Fukuda TY, Melo WP, Zaffalon BM, et al. Hip posterolateral musculature strengthening in sedentary women with patellofemoral pain syndrome: a randomized controlled clinical trial with 1-year follow-up. *J Orthop Sports Phys Ther.* 2012;42(10):823-830.

27. Myer GD, Ford KR, Brent JL, Hewett TE. Differential neuromuscular training effects on ACL injury risk factors in"high-risk" versus "low-risk" athletes. *BMC Musculoskelet Disord.* 2007;8:39.

Table 1. Characteristics of included studies

	Noehren et al., 2011	Willy et al., 2012	Willy et al., 2013	Roper et al., 2016
Study Title	The Effect of Real-Time Gait Retraining on Hip Kinematics, Pain and Function in Subjects with Patellofemoral Pain Syndrome	Mirror Gait Retraining for the Treatment of Patellofemoral Pain in Female Runners	Varied Response to Mirror Gait Retraining of Gluteus Medius Control, Hip Kinematics, Pain, and Function in 2 Female Runners with Patellofemoral Pain	The Effects of Gait Retraining in Runners with Patellofemoral Pain: A Randomized Trial
Study Participants	10 female subjects with patellofemoral pain. Average age: 23.3 y/o Duration of pain: 75.7months	10 female runners with patellofemoral pain. Average age: 22.4 y/o Duration of pain: 4.3years	2 female runners with patellofemoral pain Age: 20, 23 Duration of pain: 12, 30 months	16 subjects (11 females, 5 males) were randomly placed in the control (n=8) or experimental group (n=8). Age: Control 21.5 y/o Experimental: 24.6 y/o
Inclusion/ Exclusion Criteria	Inclusion Criteria: • Patellofemoral pain • Recreational Runners (3times/week, total 6miles/week or greater) • Between ages of 18 and 45 • Symptom longer than 2 months • Excessive hip adduction, pelvic drop during treadmill running Exclusion Criteria: • Cardiovascular condition • Injury which can influence gait	Inclusion Criteria: • Patellofemoral pain • Run at least 10km/week • Comfortable with treadmill running at 3.35m/sec • Free of any cardiac risk factors • Retropatellar or peripatellar pain • Visual analog scale ≥ 3 during running Exclusion Criteria: • Patellar instability or other knee diagnoses • History of any lower extremity surgery • Unhealthy	Inclusion Criteria: • Patellofemoral pain • Run at least 10km/week • Comfortable with treadmill running at 3.35m/sec • Free of any cardiac risk factors • Retropatellar or peripatellar pain • Visual analog scale ≥ 3 during running • Excessive hip adduction during running Exclusion Criteria: • Patellar instability or other knee diagnoses	Inclusion Criteria: • Patellofemoral pain during/after running, squatting, kneeling, stair ascent/descent, and prolonged sitting • Visual analog scale between 3 and 7 • Self-reported rearfoot strike runner Exclusion Criteria: • Pregnancy • History of knee surgery on the affected knee • Traumatic patellar dislocation • Any neurological impediments that would influence gait

			• History of any lower extremity surgery • Unhealthy	
Outcome Measures	Data points: Pre-post treatment Follow up: 1 month	Data points: Pre-post treatment Follow up: 1, 3 month	Data points: Pre-post treatment Follow up: 1, 3 month	Data points: Pre-post treatment Follow up: 1 month
	Hip adduction angle Hip internal rotation angle Contralateral pelvic drop angle Visual analog scale Lower extremity function index Vertical impact load	Hip adduction angle Contralateral pelvic drop angle Hip internal rotation Internal hip abduction moment Thigh adduction Lower extremity function scale Visual analog scale During: running, squatting, stepping	Contralateral pelvic drop Hip adduction angle Hip internal rotation angle Gluteus medius EMG activity During Running, Step ascending Pain (Visual analog scale) Self-reported function (Lower extremity functional scale)	Knee pain during and after running Knee abduction at initial contact Knee flexion at initial contact Range of motion in the sagittal plane through the loading response Ankle plantar/dorsiflexion at initial contact Peak patellofemoral stress Achilles tendon force Patellofemoral contact force
Results	Hip adduction significantly decreased (Pre=22.0°±1.5, Post=16.5°±2.2, mean diff=5.1, $p<0.01$). Pelvic drop decreased (Pre=-9.4°±2.5, Post=-7.1°±1.6, mean diff=-2.3, $p<0.05$) during running. Pain (Pre=5.0±2.0, Post=0.5±1.3) decreased by 86% at the end of gait retraining.	Running: significant ($p<0.05$) visible reduction in peak hip adduction ($d=2.91$), contralateral pelvic drop ($d=0.82$), thigh adduction angle ($d=1.32$), internal hip abduction ($d=0.69$) moment, hip internal rotation ($d=0.21$). Squat: Hip adduction angle ($d=1.35$), thigh adduction angle ($d=0.68$), internal hip abduction moment ($d=0.91$) were reduced ($p<0.05$).	During running, peak contralateral pelvic drop (Runner 1: 2.6°, Runner 2: 1.7°) and peak hip adduction (Runner 1: 5.2°, Runner 2: 6.3°) were reduced after intervention. Earlier activation of the gluteus medius relative to foot strike (Runner 1: 12.6ms, Runner 2: 37.3ms) and longer duration of gluteus medius activity (Runner 1: 55.8ms, Runner 2: 44.4ms) after intervention.	Significant knee abduction angle improvement immediately post-retraining ($\eta^2=0.29$, $p<0.05$) and at one month follow up ($p<0.05$). Increased ankle plantarflexion ($\eta^2=0.55$) and ankle range of motion ($\eta^2=0.43$) immediately post-retraining ($p<0.05$) and at one month follow up ($p<0.05$). Significant reduction in knee pain immediately post-retraining

	Lower extremity function index improved by 11 points. (Pre=64.0±11, Post=75.0±3.5) Impact loading variables reduced with moderate to large effect sizes (0.45-1.10). Improvements in running mechanics, pain and function retained at 1 month follow up	Stepping: Hip adduction angle was reduced (d=0.69, p<0.05). Pain and lower extremity function scale improved with large effect sizes (d=7.61, d=3.81). Retention was observed in hip adduction angle and internal hip abduction moment improvement for 3 months during running	Early onset of gluteus medius activity during step ascent (Runner 1: 48.0ms, Runner 2: 28.3ms). Improvements in pain and function maintained for 3 months.	(η^2=0.29, p<0.05) and at one month follow up (p<0.05).
SORT	2	2	3	1
Quality assessment	STROBE 15/20	STROBE 17/20	STROBE 10/20	PEDro 8/10
Support for the Answer	Yes	Yes	Yes	Yes

Table 2. Feedback interventions

	Type	Duration	Sessions	Volume	Aid	Feedback Cues	Removal	Follow up
Noehren et al., 2011	Gait retraining	2 weeks	8 sessions	15-30 min of treadmill running	Visual	Real time system Valgus angle	Last 4 sessions	1 month
Willy et al., 2012	Gait retraining	2 weeks	8 sessions	15-30 min of treadmill running with gradual increment	Mirror Script *Verbal	Script: Run with your knees apart with your kneecaps pointing straight ahead Squeeze your buttocks	Last 4 sessions	1 month 3 month
Willy et al., 2013	Gait retraining	2 weeks	8 sessions	15-24 min of treadmill running with gradual increment	Mirror Script *Verbal	Script: Run with your knees apart with your kneecaps pointing straight ahead Squeeze your buttocks	Last 4 sessions	1 month 3 month
Roper et al., 2016	Gait retraining	2 weeks	8 sessions	15-30 min of treadmill running with gradual increment	Mirror Script Verbal	Script: Run on your toes Run on the balls of your feet	Last 4 sessions	1 month

**Verbal: Additional verbal feedback was provided if undesired biomechanics were observed.*

2.9 Figures

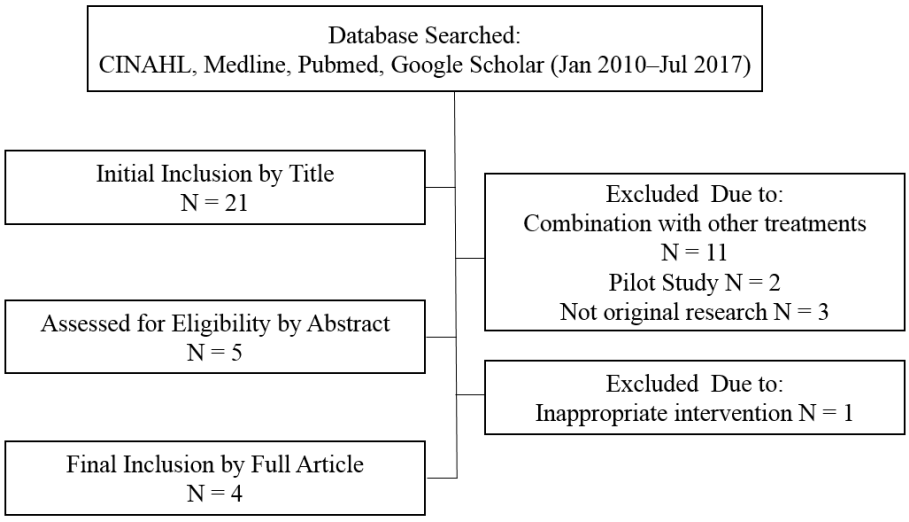


Figure 1. Flow Diagram to Illustrate the Search Results

CHAPTER 3: EXERCISE-INDUCED CHANGES IN FEMORAL CARTILAGE THICKNESS IN PATIENTS WITH PATELLOFEMORAL PAIN

3.1 INTRODUCTION

Patellofemoral pain (PFP) is a prevalent lower extremity disorder often observed in physically active individuals.[1,2] Though PFP often arises during adolescence, it is a lifelong condition for many patients.[3] Unfortunately, prolonged symptoms of PFP may contribute to the development of patellofemoral osteoarthritis (PFOA), increasing the healthcare burden for affected individuals.[4,5] Individuals with PFOA experience joint deformation and increased pain on joint compression that occurs with flexion of the knee.[6] Symptomatic PFOA may also contribute to tibiofemoral osteoarthritis (TFOA) development, which indicates the urgent need for the early diagnosis and management of PFP.[7]

Patients with PFP experience peripatellar and/or retropatellar pain during activities such as squatting, running and jumping,[8-10] which often leads to the reduction or cessation of physical activity participation in these patients.[11] The aforementioned activities are known to be beneficial to overall health but can increase stress to the patellofemoral joint especially in individuals with PFP.[12] During closed kinetic chain activities such as running or jumping, the femoral cartilaginous surface glides behind the patella. There is dysfunction in this articulation with PFP, whereby patellofemoral cartilage loading increases or decreases, ultimately leading to reduced deformative behavior.[13] This increased patellofemoral joint stress during weight-bearing exercises is similar to that observed in individuals with PFOA, suggesting a potential continuum from

PFP to PFOA.[14,15] Further, reduced deformative behavior is a representative characteristic of arthritic cartilage. Therefore, in addition to early identification of the presence of PFP, there is a need for monitoring patellofemoral joint health to detect persons at risk for progression to PFOA.

The current standard for diagnosing osteoarthritis remains plain radiography to examine joint space width and the presence of osteophytes. In addition to these measures, cartilage health can be assessed through thickness measures. Magnetic resonance imaging (MRI) has been used previously to measure changes in cartilage thickness in patients with osteoarthritis and PFP. Farrokhi et al., for example, used MRI on patients with PFP and healthy controls finding 14% less cartilage thickness in individuals with PFP at baseline compared to controls.[16] While useful, MRI is a costly alternative to plain x-ray. Diagnostic ultrasound may provide a valid,[17,18] cost-effective alternative to MRI. Further, diagnostic ultrasound provides a real-time image that may aid in assessing femoral cartilage thickness, a benefit that MRI does not offer.

While measuring cartilage thickness is important to the diagnosis and progression of osteoarthritis, early stage osteoarthritis shows cartilage compositional changes prior to the loss of cartilage thickness.[19] Cartilage undergoes remodeling throughout the lifespan but the ability of osteoarthritic cartilage to regenerate is compromised due to reduced extracellular matrix quality combined with a quick turnover rate.[20,21] X-rays are not able to detect these biochemical alterations in the cartilage. MRI does afford the capability to detect early biochemical alterations in cartilage, but, at a high cost to the healthcare system.[22] Similar to its ability to provide cost-effective cartilage thickness measures, diagnostic ultrasound can detect alterations in cartilage composition. Diagnostic

ultrasound can be used to measure echo intensity (EI). EI quantifies the amount of water present in the articular cartilage, which is determined by the brightness of the image.[23-25] A hypoechoic (dark) zone is often found in early OA cartilage, indicating an altered echotexture and increased water content in the cartilage.[26,27]

Recent evidence suggests there is significant deformation of femoral cartilage following joint loading through MRI[28] and diagnostic ultrasound in healthy individuals.[18] Despite the potential link between PFP and both PFOA and TFOA, not many researchers studied the deformative characteristics of femoral cartilage in patients with PFP. Therefore, our purpose was to quantify the deformative behavior of femoral cartilage following different movements. We additionally sought to determine the association between femoral cartilage cross-sectional area (CSA) and EI alteration following loading conditions with clinical measures of patient-reported outcomes (PROs) and pain. We hypothesized that individuals with PFP will show less deformative characteristics of femoral cartilage compared to pain-free individuals following loading conditions. We also hypothesized that percent-change of quantitative US measures will be associated with PROs and pain.

3.2 METHODS

Prior to conducting the study, the study protocol was approved by the institutional review board at the University of North Carolina at Charlotte. We used G*Power software (Version 3.1.9.3; Kiel University) and used a previous investigation to determine the number of participants required to detect changes in femoral cartilage thickness after knee joint loading physical activities.[18] Using following parameters

(α=0.05, 1-β=0.8) with moderate effect size (d=0.5), it was determined that 8 participants per group would be necessary to adequately power this study. To account for potential participant dropout, we enrolled twelve participants per group.

Participants

Twenty-four individuals (n=12 with PFP; n=12 healthy) between the 18 and 35 years were recruited from the university campus via flyers and campus-wide email in January 2018. All participants were physically active, defined as performing activities that are included in the Tegner Activity Scale of ≥ 5 for at least 30 minutes 3 or more days per week. All participants were excluded if they had a: 1) history of orthopedic injuries, fractures, or surgeries to either limb or the low back with the exception of PFP in the patient group; 2) severe osteochondral defect in either knee; 3) history of cardiovascular, neurological, or balance disorder that precludes safe participation in exercise; and 4) body mass index > 40 kg/m^2.

Patients with PFP were required to have: 1) retropatellar pain during at least two of the following activities – prolonged sitting, stair ascent/descent, squatting, hopping, kneeling, running, and jumping; 2) pain with compression of the patella; and 3) pain on palpation on patellar facets.[29] Twelve participants with PFP were enrolled and matched twelve healthy individuals were enrolled following screening procedure (Figure 1). Participants were matched based on age, Tegner Activity Scale (±1), and body mass index (±5%). All participants provided written informed consent prior to enrollment.

Patient-Reported Outcomes

Anterior Knee Pain Scale (AKPS), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Knee Injury and Osteoarthritis Outcome Score for Patellofemoral Pain and

Osteoarthritis (KOOSPF) were used to quantify self-reported symptoms and perceived knee function. The AKPS is considered a gold standard in evaluating the severity of PFP and it is a valid and reliable 13 question survey scored from 0-100 with lower scores indicating worse symptoms and function.[30] KOOS contains five subscales related to pain, symptoms, function during daily living and sports, and quality of life specifically for those who are at risk of posttraumatic osteoarthritis (PTOA). It is scored from 0-100 with lower scores indicating greater symptoms and dysfunctions.[31] KOOSPF is most recently designed responsive questionnaire specifically aimed to assess function of individuals affected with PFP and OA.[32] To test participants' pain level, we used visual analog scale (VAS). It utilizes a 10cm straight line which gives a continuous scale measuring the severity of pain. All PROs were completed at each session.

Overview of Testing Procedure

Testing Protocol

Participants reported to the research laboratory on three occasions, completing 1 exercise condition during on each occasion. Each session was completed at the same time of day and separated by one week. All sessions began with the participant sitting on a treatment table with the knees fully extended for 30 minutes to mitigate cartilage compression that occurred walking to the laboratory.[18] The order of conditions was randomized for all participants by means of a randomization table completed prior to initiation of the study.

Ultrasound Imaging of the femoral articular cartilage

Identical procedures were performed before and after the various loading conditions (Figure 2). Participants sat on a treatment table with their back against a wall

and the test knee flexed to 140°. A LOGIQe ultrasound system (General Electric Co., Fairfield, CT) with a 12MHz linear probe was used to collect femoral cartilage image. The ultrasound probe was placed transversely in line with the femoral condyles above the superior pole of the patella as previously reported.[18] A transparent grid was secured to the computer screen to improve reproducibility.

Loading Conditions

Participants performed the assigned loading condition immediately following the pre-ultrasound imaging. Loading conditions included strengthening exercises, plyometric exercises and treadmill running (Table 1). All loading conditions were designed to be completed within thirty minutes. For strength training, participants completed a series of exercises designed to mimic a rehabilitation session for patients with PFP. These included body weight squats step-downs, and other similar weight-bearing exercises to improve lower extremity muscle strength.[33] The plyometric exercise loading condition included single-and double-leg landings and drop vertical jumps mimicking explosive exercises which may provoke symptoms of PFP. Lastly, participants jogged on a treadmill for thirty minutes at their self-selected comfortable jogging speed which they could sustain for thirty minutes.

Femoral articular cartilage image analysis

All obtained ultrasound images were processed using ImageJ software (National Institutes of Health, Bethesda, MD). Femoral cartilage was divided into medial and lateral sections from the midpoint (intercondylar notch) and each section's CSA was measured. Further, average water content level within each segment was measured by mean EI.[34] EI is defined as the average grayscale from 0 to 255. Lower EI appears darker

and indicates greater water content within the region of interest.[35,36] Three images per time point (pre and post loading) and loading condition (strength exercise, plyometric exercise, and jogging) were obtained and the CSA and EI values were averaged within each time point and loading condition for statistical analysis. A percent change score from baseline to post-loading was calculated to determine the alteration of cartilage segment using the following equation.

Percent change = $\left(\frac{Mean_{post} - Mean_{pre}}{Mean_{pre}}\right) * 100$

Statistical Analysis

Separate one-way analysis of variance (One-ANOVA) were utilized to compare the PROs and cartilage status at the baseline measures of each group. We used repeated measures of analysis of variance (RM-ANOVA) to determine differences of PROs, CSA and EI in different pre-loading conditions (strength exercise, plyometric exercise, and jogging). Tukey post-hoc analyses was used in the presence of significant interactions. Cohen's d effect size and associated 95% confidence intervals were calculated to quantify the magnitude of change in cartilage alterations and PROs (<0.2: weak; 0.21-0.5: small; 0.51-0.8: medium; and >0.8: large).[37] Lastly, Pearson product moment correlation analysis was performed to determine the association between percent cartilage alteration and PROs. Statistical significance was set *a priori* at $\alpha<0.05$ and all statistical procedures were performed using SPSS v26 (IBM Inc., Armonk, New York, USA).

3.3 RESULTS

No significant differences in height, body mass, or age were observed between groups ($p>0.05$, Table 1). The symptom duration was significantly longer in the PFP

group compared to the healthy group ($p<0.001$). There was no participant drop out. As a result, there were 24 participants' data included in the assessment.

There were no significant differences in the inter-session baseline measures of pain, function, cartilage CSA and EI ($p>0.78$, Table 2). Pain level significantly increased in the PFP group following all loading conditions compared to the healthy group ($p<0.002$, Table 3). Plyometric exercises produced the greatest magnitude of increase in pain followed by running then strengthening exercises (Cohen's d [95% CI]: Plyometric = 2.21 [1.17,3.19], Strengthening = 1.35 [0.54,2.33], Running = 2.01[0.84,2.74]). There were no statistically significant differences in PROs following any loading condition ($p>0.05$). Finally, there were no statistically significant differences in cartilage CSA or EI alteration between or within groups ($p>0.06$, Table 4).

Table 5 shows the associations between cartilaginous alteration and changes of PROs. KOOS score was negatively associated with the percent change of the EI in the lateral femoral cartilage after the plyometric loading condition ($r=-0.75$, $p=0.010$). Following strengthening exercises, the decreased AKPS was positively correlated to the lateral femoral cartilage EI ($r=0.66$, $p=0.020$). There was no significant association between cartilaginous alteration and PROs following running.

3.4 DISCUSSION

The main purpose of this research was to determine if patients with PFP would demonstrate lesser femoral cartilage deformation than individuals without PFP. Secondarily we tested if percent change of femoral cartilage US quantitative measures are associated with PROs. There were no significant differences in cartilage CSA measures

between sessions prior to exercise performance. This indicates the imaging methods and analyses utilized in the current research were able to provide consistent readings for the collected images.

Pain severity significantly increased following all loading conditions for patients with PFP. Interestingly, other PROs including AKPS, KOOS, and KOOS-PF did not show significant changes following 30-minute loading conditions. Though the aforementioned PROs are valid and reliable[30-32] for quantifying subjective ratings of knee pain and function in individuals with PFP, they do not appear optimized to detect short-period (30 minute) changes in self-perceived pain and function. Another possible reason for statistically non-significant changes in the majority of questionnaires is that the participants were physically active, performing at least 30 minutes of exercise more than 3 times a week. Thus, 30 minutes of loading conditions may not have been sufficient to induce functional decreases in spite of increased pain. It has been suggested that self-reported disability and performance-based assessments of pain and function are influenced by different patient characteristics in patients with low back pain.[38] Specifically, pain intensity, healthy-related quality of life, and depression were significant contributors to self-reported disability. In our study, the self-reported measure of VAS detected an increase in pain but the function-based assessments of AKPS, KOOS, and KOOS-PF did not detect any changes in PROs. Thus, it appears that the previously reported disparity in what self-reported versus performance-based assessments are quantifying may also be true of patients with PFP. Future studies should consider including depression and quality of life measure in understanding the PFP.

Contrary to our hypothesis, individuals with PFP did not demonstrate reduced baseline cartilage thickness and deformative characteristics of femoral cartilage compared to healthy controls. Previous researchers have reported that individuals with PFP show reduced baseline patellar cartilage thickness and decreased deformative behavior of patellar cartilage following acute knee joint loading.[16] There are substantial differences in the material properties of patellar and femoral cartilage that should be noted.[39] Patellar cartilage is thicker than the femoral cartilage but has a lower compressive aggregate modulus and higher permeability to fluid flow, explaining the earlier fibrillation of patellar cartilage compared to the femoral cartilage.[39] Further work is needed to confirm the deformative characteristics of femoral cartilage in patients with PFP through other imaging methods (e.g., MR imaging) since individuals with PFP are at risk of TFOA.

It is imperative to assess the femoral cartilage since PFP may be an indication of poor femoral cartilage health. The percent change of femoral cartilage CSA was not associated with pain level or PROs following any loading condition in individuals with PFP. Our results complement preceding studies which identified non-significant associations between cartilaginous abnormalities and clinical symptoms.[40] It is possible that the pain reported by our participants was coming from a structure other than the femoral cartilage. Joint effusion, development of an osteophyte in the patellofemoral compartment, and the infrapatellar fat pad have all been reported sources of pain for patients with PFP.[40,41] These pain-inducing factors and tissues were not assessed in the present study but should be considered for inclusion in future investigations of diagnostic ultrasound in patients with PFP.

Contrary to our finding, previous research demonstrated that individuals with a history of anterior cruciate ligament tear showed less femoral cartilage deformation following walking that was significantly correlated to worse subjective function (i.e., lower KOOS scores).[42] The different findings between the previous and present study may be due to the patient demographic differences between studies. Despite the participants' ages being similar between the previous study[42] and our research (Age 22±4 years vs. 21±2 years, respectively), our participants did not sustain a traumatic ACL tear that is reported to initiate the degenerative process at the time of injury.[43] It is also possible that it was too early to detect cartilaginous changes in all of our participants with PFP. The average symptom duration of our participants was 54 months which ranged from 18 to 125 months. The exact timing of the transition between PFP and PFOA remains unknown but warrants further investigation.

Research in individuals with a history of anterior cruciate ligament reconstruction reported EI alteration of medial femoral cartilage, whereas individuals with PFP showed changes in EI in the lateral femoral cartilage.[44] A laterally tilted and tracking patella is common in patients with PFP, thus it is unsurprising that these patients may have altered EI in the lateral region of femoral cartilage in individuals with PFP following loading conditions.[45] Our participants supported this previous work demonstrating negative percent change scores of lateral cartilage EI following both plyometric and strengthening loading conditions with significant correlations with KOOS and AKPS changes, respectively. Interestingly, KOOS score increased after plyometric loading condition and AKPS score decreased following strengthening loading condition. This indicates participants felt better after plyometric loading conditions and worse following

strengthening exercises. This caused the association value to be different between those two conditions. Majority of participants in the current study were active in recreational level of sports (i.e., Tegner Activity Scale 6-7). Therefore, those score changes may have differed since participants put more effort during strengthening exercises since they were familiar with the style and then adjusted their movement to reduce intensity during plyometric exercises. A similar association between KOOS and plyometric exercise and AKPS with strengthening exercise may not be observed in persons with different Tegner Activity Scale scores.

We acknowledge several limitations in this research. Participants did not reach the angle of knee flexion (140°) during loading conditions which we used in the data collection process. Patellofemoral contact area changes throughout the knee flexion range of motion, potentially increasing the joint contact pressure due to the reduced contact area within the intercondylar notch at full knee flexion.[46,47] Also, patellofemoral cartilage contact area increases while weight bearing but we collected sonographic images while seated.[48] Thus, it is unlikely for us to have assessed the femoral cartilage where the patellofemoral joint undergoes greatest stress since the transverse imaging on the knee joint may provide only the most anterior portion of femoral cartilage. Ultrasonography for the knee joint lacks the ability to provide thorough understanding of entire joint when compared to the MRI. Therefore, future study utilizing MRI is needed for individuals with PFP after acute bout of loading conditions. Secondly, we could not quantify the amount of loading applied to the joint since participants were asked to perform those loading conditions based on repetitions or time. This may have increased the variability of response in PROs and also cartilaginous alteration. Therefore, future study should

consider controlling the loading conditions. Lastly, while we matched age and BMI between groups, those factors may increase odds for the progressive loss of patellar cartilage.[49] It is recommendable for the future cohort study to assess the effect of age and BMI on cartilaginous response following loading conditions.

3.5 CONCLUSION

Ultrasound imaging was useful in monitoring the lateral femoral cartilage EI in patients with PFP and detecting the water content level alteration following loading. This was the first sonographic research to analyze cartilage CSA and EI changes following exercises in patients with PFP. As cartilaginous EI changes were associated with PROs, future research may be able to use PROs to monitor for early changes of cartilage health.

3.6 References

1. Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis. *PLoS One.* 2018;13(1):e0190892.
2. Witvrouw E, Callaghan MJ, Stefanik JJ, et al. Patellofemoral pain: consensus statement from the 3rd International Patellofemoral Pain Research Retreat held in Vancouver, September 2013. *Br J Sports Med.* 2014;48(6):411-414.
3. Glaviano NR, Kew M, Hart JM, Saliba S. Demographic and depidemiological trends in pteallofemoral pain. *Int J Sports Phys Ther.* 2015;10(3):281-290.
4. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord.* 2010;11:201.
5. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med.* 2014;48(6):409-410.
6. Peat G, Duncan RC, Wood LR, Thomas E, Muller S. Clinical features of symptomatic patellofemoral joint osteoarthritis. *Arthritis Res Ther.* 2012;14(2):R63.
7. Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. *Ann Rheum Dis.* 2011;70(11):1944-1948.
8. Nakagawa TH, ET. M, CD. M, FV. S. Trunk, Pelvis, Hip, and Knee Kinematics, Hip Strength, and Gluteal Muscle Activation During a Single-Leg Squat in Males

and Females With and Without Patellofemoral Pain Syndrome. *J Orthop Sports Phys Ther*. 2012;42(6):491-501.

9. Willson JD, Davis IS. Lower extremity mechanics of females with and without patellofemoral pain across activities with progressively greater task demands. *Clinical Biomechanics.* 2008;23(2):203-211.

10. Willson JD, Binder-Macleod S, Davis IS. Lower extremity jumping mechanics of female athletes with and without patellofemoral pain before and after exertion. *Am J Sports Med.* 2008;36(8):1587-1596.

11. Rathleff MS, Rasmussen S, Olesen JL. [Unsatisfactory long-term prognosis of conservative treatment of patellofemoral pain syndrome]. *Ugeskr Laeger.* 2012;174(15):1008-1013.

12. Farrokhi S, Keyak JH, Powers CM. Individuals with patellofemoral pain exhibit greater patellofemoral joint stress: a finite element analysis study. *Osteoarthritis Cartilage.* 2011;19(3):287-294.

13. Powers CM, Ward SR, Fredericson M, Guillet M, Shellock FG. Patellofemoral kinematics during weight-bearing and non-weight-bearing knee extension in persons with lateral subluxation of the patella: a preliminary study. *J Orthop Sports Phys Ther.* 2003;33(11):677-685.

14. Teng HL, MacLeod TD, Link TM, Majumdar S, Souza RB. Higher Knee Flexion Moment During the Second Half of the Stance Phase of Gait Is Associated With the Progression of Osteoarthritis of the Patellofemoral Joint on Magnetic Resonance Imaging. *J Orthop Sports Phys Ther.* 2015;45(9):656-664.

15. Eijkenboom JFA, van der Heijden RA, de Kanter JLM, Oei EH, Bierma-Zeinstra SMA, van Middelkoop M. Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population. *Scand J Med Sci Sports.* 2020;30(5):885-893.

16. Farrokhi S, Colletti PM, Powers CM. Differences in patellar cartilage thickness, transverse relaxation time, and deformational behavior: a comparison of young women with and without patellofemoral pain. *Am J Sports Med.* 2011;39(2):384-391.

17. Ostergaard M, Court-Payen M, Gideon P, et al. Ultrasonography in arthritis of the knee. A comparison with MR imaging. *Acta Radiol.* 1995;36(1):19-26.

18. Harkey MS, Blackburn JT, Davis H, Sierra-Arevalo L, Nissman D, Pietrosimone B. Ultrasonographic assessment of medial femoral cartilage deformation acutely following walking and running. *Osteoarthritis Cartilage.* 2017;25(6):907-913.

19. Li X, Majumdar S. Quantitative MRI of articular cartilage and its clinical applications. *J Magn Reson Imaging.* 2013;38(5):991-1008.

20. Martel-Pelletier J, Boileau C, Pelletier JP, Roughley PJ. Cartilage in normal and osteoarthritis conditions. *Best Pract Res Clin Rheumatol.* 2008;22(2):351-384.

21. Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. *BioMed research international.* 2013;2013:284873.

22. Atkinson HF, Birmingham TB, Moyer RF, et al. MRI T2 and T1ρ relaxation in patients at risk for knee osteoarthritis: a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2019;20(1).

23. Saarakkala S, Waris P, Waris V, et al. Diagnostic performance of knee ultrasonography for detecting degenerative changes of articular cartilage. *Osteoarthritis Cartilage.* 2012;20(5):376-381.

24. Kuroki H, Nakagawa Y, Mori K, et al. Ultrasound properties of articular cartilage in the tibio-femoral joint in knee osteoarthritis: relation to clinical assessment (International Cartilage Repair Society grade). *Arthritis Res Ther.* 2008;10(4):R78.

25. Möller I, Bong D, Naredo E, et al. Ultrasound in the study and monitoring of osteoarthritis. *Osteoarthritis Cartilage.* 2008;16 Suppl 3:S4-7.

26. Finucci A, Iorgoveanu V, Rutigliano IM, Scirocco C, Iagnocco A. Utilizing ultrasound in the diagnosis and management of osteoarthritis. *International Journal of Clinical Rheumatology International Journal of Clinical Rheumatology*. 2015;10(6):433-440.

27. Chou MC, Tsai PH, Huang GS, et al. Correlation between the MR T2 value at 4.7 T and relative water content in articular cartilage in experimental osteoarthritis induced by ACL transection. *Osteoarthritis Cartilage.* 2009;17(4):441-447.

28. Niehoff A, Müller M, Brüggemann L, et al. Deformational behaviour of knee cartilage and changes in serum cartilage oligomeric matrix protein (COMP) after running and drop landing. *Osteoarthritis Cartilage.* 2011;19(8):1003-1010.

29. Dolak KL, Silkman C, Medina McKeon J, Hosey RG, Lattermann C, Uhl TL. Hip strengthening prior to functional exercises reduces pain sooner than quadriceps strengthening in females with patellofemoral pain syndrome: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2011;41(8):560-570.

30. Watson CJ, Propps M, Ratner J, Zeigler DL, Horton P, Smith SS. Reliability and responsiveness of the lower extremity functional scale and the anterior knee pain scale in patients with anterior knee pain. *J Orthop Sports Phys Ther.* 2005;35(3):136-146.

31. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.

32. Crossley KM, Macri EM, Cowan SM, Collins NJ, Roos EM. The patellofemoral pain and osteoarthritis subscale of the KOOS (KOOS-PF): development and validation using the COSMIN checklist. *Br J Sports Med.* 2018;52(17):1130-1136.

33. Ferber R, Bolgla L, Earl-Boehm JE, Emery C, Hamstra-Wright K. Strengthening of the hip and core versus knee muscles for the treatment of patellofemoral pain: a multicenter randomized controlled trial. *Journal of athletic training.* 2015;50(4):366-377.

34. Harkey MS, Blackburn JT, Hackney AC, et al. Comprehensively Assessing the Acute Femoral Cartilage Response and Recovery after Walking and Drop-Landing: An Ultrasonographic Study. *Ultrasound Med Biol.* 2018;44(2):311-320.

35. Watanabe Y, Yamada Y, Fukumoto, et al. Echo intensity obtained from ultrasonography images reflecting muscle strength in elderly men. *Clin Interv Aging.* 2013:993.

36. Töyräs JL, Mikko; Saarakkala, Simo; Lammi, Mikko; Rieppo, Jarno; Kurkijärvi, Jatta; Lappalainen, Reijo; Jurvelin, Jukka. Speed of sound in normal and degenerated bovine articular cartilage. 2003.

37. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2013.

38. Wand BM, Chiffelle LA, O'Connell NE, McAuley JH, Desouza LH. Self-reported assessment of disability and performance-based assessment of disability are influenced by different patient characteristics in acute low back pain. *Eur Spine J.* 2010;19(4):633-640.

39. Froimson MI, Ratcliffe A, Gardner TR, Mow VC. Differences in patellofemoral joint cartilage material properties and their significance to the etiology of cartilage surface fibrillation. *Osteoarthritis Cartilage.* 1997;5(6):377-386.

40. Kornaat PR, Bloem JL, Ceulemans RYT, et al. Osteoarthritis of the Knee: Association between Clinical Features and MR Imaging Findings. *Radiology.* 2006;239(3):811-817.

41. Widjajahakim R, Roux M, Jarraya M, et al. Relationship of Trochlear Morphology and Patellofemoral Joint Alignment to Superolateral Hoffa Fat Pad Edema on MR Images in Individuals with or at Risk for Osteoarthritis of the Knee: The MOST Study. *Radiology.* 2017;284(3):806-814.

42. Davis-Wilson HC, Johnston CD, Pfeiffer SJ, et al. Less femoral cartilage deformation following walking associates with clinically relevant symptoms in individuals with anterior cruciate ligament reconstruction. *Osteoarthritis Cartilage.* 2019;27:S361.

43. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. *Arthritis Rheum.* 2004;50(10):3145-3152.

44. Harkey MS, Little E, Thompson M, Zhang M, Driban JB, Salzler MJ. Femoral Cartilage Ultrasound Echo Intensity Associates with Arthroscopic Cartilage Damage. *Ultrasound Med Biol.* 2021;47(1):43-50.

45. Esfandiarpour F, Lebrun CM, Dhillon S, Boulanger P. In-vivo patellar tracking in individuals with patellofemoral pain and healthy individuals. *Journal of Orthopaedic Research®.* 2018;36(8):2193-2201.

46. Feller JA, Amis AA, Andrish JT, Arendt EA, Erasmus PJ, Powers CM. Surgical biomechanics of the patellofemoral joint. *Arthroscopy.* 2007;23(5):542-553.

47. Connolly KD, Ronsky JL, Westover LM, Küpper JC, Frayne R. Differences in patellofemoral contact mechanics associated with patellofemoral pain syndrome. *J Biomech.* 2009;42(16):2802-2807.

48. Gold GE, Besier TF, Draper CE, Asakawa DS, Delp SL, Beaupre GS. Weight-bearing MRI of patellofemoral joint cartilage contact area. *J Magn Reson Imaging.* 2004;20(3):526-530.

49. Cicuttini FM, Forbes A, Yuanyuan W, Rush G, Stuckey SL. Rate of knee cartilage loss after partial meniscectomy. *J Rheumatol.* 2002;29(9):1954-1956.

3.7 Tables

Table 3. Descriptive characteristics of the study population (Mean±SD)

	PFP	Healthy	t	p
Height (m)	1.72±0.09	1.71±0.09	0.09	0.92
Mass (kg)	68.66±12.61	65.99±12.23	0.53	0.60
Age (yrs)	21.00±2.04	21.25±2.77	0.25	0.80
Symptom duration* (months)	54.00±34.69	0.00±0.00	5.39	0.00

* Statistically significant difference ($p<0.05$)

Table 4. Within-group baseline comparison of pain, function, cartilage CSA and EI (Mean±SD)

		PFP		Healthy	
			p		p
VAS	Plyo	1.08±0.90	0.81	0.00±0.00	-
	Str	1.17±1.03		0.00±0.00	
	Run	0.92±0.90		0.00±0.00	
AKPS	Plyo	76.83±12.98	0.99	99.00±2.89	0.95
	Str	76.05±13.57		99.33±2.31	
	Run	76.08±12.91		99.17±2.54	
KOOS	Plyo	38.33±21.46	0.99	2.08±6.02	0.91
	Str	39.00±20.69		1.67±3.82	
	Run	38.25±21.92		2.75±7.72	
KOOSPF	Plyo	67.01±16.89	0.78	96.97±7.14	0.79
	Str	67.76±18.39		96.97±7.14	
	Run	62.84±17.66		95.08±7.76	
MedCSA	Plyo	27.41±6.69	0.94	29.14±8.92	0.97
	Str	28.14±5.59		29.04±8.33	
	Run	28.27±6.35		29.80±9.11	
MedEI	Plyo	109.99±4.73	0.79	110.56±9.95	0.89
	Str	110.62±4.98		110.02±9.29	
	Run	111.62±7.42		108.79±8.94	
LatCSA	Plyo	28.58±6.96	0.98	30.47±8.99	0.96
	Str	28.85±5.40		30.95±8.85	
	Run	28.39±6.33		31.50±9.79	
LatEI	Plyo	109.11±5.00	0.89	108.54±9.01	0.98
	Str	108.56±4.81		108.32±8.34	
	Run	109.60±6.12		107.84±9.62	

VAS = Visual Analog Scale; AKPS = Anterior Knee Pain Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOSPF = Knee Injury and Osteoarthritis Outcome Score for Patellofemoral Pain and Osteoarthritis; MedCSA = Medial Cross-Sectional Area; MedEI = Medial Echo Intensity; LatCSA = Lateral Cross-Sectional Area; LatEI = Lateral Echo Intensity

Table 5. Effects of loading conditions on pain and function (Mean±SD)

	PFP		Healthy		P
	Pre	Post	Pre	Post	
VAS					
Plyometric	1.08±0.90	5.00±2.34*	0.00±0.00	0.50±1.17§	0.00
Strengthening	1.17±1.03	3.75±2.49*	0.00±0.00	0.42±0.99§	0.002
Running	0.92±0.90	4.50±2.35*	0.00±0.00	0.58±1.38§	0.00
AKPS					
Plyometric	76.83±12.98	73.83±12.50	99.00±2.89	98.42±4.38	0.19
Strengthening	76.05±13.57	74.42±15.28	99.33±2.31	98.42±3.70	0.66
Running	76.08±12.91	75.67±12.29	99.17±2.59	98.67±4.62	0.96
KOOS					
Plyometric	38.33±21.46	40.83±25.81	2.08±6.02	3.00±8.58	0.55
Strengthening	39.00±20.69	50.58±23.46	1.67±3.82	4.00±10.19	0.76
Running	38.25±21.92	41.25±25.27	2.75±7.72	2.75±8.31	0.19
KOOS-PF					
Plyometric	67.01±16.89	66.07±20.14	96.97±7.14	96.21±9.31	0.95
Strengthening	67.76±18.39	66.29±19.69	96.97±7.14	97.16±7.94	0.44
Running	62.84±17.66	64.77±20.15	95.08±9.34	97.54±8.53	0.87

* Significant within-group differences ($p<0.05$)

§ Significant between-group differences ($p<0.05$)

VAS = Visual Analog Scale; AKPS = Anterior Knee Pain Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOSPF = Knee Injury and Osteoarthritis Outcome Score for Patellofemoral Pain and Osteoarthritis

Table 6. Effects of loading conditions on cartilage CSA and echo intensity (Mean±SD)

	PFP		Healthy		P
	Pre	Post	Pre	Post	
Plyometric					
CSA					
Medial	27.41±6.69	26.98±6.01	29.14±8.92	27.86±7.42	0.43
Lateral	28.58±6.96	28.43±6.55	30.47±8.99	28.43±8.43	0.11
EI					
Medial	109.99±4.73	109.84±5.53	110.56±9.95	111.00±8.72	0.70
Lateral	109.11±5.00	108.25±4.85	108.54±9.02	107.95±8.51	0.88
Strengthening					
CSA					
Medial	28.14±5.59	26.63±5.24	29.04±8.33	28.42±8.17	0.49
Lateral	28.85±5.40	27.98±5.92	30.95±8.85	29.42±8.43	0.53
EI					
Medial	110.62±4.98	108.79±5.41	110.02±9.29	110.88±9.45	0.06
Lateral	108.56±4.81	107.75±4.60	108.32±8.34	109.85±8.18	0.07
Running					
CSA					
Medial	28.27±6.35	27.38±7.13	29.80±9.11	30.15±9.47	0.13
Lateral	28.39±6.33	28.05±6.86	31.50±9.79	29.44±9.15	0.06
EI					
Medial	111.62±7.42	111.75±5.87	108.79±8.94	112.34±10.91	0.11
Lateral	109.60±6.12	110.32±5.24	107.83±9.62	111.58±9.36	0.09

CSA = Cross-sectional area; EI = Echo intensity

Table 7. Association between cartilaginous alteration and patient reported outcome changes. [r(p)]

	PFP				Healthy			
	MedCSA	LatCSA	MedEI	LatEI	MedCSA	LatCSA	MedEI	LatEI
Plyometric								
VAS	-0.32(0.31)	0.06(0.86)	-0.04(0.89)	-0.51(0.09)	0.14(0.66)	0.16(0.62)	-0.01(0.97)	-0.05(0.87)
AKPS	-0.12(0.72)	-0.19(0.55)	-0.37(0.23)	0.15(0.65)	-0.08(0.81)	-0.21(0.52)	0.01(0.98)	0.03(0.93)
KOOS	-0.38(0.22)	-0.26(0.42)	-0.41(0.19)	-0.75(0.01)*	0.10(0.76)	0.14(0.67)	-0.03(0.93)	0.02(0.95)
KOOS-PF	00.07(0.82)	0.36(0.25)	0.08(0.81)	0.55(0.06)	-0.12(0.70)	-0.20(0.53)	0.06(0.84)	0.13(0.69)
Strengthening								
VAS	-0.47(0.12)	-0.39(0.20)	0.01(0.99)	-0.13(0.69)	0.36(0.26)	0.47(0.12)	0.05(0.87)	0.19(0.54)
AKPS	-0.52(0.08)	0.23(0.47)	0.40(0.19)	0.66(0.02)*	-0.03(0.94)	0.02(0.95)	0.27(0.40)	0.11(0.74)
KOOS	0.37(0.24)	-0.23(0.47)	0.08(0.81)	-0.03(0.92)	0.41(0.18)	0.57(0.06)	0.17(0.59)	0.28(0.39)
KOOS-PF	-0.32(0.31)	0.08(0.80)	0.36(0.24)	0.24(0.45)	-0.45(0.15)	-0.27(0.39)	-0.02(0.95)	-0.11(0.74)
Running								
VAS	0.43(0.16)	-0.04(0.90)	-0.23(0.48)	-0.27(0.39)	-0.21(0.52)	-0.18(0.58)	-0.10(0.76)	-0.34(0.27)
AKPS	-0.16(0.61)	0.05(0.89)	-0.07(0.84)	0.19(0.54)	0.16(0.62)	0.27(0.39)	-0.25(0.43)	0.07(0.82)
KOOS	0.15(0.63)	0.39(0.21)	-0.19(0.56)	0.24(0.46)	-0.06(0.86)	-0.23(0.46)	0.42(0.17)	0.17(0.61)
KOOS-PF	0.13(0.69)	-0.04(0.89)	0.15(0.63)	-0.26(0.41)	0.38(0.22)	-0.11(0.72)	-0.29(0.35)	-0.11(0.73)

* Statistically significant association ($p<0.05$)

VAS = Visual Analog Scale; AKPS = Anterior Knee Pain Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOSPF = Knee Injury and Osteoarthritis Outcome Score for Patellofemoral Pain and Osteoarthritis; MedCSA = Medial Cross-Sectional Area; MedEI = Medial Echo Intensity; LatCSA = Lateral Cross-Sectional Area; LatEI = Lateral Echo Intensity

3.8 Figures

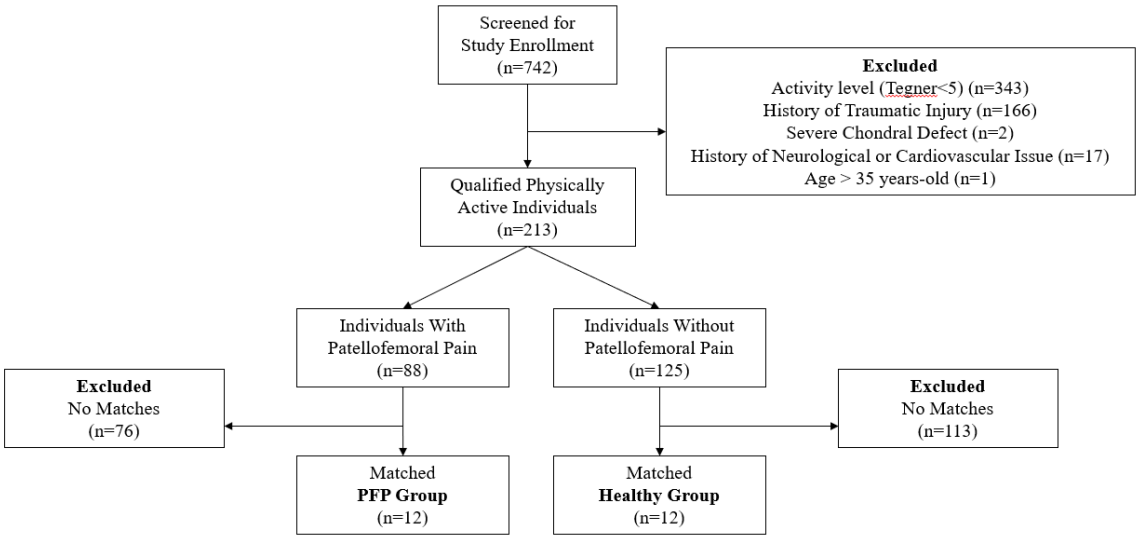


Figure 2. CONSORT flow chart.

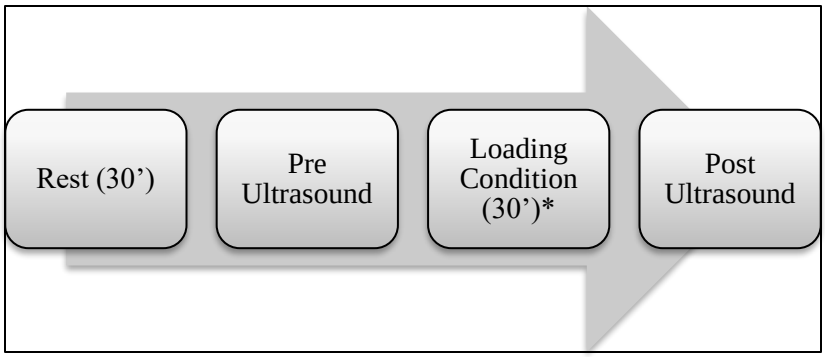


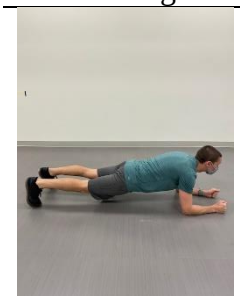
Figure 3. Testing overview. *indicates conditions: running, strength training, or plyometrics.

3.9 Appendices

Appendix. Loading conditions

Strengthening Exercises		Plyometric Exercises		Running
Name	Volume	Name	Volume	
Prone plank	30sec	Squat jumps	10sec	Selected
Side plank	30sec/side	Tuck jumps	10sec	Speed
Double leg bridges	20rep	Scissor jumps	10sec	(30min)
Single leg bridges	15sec/side	Lateral skate leap	10sec	
Standing hip abduction	15rep/side			
Double legged squat	15rep			
Single legged squat	8rep/side	Forward-backward line/cone jump and hops	10sec	
Forward lunges	10rep/side	Sideways line/cone jumps and hops	10sec	
Lateral lunges	10rep/side	Forward-backward jog (15m)	6rep	
Diagonal lunges	10rep/side			
Step downs	10rep/side			

Strengthening Exercises


Prone plank


Side plank


Double leg bridges


Single leg bridges


Standing hip abduction


Double leg squat


Single leg squat

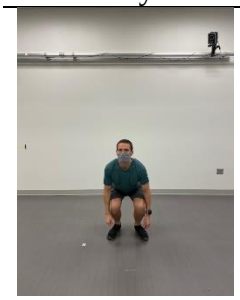

Lunges


Side lunges


Diagonal lunges


Step downs

Plyometric Exercises




Squat jumps


Tuck jumps


Scissor jumps

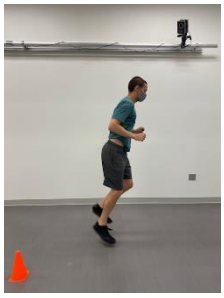

Lateral skate leap


Forward / Backward jumps


Forward / Backward hops


Side jumps


Side hops




Forward / Backward jog

CHAPTER 4: OSTEOARTHRITIC CHARACTERISTICS OF FEMORAL CARTILAGE HEALTH IN INDIVIDUALS WITH PATELLOFEMORAL PAIN: SONOGRAPHIC IMAGE QUALITY ANALYSIS

4.1 INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of pain and disability among adults, often requiring surgical intervention.[1] Radiographic evidence of knee OA is scarcely found in people aged between 25-34 years but individuals with age over 50 start to show significantly increased prevalence of the disease on plain x-ray.[2] Younger individuals, those ages 45 and under, often experience symptomatic OA without radiographic evidence of joint degeneration.[3] Symptomatic knee OA involves pain, stiffness, and associated functional loss.[3] Symptomatic knee OA typically progresses to radiographic, end-stage disease as the person ages. Therefore, there is an urgent need for early diagnosis of the disease in order to be able to intervene and delay the progression to end-stage knee OA.

Patellofemoral pain (PFP) is a prevalent musculoskeletal condition characterized by pain localized to the anterior retropatellar and/or peripatellar regions of the knee.[4] PFP has been reported in individuals ages 12 to 60 years.[5,6] PFP can arise during or after activities loading the lower limb (e.g., squatting, jumping, running, or ascending/descending stairs) or prolonged sitting with bent knee which loads the patellofemoral joint. The pain and symptoms associated with PFP may cause the affected person to restrict or refrain from physical activities, sports, and work. Unfortunately, PFP often becomes a persistent condition[7] that may contribute to the development of

patellofemoral osteoarthritis (PFOA), further worsening the quality of life for affected individuals.[8-12] Though tibiofemoral OA (TFOA) is more frequently reported, the majority of individuals with symptomatic knee OA have PFOA.[13] Further, PFOA may serve as a potential marker for future development of TFOA.[13] Therefore, because PFP can lead to PFOA and potentially TFOA and because the femoral cartilage will degenerate in both PFOA and TFOA, it is important to take examine femoral cartilage health in individuals with PFP.

Femoral cartilage health is assessed via imaging techniques. There are varied definitions and classifications of radiographic PFOA, but its presence is usually determined by the skyline view of the patellofemoral joint at 45° knee flexion on plain radiography.[14] The radiographic evidence of PFOA is determined by the presence of osteophytes or decreased joint space.[15] Plain radiography is a costly method which is effective in providing images for hard tissues (e.g., bones). X-ray can provide indirect measures of cartilage by allowing for detection of joint space narrowing or presence of osteophytes, but x-rays may not be able to detect changes associated with early-stage OA. Ultrasound (US) is an affordable alternative providing a real-time image to evaluate soft tissue abnormality.[16] US is capable of detecting early changes of femoral cartilage in individuals with history of traumatic lower extremity injury[17] but has not been utilized often in the evaluation of femoral cartilage health of individuals with PFP.[18]

Clinically, femoral cartilage thickness, volume, and echo intensity can be measured with US to provide a comprehensive overview of cartilage health.[19,20] In addition to those measures, Lee et al. identified[21] that the lack of femoral US image clarity is correlated to the histological evidence of TFOA. However, the study was

performed on individuals with severe TFOA who were scheduled for total knee arthroplasty. The quality of femoral cartilage US images provides an earlier indication of cartilage health than traditional measures and, therefore, may be important for early detection of knee OA. However, the quality of femoral cartilage US images in patients with PFP has not been determined. Therefore, the main purpose of our study was to compare femoral cartilage US image quality between individuals with and without PFP. Secondarily, we wanted to establish intra and inter assessor reliability of the femoral cartilage US image quality grading scheme. We hypothesized that individuals with PFP will show worse US image quality based on US grading scheme by Lee et al.[21] We also hypothesized that assessors will be able to establish strong intra and inter assessor reliability.

4.2 METHODS

Twenty-four individuals (n=12 with PFP; n=12 healthy) between the 18 and 35 years were recruited from the university campus via flyers and campus-wide email in January 2018. All participants were physically active, defined as performing activities that are included in the Tegner Activity Scale of ≥ 5 for at least 30 minutes 3 or more days per week. However, type of physical activities and other behavioral characteristics were not controlled. Potential participants were excluded if they had a: 1) history of orthopedic injuries, fractures, or surgeries to either limb or the low back with the exception of PFP in the patient group; 2) severe osteochondral defect in either knee; 3) history of cardiovascular, neurological, or balance disorder that precludes safe participation in exercise; and 4) body mass index > 40 kg/m^2.

Patients with PFP were required to have: 1) retropatellar pain during at least two of the following activities – prolonged sitting, stair ascent/descent, squatting, hopping, kneeling, running, and jumping; 2) pain with compression of the patella; and 3) pain on palpation on patellar facets.[22] Twelve participants with PFP were enrolled and matched twelve healthy individuals were enrolled following screening procedure. Healthy participants were matched to those in the PFP group based on age, Tegner Activity Scale (±1), and body mass index (±5%). All participants provided written informed consent prior to enrollment. This study was approved by the university institutional review board.

Data collection

Participants completed a single testing session during which femoral cartilage US measures were obtained. The testing session began with the participant sitting on a treatment table with the knees fully extended for 30 minutes to mitigate cartilage compression that occurred walking to the laboratory.[23] While resting, participants were asked to fill out questionnaires to measure their current pain level with Visual Analog Scale (VAS), Anterior Knee Pain Scale (AKPS), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Knee Injury and Osteoarthritis Score for Patellofemoral Pain and Osteoarthritis (KOOSPF). To test participants' pain level, we used visual analog scale (VAS). It utilizes a 10cm straight line which gives a continuous scale measuring the severity of pain. The AKPS is valid and reliable questionnaire which is considered a gold standard in assessing the severity of PFP.[24] KOOS is used to assess the function of those who are at risk of posttraumatic osteoarthritis (PTOA).[25] KOOSPF is most recently

developed questionnaire to evaluate function of individuals affected with PFP and OA and it is reported to be responsive.[26]

After this 30-minute period was over, participants remained seated on the treatment table with their back against a wall and the test knee flexed to 140°. Test knee was determined as the most painful leg for PFP group and dominant leg (the one with which they would kick a ball) for healthy group. A LOGIQe ultrasound system (General Electric Co., Fairfield, CT) with a 12MHz linear probe was used to collect femoral cartilage images. The ultrasound probe was placed transversely in line with the femoral condyles above the superior pole of the patella.[23] Three images were collected and used for analysis.

Imaging data analysis

All obtained ultrasound images were processed using ImageJ software (National Institutes of Health, Bethesda, MD). Imaging data were analyzed by a single, experienced researcher who was blinded to group assignment (HJJ). The diagnostic grading scheme was adopted from Lee et al (Figure 1).[21] In vivo US image quality grade varies from 0 to 6, where 0 indicates clean and sharp cartilage edges and 6 indicates no visualized cartilage band. The US image quality grade is significantly associated with osteoarthritic evidence in the histologic images.

Reliability Assessment

Both intra- and inter-rater reliability were assessed. Fifteen US images were evaluated three times and their image quality scores recorded. Image evaluation took

place on 2 different occasions each separated by 4 days to minimize memory-based bias. Separate records were kept for each evaluation day. For inter-rater reliability, a second investigator independently scored the image quality of the same 15 US images using the same procedures.

Statistical analysis

Statistical analysis was performed using SPSS 26.0 (IBM, Armonk, NY). To ensure the consistency of the reading, intra-tester reliability was measured with weighted-kappa.

Independent T-test was used to compare group mean of patient reported outcomes (VAS, AKPS, KOOS, and KOOSPF). Mann-Whitney U test was performed to compare the mean rank of ultrasound image quality grade between groups. Three evaluation per images were performed and most observed grading was used and entered for the dataset. Alpha was set at < 0.05 for all statistical procedures.

4.3 RESULTS

Weighted-kappa coefficients for inter-rater and intra-rater reliability showed strong agreement (Weighted-kappa= 0.82, $p<0.001$; and 0.86, $p<0.001$; respectively). Pain level (VAS) and patient-reported outcomes (AKPS, KOOS, KOOSPF) were significantly different between groups ($p<0.002$, Table 1). There was a significant rank difference between two groups with greater grading score in PFP group (PFP: Mean rank=17.58, Healthy: Mean rank=7.42, Mann-Whitney U-test = 11.0; $p<0.001$) (Figure 2).

4.4 DISCUSSION

This study is the first to investigate cartilage surface integrity using US comparing between individuals with and without PFP. The purpose of this research was to compare the femoral cartilage US image quality between individuals with and without PFP. Healthy articular cartilage contains abundant extracellular matrix, which demonstrates clear contrast between homogenous anechoic band and margin in US image.[27] Cartilage fibrillation is one of the early signs of OA due to the breakdown of collagen fibril network and results in softening of articular cartilage and development of vertical clefts. Hyalinized cartilages experiences deterioration of chondrocytes, turning the chondrocytes into a glass-like substance. These conditions can be observed as a loss of sharpness of the margin on US images.[21,28] The grading scheme by Lee et al[21] showed a significant correlation between femoral cartilage image quality and histologic grades. Cartilage fibrillation was most observed in US grade of 2 to 3, hyalinization in grade 3, deep fibrillation in grade 5, partial to complete loss of cartilage in grade 5 to 6.

US grade of Femoral cartilage image quality was worse in patients with PFP which may indicate cartilage surface flaking, fibrillation, pitting and partial cartilage loss based on the grading scheme.[21,29] Individuals without symptoms of PFP showed relatively sharp edges of the cartilage which indicates the smooth surface of healthy cartilage.[21,30] Our results indicate that individuals with PFP may be at increased risk of developing TFOA (Grade 1-5) and suggest that some of the individuals without the pain or functional limitations associated with PFP have altered cartilage health (Grade 0-2). Those healthy individuals who showed grade 2 had relatively high BMI compared to other individuals in the group, potentially indicating thicker overlying tissue which may

affect the echogenicity.[30] Based on this outcome, it is recommended to assess the cartilage health for those who are actively participating in physical activities with or without pain. Both radiographic and symptomatic evidence of knee OA may contribute to increased risk of all-cause mortality; therefore, frequent assessment of femoral cartilage health and appropriate treatment are warranted.[16,31]

The US grading scheme measure can be subjective. However, weighted-kappa coefficients for inter-rater and intra-rater reliability showed almost perfect agreement. This result indicates a single investigator will be able to assess the cartilage health longitudinally using the US grading scheme, allowing for tracking of degeneration over time. Also, a group of analyzers will be able to work together in the evaluation of the US image. However, a single expert should collect the data to have consistency in the collection and US setting should be kept same.

Our study is not free from limitations. First, the small sample size with strict inclusion criteria could not cover the variety of risk factors associated with PFP. The unbalanced sample between males and females also limited sex-based analysis. Future study should consider comparing the cartilage health based on sex,[32] symptom duration,[33] and obesity.[34,35] Secondly, we could not analyze the patellar cartilage due to the technical limitation. However, based on differences in the material properties of patellar and femoral cartilage, it is likely to signs of degeneration in the patellar cartilage prior to the femoral cartilage;[36] therefore, detection of poor cartilage health on femoral US suggests similar or more advanced degeneration of patellar cartilage health. Regardless, further study utilizing both MRI and US to assess femoral and patellar cartilage health in individuals with PFP is needed. Lastly, the superficial soft tissue could influence reading

the underlying tissues. Synovitis[29] and overlying tissue thickness[30] may also affect the echogenicity but those were not addressed in the current study. Future studies should consider testing the synovitis prior to the data collection.

4.5 CONCLUSION

In conclusion, US femoral cartilage image quality grading system is an accessible and easy tool for detecting early knee OA with sufficient sensitivity. The result of this research suggests that individuals with PFP show signs of early knee OA but also individuals without PFP may be at risk of developing radiographic OA. Therefore, clinicians or other healthcare providers should consider utilizing US in the evaluation of knee cartilage health and provide early intervention in individuals with PFP.

4.6 References

1. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum.* 1995;38(8):1134-1141.
2. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. *Br Med Bull.* 2013;105:185-199.
3. Deshpande BR, Katz JN, Solomon DH, et al. Number of Persons With Symptomatic Knee Osteoarthritis in the US: Impact of Race and Ethnicity, Age, Sex, and Obesity. *Arthritis Care Res (Hoboken).* 2016;68(12):1743-1750.
4. Powers CM, Witvrouw E, Davis IS, Crossley KM. Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: part 3. *Br J Sports Med.* 2017;51(24):1713-1723.
5. Witvrouw E, Callaghan MJ, Stefanik JJ, et al. Patellofemoral pain: consensus statement from the 3rd International Patellofemoral Pain Research Retreat held in Vancouver, September 2013. *Br J Sports Med.* 2014;48(6):411-414.
6. Glaviano NR, Kew M, Hart JM, Saliba S. DEMOGRAPHIC AND EPIDEMIOLOGICAL TRENDS IN PATELLOFEMORAL PAIN. *Int J Sports Phys Ther.* 2015;10(3):281-290.
7. Nimon G, Murray D, Sandow M, Goodfellow J. Natural history of anterior knee pain: a 14- to 20-year follow-up of nonoperative management. *J Pediatr Orthop.* 1998;18(1):118-122.

8. Utting MR, Davies G, Newman JH. Is anterior knee pain a predisposing factor to patellofemoral osteoarthritis? *The Knee.* 2005;12(5):362-365.

9. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord.* 2010;11:201.

10. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med.* 2014;48(6):409-410.

11. Eijkenboom JFA, Waarsing JH, Oei EHG, Bierma-Zeinstra SMA, van Middelkoop M. Is patellofemoral pain a precursor to osteoarthritis?: Patellofemoral osteoarthritis and patellofemoral pain patients share aberrant patellar shape compared with healthy controls. *Bone Joint Res.* 2018;7(9):541-547.

12. Eijkenboom JFA, van der Heijden RA, de Kanter JLM, Oei EH, Bierma-Zeinstra SMA, van Middelkoop M. Patellofemoral alignment and geometry and early signs of osteoarthritis are associated in patellofemoral pain population. *Scand J Med Sci Sports.* 2020;30(5):885-893.

13. Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. *Ann Rheum Dis.* 2011;70(11):1944-1948.

14. Heng HY, Bin Abd Razak HR, Mitra AK. Radiographic grading of the patellofemoral joint is more accurate in skyline compared to lateral views. *Annals of translational medicine.* 2015;3(18):263.

15. Jones AC, Ledingham J, McAlindon T, et al. Radiographic assessment of patellofemoral osteoarthritis. *Ann Rheum Dis.* 1993;52(9):655-658.

16. Iagnocco A. Imaging the joint in osteoarthritis: a place for ultrasound? *Best Pract Res Clin Rheumatol.* 2010;24(1):27-38.

17. Harkey MS, Blackburn JT, Nissman D, et al. Ultrasonographic Assessment of Femoral Cartilage in Individuals With Anterior Cruciate Ligament Reconstruction: A Case-Control Study. *Journal of athletic training.* 2018;53(11):1082-1088.

18. Fischhoff C. Patellofemoral pain syndrome: Ultrasound measurements for diagnosis. *International Musculoskeletal Medicine International Musculoskeletal Medicine.* 2015;37(2):54-58.

19. Harkey MS, Blackburn JT, Hackney AC, et al. Comprehensively Assessing the Acute Femoral Cartilage Response and Recovery after Walking and Drop-Landing: An Ultrasonographic Study. *Ultrasound Med Biol.* 2018;44(2):311-320.

20. Harkey MS, Little E, Thompson M, Zhang M, Driban JB, Salzler MJ. Femoral Cartilage Ultrasound Echo Intensity Associates with Arthroscopic Cartilage Damage. *Ultrasound Med Biol.* 2021;47(1):43-50.

21. Lee CL, Huang MH, Chai CY, Chen CH, Su JY, Tien YC. The validity of in vivo ultrasonographic grading of osteoarthritic femoral condylar cartilage: a comparison with in vitro ultrasonographic and histologic gradings. *Osteoarthritis Cartilage.* 2008;16(3):352-358.

22. Dolak KL, Silkman C, Medina McKeon J, Hosey RG, Lattermann C, Uhl TL. Hip strengthening prior to functional exercises reduces pain sooner than quadriceps

strengthening in females with patellofemoral pain syndrome: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2011;41(8):560-570.

23. Harkey MS, Blackburn JT, Davis H, Sierra-Arevalo L, Nissman D, Pietrosimone B. Ultrasonographic assessment of medial femoral cartilage deformation acutely following walking and running. *Osteoarthritis Cartilage.* 2017;25(6):907-913.
24. Watson CJ, Propps M, Ratner J, Zeigler DL, Horton P, Smith SS. Reliability and responsiveness of the lower extremity functional scale and the anterior knee pain scale in patients with anterior knee pain. *J Orthop Sports Phys Ther.* 2005;35(3):136-146.
25. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.
26. Crossley KM, Macri EM, Cowan SM, Collins NJ, Roos EM. The patellofemoral pain and osteoarthritis subscale of the KOOS (KOOS-PF): development and validation using the COSMIN checklist. *Br J Sports Med.* 2018;52(17):1130-1136.
27. Saarakkala S, Laasanen MS, Jurvelin JS, Töyräs J. Quantitative ultrasound imaging detects degenerative changes in articular cartilage surface and subchondral bone. *Phys Med Biol.* 2006;51(20):5333-5346.
28. Saarakkala S, Waris P, Waris V, et al. Diagnostic performance of knee ultrasonography for detecting degenerative changes of articular cartilage. *Osteoarthritis Cartilage.* 2012;20(5):376-381.

29. Grassi W, Lamanna G, Farina A, Cervini C. Sonographic imaging of normal and osteoarthritic cartilage. *Semin Arthritis Rheum.* 1999;28(6):398-403.

30. McCune WJ, Dedrick DK, Aisen AM, MacGuire A. Sonographic evaluation of osteoarthritic femoral condylar cartilage. Correlation with operative findings. *Clin Orthop Relat Res.* 1990(254):230-235.

31. Wang Y, Nguyen U-SDT, Lane NE, et al. Knee Osteoarthritis, Potential Mediators, and Risk of All-Cause Mortality: Data From the Osteoarthritis Initiative. *Arthritis Care Res (Hoboken).* 2021.

32. Boling M, Padua D, Marshall S, Guskiewicz K, Pyne S, Beutler A. Gender differences in the incidence and prevalence of patellofemoral pain syndrome. *Scand J Med Sci Sports.* 2010;20(5):725-730.

33. Hott A, Brox JI, Pripp AH, Juel NG, Liavaag S. Predictors of Pain, Function, and Change in Patellofemoral Pain. *Am J Sports Med.* 2020;48(2):351-358.

34. Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. *Int J Obes Relat Metab Disord.* 2001;25(5):622-627.

35. Lotz MK, Kraus VB. New developments in osteoarthritis. Posttraumatic osteoarthritis: pathogenesis and pharmacological treatment options. *Arthritis Res Ther.* 2010;12(3):211.

36. Froimson MI, Ratcliffe A, Gardner TR, Mow VC. Differences in patellofemoral joint cartilage material properties and their significance to the etiology of cartilage surface fibrillation. *Osteoarthritis Cartilage.* 1997;5(6):377-386.

4.7 Tables

Table 8. Group comparison of patient-reported outcomes

	PFP	Healthy	p
VAS	0.92±0.90	0.00±0.00	0.002
AKPS	76.08±12.91	99.17±2.59	0.00
KOOS	38.25±21.92	2.75±7.72	0.00
KOOSPF	62.84±17.66	95.08±9.34	0.00

VAS = Visual Analog Scale; AKPS = Anterior Knee Pain Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOSPF = Knee Injury and Osteoarthritis Outcome Score for Patellofemoral Pain and Osteoarthritis

4.8 Figures

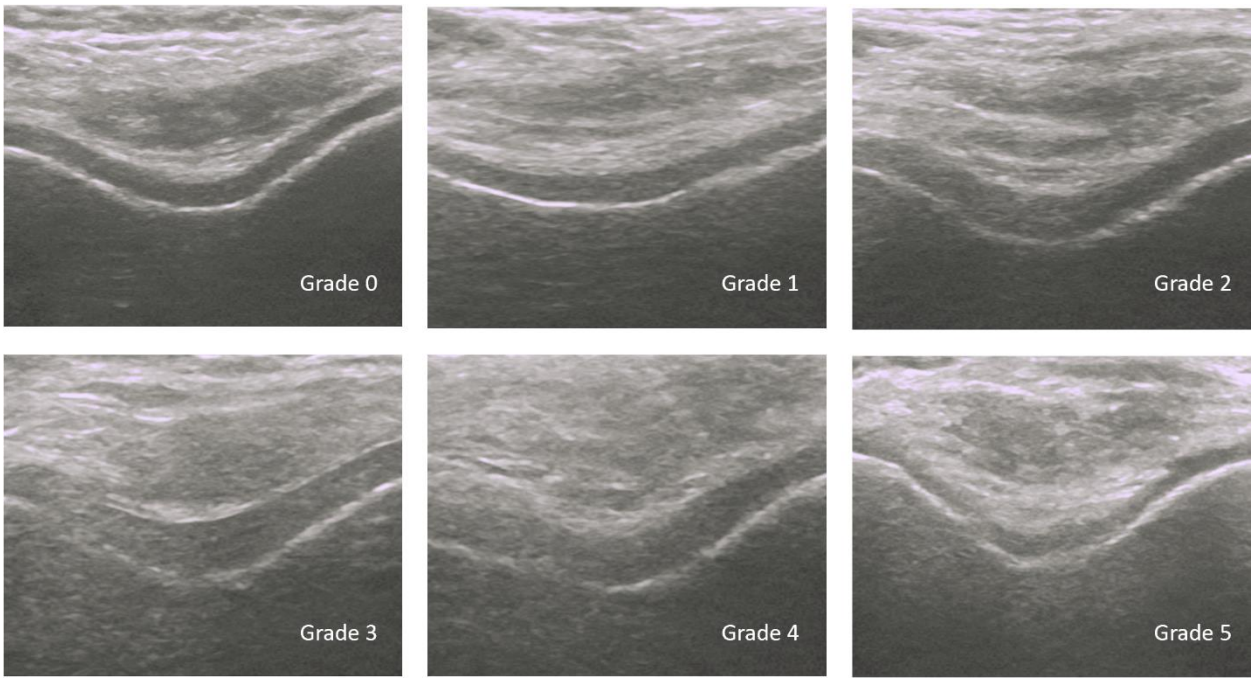


Figure 4. Ultrasound grading of femoral cartilage. Grade 0: Sharp cartilage edges. Grade 1: blurred margin or partial lack of the clarity, without thickness change. Grade 2: blurred margin and partial lack of the clarity, without thickness change. Grade 3: blurred margin and complete lack of the clarity. Grade 4: difficult-defined margin and the complete-opaque band. Grade 5: marked thickness change.

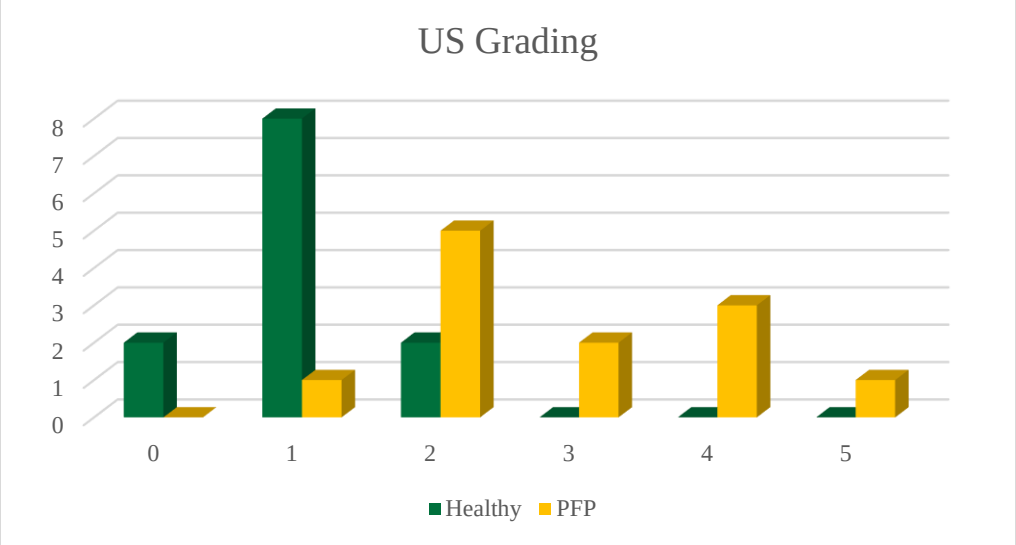


Figure 5. Number of participants per ultrasound image grades.

CHAPTER 5: OVERALL CONCLUSION

5.1 Summary

PFP is a multifactorial knee pathology prevalent in physically active individuals. Activities that load the patellofemoral joint, such as stair ambulation, jumping, and prolonged running typically exacerbate the pain. Recent studies claim prolonged symptoms of PFP may propagate to PFOA further compromising the affected person's quality of life. Additionally, isolated PFOA serves as a potential marker for future development of TFOA, which is traditionally perceived as a knee OA.[43]

The purpose of my dissertation was to address several gaps in the treatment and evaluation of joint health in individuals with PFP. First, we have assessed the effectiveness of feedback motion retraining for individuals with PFP. Also, we tested if diagnostic US is viable in testing the knee cartilage health in individuals with PFP.

Various studies identified altered movement patterns during dynamic activities as modifiable risk factors of PFP and these are currently a focus for rehabilitation.[44] Patients with PFP demonstrate altered joint movements compared to individuals without knee pain. Reduced knee flexion during dynamic activities is observed in individuals with PFP and it is also considered a risk factor for PFP development.[45] Frontal plane movement alteration is widely reported throughout various movement tasks such as squatting, stepping, and hopping. Increased knee abduction during step-down task is observed in males and females with PFP and the increased frontal projection angle is associated with pain level. Traditionally, hip musculature strengthening exercise was prescribed to treat the PFP symptom. Muscle strengthening was successful in reducing pain but was ineffective in altering movement pattern.[27] Feedback movement modification gained

attention in PFP rehabilitation; however, there is a lack of synthesized evidence which analyzed the efficacy of feedback motion retraining in individuals with PFP.

In Chapter 2, we established the overall efficacy of visual feedback motion retraining for individuals with PFP. In all included studies, eight sessions of short term (15-30 minutes) gait retraining with verbal feedback showed significant reduction in pain, improved PROs, with movement alterations. This suggests the usefulness of feedback movement retraining in individuals with PFP.

Diagnostic US is an useful imaging method to evaluate soft tissues. It is clinical-setting friendly since it is capable to provide real-time imaging at an affordable cost. Cartilage undergoing early OA changes may show reduced CSA, deformative characteristics, and altered EI. In quantitative analysis, we did not identify statistically significant cartilage deformative characteristics or EI between individuals with and without PFP. However, there were significant associations between percent change cartilage EI and PROs. This suggests the potential utility of PROs to detec early changes of cartilage health.

Moving from the quantitative assessment of femoral cartilage US measures, Chapter 4 focused on assessing the cartilage US image quality. Histological changes of cartilage surface due to cartilage fibrillation and hyalinization induces surface irregularity and it is shown in the loss of sharp margin in the US image. Thus, we compared US image quality between patients with and without PFP to understand if individuals with PFP shows worse image quality. In this chapter, we identified that patients with PFP had poorer quality cartilage images, which indicates they may be at risk of TFOA.

5.2 Limitations

Participants included in the US study were those who identified themselves as physically active. However, we could not match participants based on their major physical activity type due to the limited participant pool. Also, there was limitation in controlling the intensity between loading conditions. Varied participants' physical activity type and potentially having different level of loading onto the joint cartilage could have affected large variability in PROs and US measures.

An additional potential pitfall of this study design relates to US methodology. US image clarity can be affected by the thickness and composition of overlying tissues. Even though we matched participants based on BMI measures, US image sharpness could have varied since we did not utilize dual energy X-ray absorptiometry (DEXA) to more accurately describe body type. Therefore, it is possible healthy participants showing worsened image quality (Grade 2) due to thicker overlying tissues in the knee (Figure 4 and 5).

5.3 Future Directions

Although this project contributes to the knowledge base regarding the movement modifying intervention for individuals with PFP and their risk of development of OA, there is still much work to do. It is recommended that future studies to consider using the visual feedback motion retraining, included studies to synthesize the outcome used internal focus of attention (focus on the movement themselves), which is known to have restraints in acquiring complex motor skills. Thus, feedback intervention studies for individuals PFP should consider using external focus of attention (focus on the movement effect).

In order to reduce the effect of overlying tissue morphology on US image quality, accurate measures of participants' body composition should be measured in US-cartilage research. Thus, future studies should consider DEXA scan or hydrostatic weighing as their inclusion criteria and include those outcomes as covariate in the analysis.

5.4 Conclusion

My dissertation was the first investigation to establish US measures in patients with PFP. Specifically, cartilage CSA, EI, and image quality were measured using US. This approach aimed to determine if patients with PFP would demonstrate decreased cartilage CSA, altered EI, decreased deformative characteristics of cartilage, and worse image quality. We did not identify statistically significant baseline cartilage CSA difference nor deformative characteristics of volume and echo intensity between individuals with and without PFP. This indicates individuals with PFP are experiencing early stage of OA. Interestingly, there was a significant association between percent change of EI and PROs suggesting that PROs may be useful in surface morphological alteration over time. Our second US project identified worse cartilage image quality in patients with PFP. This strengthens the notion that individuals with PFP are showing signs of early TFOA. Since US imaging is inexpensive, accessible, and free from radiation concern, comprehensive US (quantitative and image quality grading) should be utilized in the evaluation of cartilage health in individuals with PFP.

REFERENCES

1. Crossley KM, Stefanik JJ, Selfe J, et al. 2016 Patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester. Part 1: Terminology, definitions, clinical examination, natural history, patellofemoral osteoarthritis and patient-reported outcome measures. *Br J Sports Med.* 2016;50(14):839-843.
2. Smith BE, Selfe J, Thacker D, et al. Incidence and prevalence of patellofemoral pain: A systematic review and meta-analysis. *PLoS One.* 2018;13(1):e0190892.
3. Glaviano NR, Kew M, Hart JM, Saliba S. DEMOGRAPHIC AND EPIDEMIOLOGICAL TRENDS IN PATELLOFEMORAL PAIN. *Int J Sports Phys Ther.* 2015;10(3):281-290.
4. Rathleff MS, Skuldbol SK, Rasch MN, Roos EM, Rasmussen S, Olesen JL. Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents. *BMC Musculoskelet Disord.* 2013;14:225.
5. Collins NJ, Bierma-Zeinstra SM, Crossley KM, van Linschoten RL, Vicenzino B, van Middelkoop M. Prognostic factors for patellofemoral pain: a multicentre observational analysis. *Br J Sports Med.* 2013;47(4):227-233.
6. Taunton JE, Ryan MB, Clement DB, McKenzie DC, Lloyd-Smith DR, Zumbo BD. A retrospective case-control analysis of 2002 running injuries. *Br J Sports Med.* 2002;36(2):95-101.
7. Lankhorst NE, van Middelkoop M, Crossley KM, et al. Factors that predict a poor outcome 5-8 years after the diagnosis of patellofemoral pain: a multicentre observational analysis. *Br J Sports Med.* 2016;50(14):881-886.
8. Utting MR, Davies G, Newman JH. Is anterior knee pain a predisposing factor to patellofemoral osteoarthritis? *The Knee.* 2005;12(5):362-365.
9. Thomas MJ, Wood L, Selfe J, Peat G. Anterior knee pain in younger adults as a precursor to subsequent patellofemoral osteoarthritis: a systematic review. *BMC Musculoskelet Disord.* 2010;11:201.
10. Crossley KM. Is patellofemoral osteoarthritis a common sequela of patellofemoral pain? *Br J Sports Med.* 2014;48(6):409-410.
11. Kannus PA. Long patellar tendon: radiographic sign of patellofemoral pain syndrome--a prospective study. *Radiology.* 1992;185(3):859-863.
12. Pal S, Besier TF, Beaupre GS, Fredericson M, Delp SL, Gold GE. Patellar maltracking is prevalent among patellofemoral pain subjects with patella alta: an upright, weightbearing MRI study. *J Orthop Res.* 2013;31(3):448-457.
13. Powers CM. The influence of altered lower-extremity kinematics on patellofemoral joint dysfunction: a theoretical perspective. *J Orthop Sports Phys Ther.* 2003;33(11):639-646.
14. Nakagawa TH, ET. M, CD. M, FV. S. Trunk, Pelvis, Hip, and Knee Kinematics, Hip Strength, and Gluteal Muscle Activation During a Single-Leg Squat in Males and Females With and Without Patellofemoral Pain Syndrome. *J Orthop Sports Phys Ther.* 2012;42(6):491-501.
15. Witvrouw E, Lysens R, Bellemans J, Cambier D, Vanderstraeten G. Intrinsic risk factors for the development of anterior knee pain in an athletic population. A two-year prospective study. *Am J Sports Med.* 2000;28(4):480-489.

16. Holden S, Boreham C, Doherty C, Delahunt E. Two-dimensional knee valgus displacement as a predictor of patellofemoral pain in adolescent females. *Scand J Med Sci Sports.* 2017;27(2):188-194.
17. Powers CM. The influence of abnormal hip mechanics on knee injury: a biomechanical perspective. *J Orthop Sports Phys Ther.* 2010;40(2):42-51.
18. Nakagawa TH, Moriya ET, Maciel CD, Serrao AF. Frontal plane biomechanics in males and females with and without patellofemoral pain. *Med Sci Sports Exerc.* 2012;44(9):1747-1755.
19. Boling M, Padua D. Relationship between hip strength and trunk, hip, and knee kinematics during a jump-landing task in individuals with patellofemoral pain. *International journal of sports physical therapy.* 2013;8(5):661-669.
20. Hungerford DS, Barry M. Biomechanics of the patellofemoral joint. *Clin Orthop Relat Res.* 1979(144):9-15.
21. Flynn TW, Soutas-Little RW. Patellofemoral joint compressive forces in forward and backward running. *J Orthop Sports Phys Ther.* 1995;21(5):277-282.
22. Saper MG, Shneider DA. Diagnosis and Treatment of Lateral Patellar Compression Syndrome. 2014;3(5):e633-e638.
23. Powers CM, Landel R, Perry J. Timing and intensity of vastus muscle activity during functional activities in subjects with and without patellofemoral pain. *Phys Ther.* 1996;76(9):946-955; discussion 956-967.
24. Waiteman MC, Briani RV, Pazzinatto MF, et al. Relationship between knee abduction moment with patellofemoral joint reaction force, stress and self-reported pain during stair descent in women with patellofemoral pain. *Clinical Biomechanics.* 2018;59:110-116.
25. Collins NJ, Barton CJ, van Middelkoop M, Callaghan MJ, Rathleff MS, Vicenzino BT. 2018 Consensus statement on exercise therapy and physical interventions (orthoses, taping and manual therapy) to treat patellofemoral pain: recommendations from the 5th International Patellofemoral Pain Research Retreat, Gold Coast, Australia, 2017. 2018;52(18):1170-1178.
26. Barton CJ, Lack S, Hemmings S, Tufail S, Morrissey D. The 'Best Practice Guide to Conservative Management of Patellofemoral Pain': incorporating level 1 evidence with expert clinical reasoning. *Br J Sports Med.* 2015;49(14):923-934.
27. Thomson C, Krouwel O, Kuisma R, Hebron C. The outcome of hip exercise in patellofemoral pain: A systematic review. *Man Ther.* 2016;26:1-30.
28. Roper JL, Harding EM, Doerfler D, et al. The effects of gait retraining in runners with patellofemoral pain: A randomized trial. *Clin Biomech (Bristol, Avon).* 2016;35:14-22.
29. Willy RW, Scholz JP, Davis IS. Mirror gait retraining for the treatment of patellofemoral pain in female runners. *Clin Biomech (Bristol, Avon).* 2012;27(10):1045-1051.
30. Noehren B, Scholz J, Davis I. The effect of real-time gait retraining on hip kinematics, pain and function in subjects with patellofemoral pain syndrome. *Br J Sports Med.* 2011;45(9):691-696.
31. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med.* 2000;133(8):635-646.

32. Duncan R, Peat G, Thomas E, Wood L, Hay E, Croft P. Does isolated patellofemoral osteoarthritis matter? *Osteoarthritis Cartilage.* 2009;17(9):1151-1155.
33. Salsich GB, Perman WH. Tibiofemoral and patellofemoral mechanics are altered at small knee flexion angles in people with patellofemoral pain. *J Sci Med Sport.* 2013;16(1):13-17.
34. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis.* 1957;16(4):494-502.
35. Duncan RC, Hay EM, Saklatvala J, Croft PR. Prevalence of radiographic osteoarthritis--it all depends on your point of view. *Rheumatology (Oxford).* 2006;45(6):757-760.
36. Farrokhi S, Colletti PM, Powers CM. Differences in patellar cartilage thickness, transverse relaxation time, and deformational behavior: a comparison of young women with and without patellofemoral pain. *Am J Sports Med.* 2011;39(2):384-391.
37. Coupal TM, Munk PL, Ouellette HA, Al-Shikarchy H, Mallinson PI, Choudur H. Popping the cap: the constellation of MRI findings in patellofemoral syndrome. *The British Journal of Radiology.* 2018:20170770.
38. Ostergaard M, Court-Payen M, Gideon P, et al. Ultrasonography in arthritis of the knee. A comparison with MR imaging. *Acta Radiol.* 1995;36(1):19-26.
39. Harkey MS, Blackburn JT, Davis H, Sierra-Arevalo L, Nissman D, Pietrosimone B. Ultrasonographic assessment of medial femoral cartilage deformation acutely following walking and running. *Osteoarthritis Cartilage.* 2017;25(6):907-913.
40. Möller I, Bong D, Naredo E, et al. Ultrasound in the study and monitoring of osteoarthritis. *Osteoarthritis Cartilage.* 2008;16 Suppl 3:S4-7.
41. Kuroki H, Nakagawa Y, Mori K, et al. Ultrasound properties of articular cartilage in the tibio-femoral joint in knee osteoarthritis: relation to clinical assessment (International Cartilage Repair Society grade). *Arthritis Res Ther.* 2008;10(4):R78.
42. Lee CL, Huang MH, Chai CY, Chen CH, Su JY, Tien YC. The validity of in vivo ultrasonographic grading of osteoarthritic femoral condylar cartilage: a comparison with in vitro ultrasonographic and histologic gradings. *Osteoarthritis Cartilage.* 2008;16(3):352-358.
43. Duncan R, Peat G, Thomas E, Hay EM, Croft P. Incidence, progression and sequence of development of radiographic knee osteoarthritis in a symptomatic population. *Ann Rheum Dis.* 2011;70(11):1944-1948.
44. Powers CM, Witvrouw E, Davis IS, Crossley KM. Evidence-based framework for a pathomechanical model of patellofemoral pain: 2017 patellofemoral pain consensus statement from the 4th International Patellofemoral Pain Research Retreat, Manchester, UK: part 3. *Br J Sports Med.* 2017;51(24):1713-1723.
45. Boling MC, Padua DA, Marshall SW, Guskiewicz K, Pyne S, Beutler A. A prospective investigation of biomechanical risk factors for patellofemoral pain syndrome: the Joint Undertaking to Monitor and Prevent ACL Injury (JUMP-ACL) cohort. *Am J Sports Med.* 2009;37(11):2108-2116.

46. Holden S, Boreham C, Doherty C, Delahunt E. Two-dimensional knee valgus displacement as a predictor of patellofemoral pain in adolescent females. *Scandinavian journal of medicine & science in sports.* 2017;27(2):188-194.
47. Willy RW, Davis IS. Varied response to mirror gait retraining of gluteus medius control, hip kinematics, pain, and function in 2 female runners with patellofemoral pain. *J Orthop Sports Phys Ther.* 2013;43(12):864-874.
48. Weakley J, Wilson K, Till K, et al. Show Me, Tell Me, Encourage Me: The Effect of Different Forms of Feedback on Resistance Training Performance. *J Strength Cond Res.* 2018.
49. Pietrosimone B, Thomas AC, Saliba SA, Ingersoll CD. Association between quadriceps strength and self-reported physical activity in people with knee osteoarthritis. *International journal of sports physical therapy.* 2014;9(3):320-328.
50. Dolak KL, Silkman C, Medina McKeon J, Hosey RG, Lattermann C, Uhl TL. Hip strengthening prior to functional exercises reduces pain sooner than quadriceps strengthening in females with patellofemoral pain syndrome: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2011;41(8):560-570.
51. Ferber R, Kendall KD, Farr L. Changes in knee biomechanics after a hip-abductor strengthening protocol for runners with patellofemoral pain syndrome. *Journal of athletic training.* 2011;46(2):142-149.
52. Ferber R, Bolgla L, Earl-Boehm JE, Emery C, Hamstra-Wright K. Strengthening of the hip and core versus knee muscles for the treatment of patellofemoral pain: a multicenter randomized controlled trial. *Journal of athletic training.* 2015;50(4):366-377.
53. Eckstein F, Collins JE, Nevitt MC, et al. Brief Report: Cartilage Thickness Change as an Imaging Biomarker of Knee Osteoarthritis Progression: Data From the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. *Arthritis & rheumatology (Hoboken, NJ).* 2015;67(12):3184-3189.
54. Munro A, Herrington L, Comfort P. The Relationship Between 2-Dimensional Knee-Valgus Angles During Single-Leg Squat, Single-Leg-Land, and Drop-Jump Screening Tests. *Journal of sport rehabilitation.* 2017;26(1):72-77.
55. Neal BS, Barton CJ, Gallie R, O'Halloran P, Morrissey D. Runners with patellofemoral pain have altered biomechanics which targeted interventions can modify: A systematic review and meta-analysis. *Gait & posture.* 2016;45:69-82.
56. Bazett-Jones DM, Huddleston W, Cobb S, O'Connor K, Earl-Boehm JE. Acute Responses of Strength and Running Mechanics to Increasing and Decreasing Pain in Patients With Patellofemoral Pain. *Journal of athletic training.* 2017;52(5):411-421.
57. Bolgla LA, Malone TR, Umberger BR, Uhl TL. Hip strength and hip and knee kinematics during stair descent in females with and without patellofemoral pain syndrome. *J Orthop Sports Phys Ther.* 2008;38(1):12-18.
58. Bley AS, Correa JC, Dos Reis AC, Rabelo ND, Marchetti PH, Lucareli PR. Propulsion phase of the single leg triple hop test in women with patellofemoral pain syndrome: a biomechanical study. *PLoS One.* 2014;9(5):e97606.

59. Ireland ML, Willson JD, Ballantyne BT, Davis IM. Hip strength in females with and without patellofemoral pain. *J Orthop Sports Phys Ther.* 2003;33(11):671-676.
60. Suresh K. An overview of randomization techniques: An unbiased assessment of outcome in clinical research. *J Hum Reprod Sci.* 2011;4(1):8-11.
61. Ericksen HM, Thomas AC, Gribble PA, Armstrong C, Rice M, Pietrosimone B. Jump-landing biomechanics following a 4-week real-time feedback intervention and retention. *Clin Biomech (Bristol, Avon).* 2016;32:85-91.
62. Sinclair J, Janssen J, Richards JD, Butters B, Taylor PJ, Hobbs SJ. Effects of a 4-week intervention using semi-custom insoles on perceived pain and patellofemoral loading in targeted subgroups of recreational runners with patellofemoral pain. *Phys Ther Sport.* 2018;34:21-27.
63. Tuna S, Balci N, Ozcakar L. The relationship between femoral cartilage thickness and muscle strength in knee osteoarthritis. *Clin Rheumatol.* 2016;35(8):2073-2077.
64. Thomas AC, Villwock M, Wojtys EM, Palmieri-Smith RM. Lower extremity muscle strength after anterior cruciate ligament injury and reconstruction. *Journal of athletic training.* 2013;48(5):610-620.
65. Kujala UM, Jaakkola LH, Koskinen SK, Taimela S, Hurme M, Nelimarkka O. Scoring of patellofemoral disorders. *Arthroscopy.* 1993;9(2):159-163.
66. Ittenbach RF, Huang G, Barber Foss KD, Hewett TE, Myer GD. Reliability and Validity of the Anterior Knee Pain Scale: Applications for Use as an Epidemiologic Screener. *PLoS One.* 2016;11(7):e0159204.
67. Watson CJ, Propps M, Ratner J, Zeigler DL, Horton P, Smith SS. Reliability and responsiveness of the lower extremity functional scale and the anterior knee pain scale in patients with anterior knee pain. *J Orthop Sports Phys Ther.* 2005;35(3):136-146.
68. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.
69. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EM. Measures of knee function: International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form, Knee Injury and Osteoarthritis Outcome Score (KOOS), Knee Injury and Osteoarthritis Outcome Score Physical Function Short Form (KOOS-PS), Knee Outcome Survey Activities of Daily Living Scale (KOS-ADL), Lysholm Knee Scoring Scale, Oxford Knee Score (OKS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Activity Rating Scale (ARS), and Tegner Activity Score (TAS). *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S208-228.
70. Crossley KM, Macri EM, Cowan SM, Collins NJ, Roos EM. The patellofemoral pain and osteoarthritis subscale of the KOOS (KOOS-PF): development and validation using the COSMIN checklist. *Br J Sports Med.* 2018;52(17):1130-1136.
71. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-

MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S240-252.

72. Crossley KM, Bennell KL, Cowan SM, Green S. Analysis of outcome measures for persons with patellofemoral pain: which are reliable and valid? *Arch Phys Med Rehabil.* 2004;85(5):815-822.
73. Thomas AC, McLean SG, Palmieri-Smith RM. Quadriceps and hamstrings fatigue alters hip and knee mechanics. *J Appl Biomech.* 2010;26(2):159-170.
74. Thomas AC, Lepley LK, Wojtys EM, McLean SG, Palmieri-Smith RM. Effects of Neuromuscular Fatigue on Quadriceps Strength and Activation and Knee Biomechanics in Individuals Post-Anterior Cruciate Ligament Reconstruction and Healthy Adults. *J Orthop Sports Phys Ther.* 2015;45(12):1042-1050.
75. Thomas AC, Palmieri-Smith RM, McLean SG. Isolated hip and ankle fatigue are unlikely risk factors for anterior cruciate ligament injury. *Scand J Med Sci Sports.* 2011;21(3):359-368.
76. Glasoe WM, Pena FA, Phadke V. Cardan angle rotation sequence effects on first-metatarsophalangeal joint kinematics: implications for measuring hallux valgus deformity. *Journal of foot and ankle research.* 2014;7:29.
77. Grood ES, Suntay WJ. A joint coordinate system for the clinical description of three-dimensional motions: application to the knee. *J Biomech Eng.* 1983;105(2):136-144.
78. Wu G, Siegler S, Allard P, et al. ISB recommendation on definitions of joint coordinate system of various joints for the reporting of human joint motion--part I: ankle, hip, and spine. International Society of Biomechanics. *J Biomech.* 2002;35(4):543-548.
79. McLean SG, Fellin RE, Suedekum N, Calabrese G, Passerallo A, Joy S. Impact of fatigue on gender-based high-risk landing strategies. *Med Sci Sports Exerc.* 2007;39(3):502-514.
80. Bresler B, P. FJ. The forces and moments in the leg during level walking. *Trans Am Soc mech Engrs.* 1950;72:27-36.
81. Dempster WT, Gabel WC, Felts WJ. The anthropometry of the manual work space for the seated subject. *Am J Phys Anthropol.* 1959;17(4):289-317.
82. Olbrantz C, Bergelin J, Asmus J, Kernozek T, Rutherford D, Gheidi N. Effect of Posttrial Visual Feedback and Fatigue During Drop Landings on Patellofemoral Joint Stress in Healthy Female Adults. *J Appl Biomech.* 2018;34(1):82-87.
83. Crossley K, Bennell K, Green S, Cowan S, McConnell J. Physical therapy for patellofemoral pain: a randomized, double-blinded, placebo-controlled trial. *Am J Sports Med.* 2002;30(6):857-865.
84. Winstein CJ, Schmidt RA. Reduced frequency of knowledge of results enhances motor skill learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition Journal of Experimental Psychology: Learning, Memory, and Cognition.* 1990;16(4):677-691.
85. Khayambashi K, Mohammadkhani Z, Ghaznavi K, Lyle MA, Powers CM. The effects of isolated hip abductor and external rotator muscle strengthening on pain, health status, and hip strength in females with patellofemoral pain: a randomized controlled trial. *J Orthop Sports Phys Ther.* 2012;42(1):22-29.

86. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2013.
87. Souza RB, Powers CM. Differences in hip kinematics, muscle strength, and muscle activation between subjects with and without patellofemoral pain. *J Orthop Sports Phys Ther.* 2009;39(1):12-19.
88. Lankhorst NE, Bierma-Zeinstra SM, van Middelkoop M. Risk factors for patellofemoral pain syndrome: a systematic review. *J Orthop Sports Phys Ther.* 2012;42(2):81-94.
89. Riel H, Matthews M, Vicenzino B, Bandholm T, Thorborg K, Rathleff MS. Feedback Leads to Better Exercise Quality in Adolescents with Patellofemoral Pain. *Med Sci Sports Exerc.* 2018;50(1):28-35.
90. Hamilton RT, Shultz SJ, Schmitz RJ, Perrin DH. Triple-hop distance as a valid predictor of lower limb strength and power. *Journal of athletic training.* 2008;43(2):144-151.
91. Earl JE, Hoch AZ. A proximal strengthening program improves pain, function, and biomechanics in women with patellofemoral pain syndrome. *Am J Sports Med.* 2011;39(1):154-163.
92. Boling M, Padua D, Marshall S, Guskiewicz K, Pyne S, Beutler A. Gender differences in the incidence and prevalence of patellofemoral pain syndrome. *Scand J Med Sci Sports.* 2010;20(5):725-730.
93. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. *Clin Orthop Relat Res.* 1985(198):43-49.
94. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes.* 2003;1:64.

APPENDIX A: RELIABILITY ASSESSMENT FOR ULTRASOUND IMAGE GRADING

Table 9. Weighted-Kappa analysis

	Kappa	Asymptotic standard error	Z	p	95% CI
Within assessor	0.86	0.07	4.39	<0.001	0.73-0.99
Between assessor	0.82	0.07	4.43	<0.001	0.67-0.96

Alternative Approach to Weighted-Kappa Analysis

As an alternative approach to the weighted-kappa, we conducted a Bland Altman analysis and have included the plots below. Both the agreement between investigators and the agreement between sessions (intra-rater) is consistent with the weighted-kappa analysis demonstrating no outliers influencing our data interpretation and all data points lying within the limits of agreement.

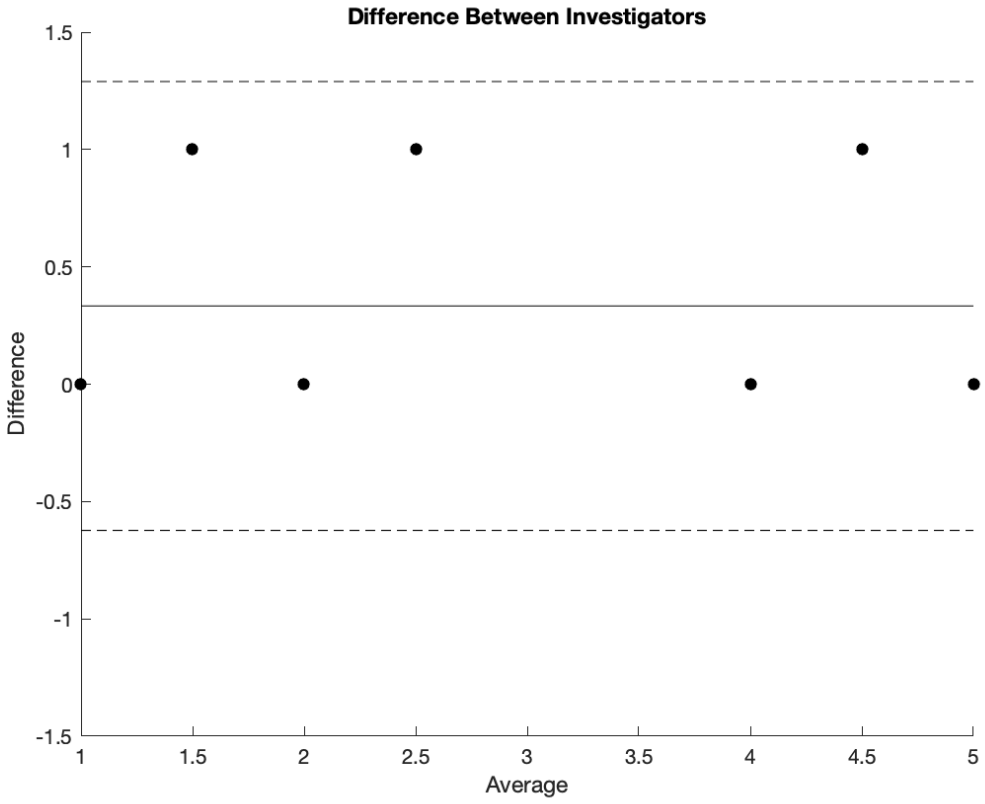


Figure A.1 Bland Altman plot between investigators

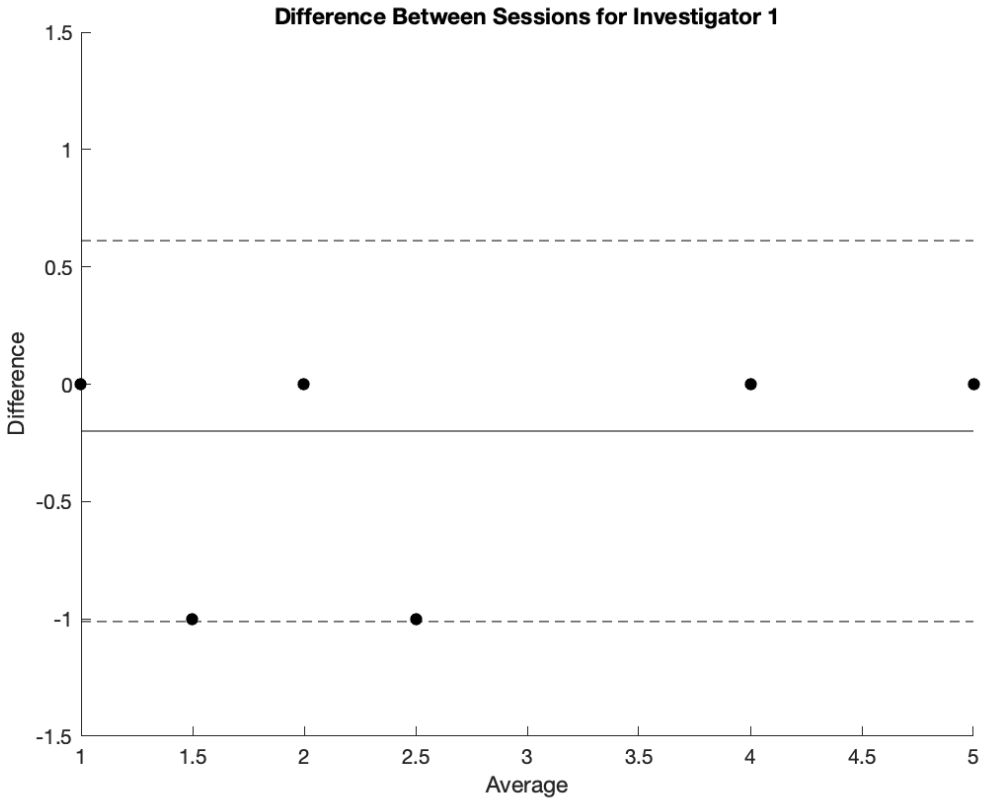


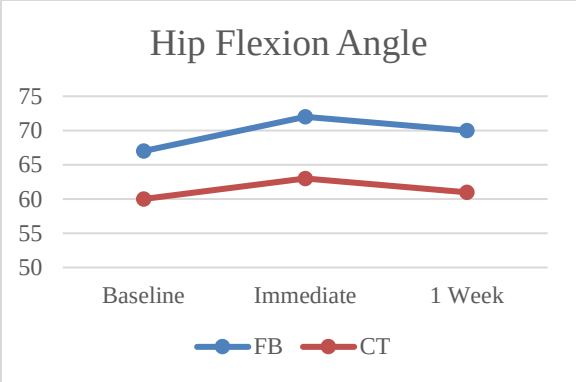
Figure A.2 Bland Altman plot within investigator 1

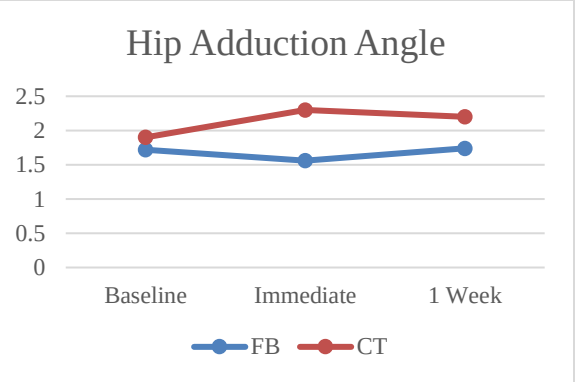
APPENDIX B: EFFECT OF FEEDBACK INCORPORATED HIP STRENGTHENING EXERCISES IN PATIENTS WITH PATELLOFEMORAL PAIN

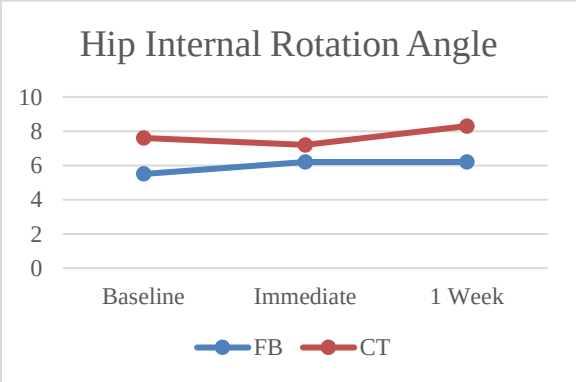
I anticipated recruiting 60 participants with PFP to be randomized into three intervention groups and one control group (Strengthening exercise+Feedback motion retraining: STFB; Strengthening exercise only: ST; Feedback motion retraining only: FB; Control group: CT). However, due to the COVID-19 pandemic, our study had to be stopped. At the time of the COVID-19 shutdown, I had enrolled 20 participants but only 4 finished the intervention and all others did only baseline tests.

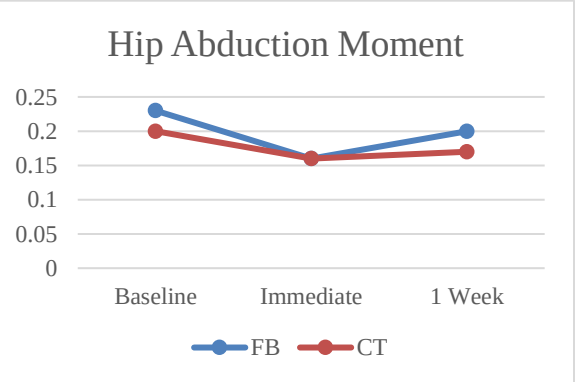
We could not run statistical analysis for movement outcome variables due to the limited sample size; however, we included information in this appendix to understand the trend of changes in movement patterns. In the graphs located on the next page, we included FB participant and CT participant. We did not have a full data set on any STFB participants. When we compare FB and CT participants, we identified differing trends in the hip adduction angle, hip external rotation moment, knee flexion angle, knee abduction angle, and knee abduction moment. Hip adduction angle and hip external rotation moment decreased after feedback motion retraining in the FB group participant when compared to CT group participant who showed increased angle and moment. Knee flexion angle increased while knee abduction angle and knee abduction moment decreased in FB group participant while CT group participant stayed the same.

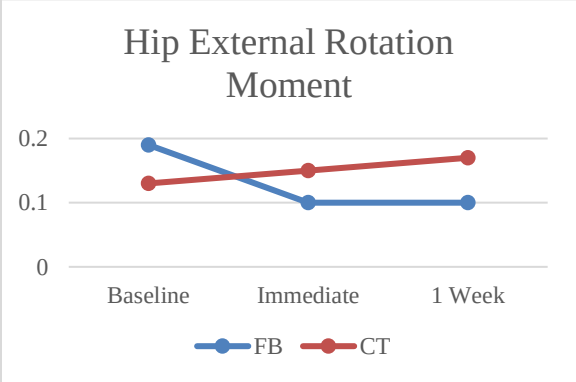
This outcome indicates the FB protocol utilized in this study was able to modify movement pattern, potentially having positive effect when carried forward to the STFB protocol. Thus, STFB protocol will be examined in the future.

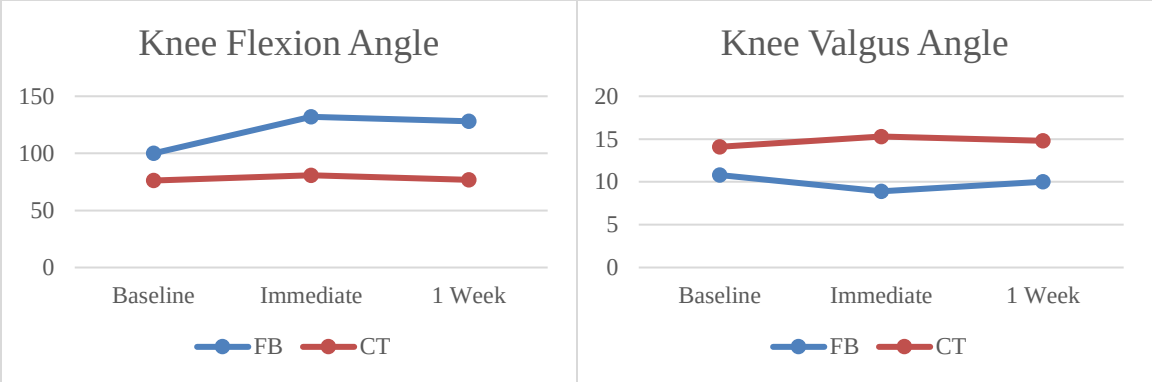

Hip Flexion Angle
75
70
65
60
55
50
Baseline
Immediate
1 Week
FB
CT


Hip Adduction Angle
2.5
2
1.5
1
0.5
0
Baseline
Immediate
1 Week
FB
CT

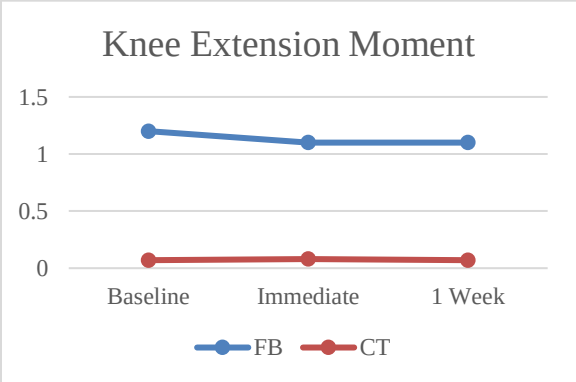

Hip Internal Rotation Angle
10
8
6
4
2
0
Baseline
Immediate
1 Week
FB
CT

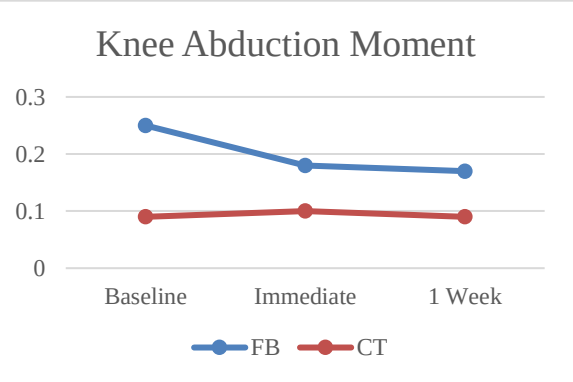

Hip Abduction Moment
0.25
0.2
0.15
0.1
0.05
0
Baseline
Immediate
1 Week
FB
CT


Hip External Rotation Moment
0.2
0.1
0
Baseline
Immediate
1 Week
FB
CT


Knee Flexion Angle
150
100
50
0
Baseline
Immediate
1 Week
FB
CT

Knee Valgus Angle
20
15
10
5
0
Baseline
Immediate
1 Week
FB
CT


Knee Extension Moment
1.5
1
0.5
0
Baseline
Immediate
1 Week
FB
CT


Knee Abduction Moment
0.3
0.2
0.1
0
Baseline
Immediate
1 Week
FB
CT

APPENDIX C: NATIONAL ATHLETIC TRAINERS' ASSOCIATION RESEARCH AND EDUCATION FOUNDATION DOCTORAL RESEARCH GRANT

ABSTRACT

Hip strengthening exercises (ST) and feedback (FB) gait retraining effectively alleviate patellofemoral pain (PFP) and improve function short-term. However, failure of conventional treatments to improve biomechanics and symptoms long-term leads to breakdown of patellofemoral cartilage and contributes to patellofemoral osteoarthritis. This investigation will determine if incorporating FB into strength training (STFB) superiorly improves laboratory, clinical, and patient-reported outcomes (PROs) compared to conventional treatments (FB, ST, and control) in patients with PFP. Laboratory (ultrasonographic femoral cartilage thickness and echo intensity; 3D biomechanics during drop vertical jump, stair ascent/descent, running), clinical (strength and single-leg triple hop test), and PROs (global and region-specific questionnaires) will be assessed before and immediately and 1-week following a 2-week intervention. PROs will be further analyzed 2- and 4-weeks post-intervention. Group differences in laboratory and clinical outcomes will be assessed via separate 4x3 repeated measures ANOVAs while 4x5 repeated measures ANOVAs will be used for PROs. We hypothesize the STFB group will demonstrate: 1) greater reductions in hip adduction and internal rotation and superior femoral cartilage health; 2) greater improvements in hip and thigh muscle strength with concurrent increases in hop distance; and 3) reduced symptoms and improved PROs at all post-intervention time points compared to conventional treatment.

BUDGET

Budget Item	**Cost**
A) Salaries	N/A
B) Equipment	$105
C) Supplies	$70
D) Animal or Subject Costs	$2,325
E) Other	N/A
Total	$2,500

Budget Justification

A. Salaries

No funds needed to pay salary, or provide for data management and analysis for this project.

B. Equipment

Funds are being requested to purchase 3 rolls each of yellow and red Theraband for the strength training + feedback and the strength training groups to use during the intervention sessions. The yellow Theraband is $17/roll ($51 total), while the red Theraband is $18/roll ($54 total), making the total cost for Therband $105.

C. Expendable Supplies

Monies are being requested to purchase two 5L containers of ultrasound gel to assist with the ultrasound imaging that will be completed on participants. Each container is priced at $35 for a total of $70.

D. Participant incentives

Participants in the 3 intervention groups (strength training + feedback, feedback, strength training) will each receive $20 for completing all testing sessions. These participants will also receive $25 as compensation for their time to complete the intervention sessions. Therefore, each participant in the intervention groups will receive $45. There are 3

intervention groups, each with 15 participants for a total of 45 intervention participants (45 people x $45 = $2,025).

Participants in the control group will receive $20 to compensate them for their time while completing the testing sessions. There will be 15 people in the control group. Therefore, we are requesting $300 to pay these individuals (15 x $20 = $300).

The total amount requested to pay participants across all groups in the study is $2,325. All payments will be made at the conclusion of the final testing session and final intervention session. This payment amount is in line with other investigations in our department.

E. Other

No funds requested in this category.

INSTITUTIONAL RESOURCES AND ENVIRONMENT

Laboratory

All data collection will take place in the Biodynamics Research Lab housed within Belk Gym at UNC Charlotte. The equipment within this laboratory includes: standard treadmill, 10 camera (Vantage 5) Vicon motion capture system, 2 Bertec force platforms (FP4060-10-2000), a Biodex System 3 Pro isokinetic dynamometer and associated attachments, LOGIQe Ultrasoundsystem, and a hand-held dynamometer. Additional equipment housed within this research space includes: Pedar plantar pressure system, AMTI force platform, BIOPAC MP150 system with 8 channels of EMG, Magstim Rapid2 transcranial magnetic stimulator, Digitimer DS7AH stimulator, Delsys Trigno 8 channel wireless EMG system, and 40-channel NuAmps EEG acquisition system.

Data management and processing will occur within the Biodynamics laboratory. For data analysis, MatLab, Vicon Nexus, Visual3D, and Microsoft Office will be used. Lastly, SPSS will be used for all statistical procedures.

Support Services

The Biodynamics laboratory has access to academic technology services within its parent College of Health and Human Services at the University should any issues arise.

Personnel

Abbey Thomas, PhD, ATC is the principal investigator's PhD advisor. Dr. Thomas will oversee all areas of this project, primarily assisting with data analysis and interpretation of findings and manuscript preparation/publication.

Luke Donovan, PhD, ATC is a member of the PI's dissertation committee. Dr. Donovan will assist with participant randomization, data analysis, and interpretation.

PURPOSE

Increased knee joint discomfort and movement alteration are observed in persons with patellofemoral pain (PFP), a condition that affects 22.7% of the United States population.[2] Patients with PFP experience pain aggravation during or after physical activities and decreased function. Moreover, prolonged symptoms of PFP may contribute to the development of patellofemoral osteoarthritis (PFOA), making this a lifelong condition for many patients. Abnormal biomechanics, specifically dynamic knee valgus—a combination of increased hip adduction and internal rotation—during weight bearing movements, are considered a modifiable cause of PFP.[17,46] Previous researchers found patients with PFP demonstrate increased hip adduction and internal rotation during daily movements[18] and this was found to have a correlation with hip abductor and external rotator muscle

weakness.[19] Thus, weakness in these muscles may contribute to dynamic knee valgus and PFP.

Various treatments for PFP exist to alleviate pain and improve function. The current evidence supports the effectiveness of lower extremity musculature strengthening exercises and movement modification in managing knee joint pain and improving function. However, current strength training interventions do not improve biomechanics. A recent series of investigations on gait retraining suggest that feedback of faulty biomechanics is necessary to improve biomechanics in the long term.[28-30,47] Building on this, recent evidence suggests that strengthening exercises performed with feedback yield greater strength gains than when no feedback is given.[48] **Improving delivery of current rehabilitation and biomechanical interventions through the use of feedback can reduce symptoms and improve function for hundreds of thousands of people with PFP.**

If not effectively managed, PFP can lead to PFOA, which is caused by breakdown of the retropatellar cartilage. Despite improvements in strength and biomechanics following rehabilitation, PFOA continues to develop, suggesting that **conventional rehabilitation does not adequately protect the patellofemoral cartilage. Therefore, we need interventions that optimize cartilage health to slow PFOA development.**

Being able to assess cartilage health as a result of exercise will lend important insight into how current rehabilitative efforts influence PFOA development. This knowledge will inform future investigations to more appropriately treat PFP and PFOA. An emerging technique to evaluate cartilage is diagnostic ultrasound (US) which can provide a real-time image of how cartilage responds to physical activity. Hyaline cartilage holds water in

unloaded conditions and this water is drained out when load is applied to the joint. Therefore, cartilage thickness should reduce after physical activities. Both cartilage thickness and echo intensity, an estimation of water content present,[39] can provide immediate knowledge of cartilage health during rehabilitation to allow clinicians to better protect cartilaginous integrity and mitigate symptoms, allowing for more efficacious rehabilitation.

The proposed investigation will determine the efficacy of rehabilitation with feedback compared to traditional rehabilitation at improving laboratory measures of biomechanics and cartilage health, clinical measures of functional performance, and patient-reported outcomes (PROs) via a randomized controlled study of 60 adults with PFP. Participants will complete 2 weeks of training (3x/week). Participants will be randomized into the following groups: strength training + feedback (STFB), strength training only (ST), feedback gait retraining (FB), or no intervention (control [CT]). Outcomes will be evaluated pre- and immediately and 1-week post-intervention. To better characterize patient outcomes, PROs will also be assessed 2- and 4-weeks post-intervention.

Specific Aim 1: **To determine if STFB superiorly improves immediate and short-term (1-week) follow-up of laboratory-based outcomes compared to standard of care (ST, FB, or CT) in patients with PFP.** Previous investigations suggest STFB yields greater improvements in strength than when using ST alone. As muscles control joint motion, greater improvements in strength should superiorly improve biomechanics. Therefore, we hypothesize that the STFB group will demonstrate greater reductions in hip adduction and internal rotation during drop vertical jump (DVJ), stair ascent/descent, and running compared to all other groups and these changes will be maintained 1-week

following the intervention. Further, because of these biomechanical improvements, the STFB group will demonstrate better cartilage health (increased thickness and cross-sectional area [CSA] and reduced echo intensity) compared to all other groups immediately and 1-week post-intervention.

Specific Aim 2: **To determine if STFB superiorly improves immediate and short-term follow-up of clinical outcomes compared to standard of care in patients with PFP.** Previous research suggests STFB exercises will yield greater strength gains compared to conventional ST; thus, we hypothesize muscle strength (isokinetic knee extension/flexion and isometric hip abduction/external rotation) will improve in the STFB group compared to all others at all time points. Further, lower extremity muscle strength is highly, positively associated with single leg triple hop test (SLTHT) distance. Therefore, we hypothesize that the STFB group will demonstrate greater improvements in SLTHT distance compared to all other groups and these changes will be maintained 1-week following the intervention.

Specific Aim 3: **To determine if STFB superiorly improves patient-reported outcomes compared to standard of care in patients with PFP.** Previous studies which provided ST exercises to patients with PFP patients showed improvements in PROs and reduction of joint pain. Another study supports greater strength gain through STFB will yield greater improvement in PROs.[49] Therefore, we hypothesize that STFB group will show greater improvement in Anterior Knee Pain Scale (AKPS), Knee Injury and Osteoarthritis Outcomes Score (KOOS), KOOS Patellofemoral (KOOS-PF) and pain reduction in visual analog scale (VAS) compared to all other groups immediately after intervention and 2- and 4-weeks post-intervention.

RATIONALE

Feedback is necessary to change biomechanics to restore joint loading and improve cartilage health in patients with PFP. Exercise is the standard of care treatment for patients with PFP. While strength training and biomechanical interventions independently improve PROs in patients with PFP,[50-52,27] improved PROs do not associate with improvements in cartilage health. Improving symptoms is an important goal of rehabilitation. However, failure to effectively manage PFP prolongs the painful experience and allows for propagation of the faulty mechanics that contribute to PFOA development. While previous studies suggest that using feedback of biomechanics can effectively change movement patterns and reduce pain up to 1[28,30] and 3 months[29] after the intervention, it is unknown how these interventions influence cartilage health. **Being able to assess cartilage's response to exercise will improve the ability to appropriately treat PFP and mitigate PFOA risk.**

Diagnostic ultrasound is a valid technique for evaluating cartilage health. The standard for diagnosing osteoarthritis is plain radiography; however, degenerative changes likely occur in the articular cartilage before radiographic evidence of OA can be observed. Magnetic resonance imaging (MRI) has also been used previously to observe cartilage health in patients with OA and PFP. Farrokhi et al., for example, used MRI on patients with PFP and healthy controls finding 14% less cartilage thickness in individuals with PFP at baseline.[36] Additionally, individuals with PFP exhibited greater femoral cartilage deformation after a single session of weighted deep knee bends.[36] A longitudinal study showed a significant association between cartilage thickness change and pain, which emphasizes the importance of frequent observation of cartilage thickness measures.[53]

Despite these findings, MRI has not been widely adopted clinically because of its high cost. **Diagnostic ultrasound provides a valid[38] and cheaper alternative to MRI.** In fact, investigators have been able to observe short term changes in cartilage thickness after a variety of physical activities in healthy adults, finding a significantly decreased thickness after 30 minutes of walking or running compared to a control condition.[39] Despite the benefits of diagnostic ultrasound over plain radiography and MRI, to our knowledge, no study has measured the effect of STFB on cartilage health compared to other forms of conventional interventions.

Preliminary data suggest immediate differences in cartilage deformation location between individuals with and without PFP following traditional rehabilitation exercises. A preliminary study compared the impact of different forms of physical activities on pain level and ultrasonographic femoral cartilage thickness in patients with PFP compared to healthy adults. Participants completed 30 minutes of treadmill running, lower extremity strengthening exercises and plyometric exercises. One activity was performed per session with each session separated by 1 week. Pain level and cartilage thickness were assessed before and after each intervention. There were significant group differences observed in pain level change (Figure 1a) and percent cartilage thickness change (Figure 1b) measures. Pain level increased in patients with PFP after all physical

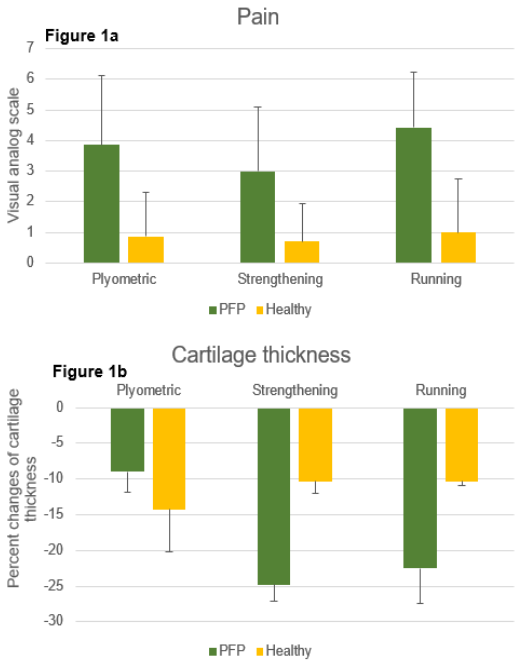


Figure 1. Pain level change (1a). Percent cartilage thickness change (1b).

activities and greater cartilage thickness reduction was observed in patients with PFP after strengthening exercises (p=0.001) and running (p=0.014). **Not only do these data support the utilization of ultrasound in assessing patellofemoral joint health, they suggest that patients with PFP experience greater deformation of femoral cartilage after strengthening exercises and running compared to healthy individuals, which may impact progression from PFP to PFOA.**

EXPERIMENTAL DESIGN AND METHODS

This study will use a randomized controlled trial research design. Our independent variables are group (STFB, ST, FB, and CT) and time (baseline, post-intervention, and 1-week follow up). Laboratory-based dependent variables will include lower extremity biomechanics (hip adduction, hip internal rotation, and knee flexion angles) during DVJ,[45,54] running[55,56] and stair ascent/descent[57] and femoral cartilage measures (thickness, CSA, echo intensity). Clinical measures will include SLTHT,[58] isokinetic knee extension/flexion strength, and isometric hip abduction and external rotation strength.[59] Only the symptomatic limb, or the more symptomatic limb in the case of bilateral PFP, will be assessed. Lastly, PROs will include AKPS, KOOS, KOOS-PF, and VAS.

METHODS

Participants

Sixty adults will be recruited from the University of North Carolina at Charlotte (UNC Charlotte) and the surrounding community. Participants will be ages 18-30 years and physically active (30+ minutes of physical activity 3+ days per week). Participants will have PFP, which is defined as: 1) retropatellar pain for 3+ months during at least two of the following activities – prolonged sitting, stair ascent/descent, squatting, hopping,

kneeling, running, and jumping; 2) pain with compression of the patella; and 3) pain on palpation on patellar facets.[50] Participants will be excluded if they have: 1) history of orthopedic injuries, fractures, or surgeries to either limb or the low back with the exception of PFP; 2) severe osteochondral defect in either knee; 3) history of cardiovascular, neurological, or balance disorder that precludes safe participation in exercise; and 4) body mass index >40kg/m^2. Though not being used as an inclusion criterion, the International Physical Activity Questionnaire (IPAQ-SF) will be used to describe participants' physical activity levels at baseline. Eligible participants will visit the Biodynamics Research Laboratory at UNC Charlotte for baseline assessment. Following the baseline assessment, participants will be randomly allocated into groups (STFB, ST, FB, and CT) by means of a sealed, opaque envelope using sex-based block randomization.[60] A member of the study team not collecting data or delivering the interventions will perform the randomization.

Testing Procedures

Laboratory measures

Biomechanical data will be collected using a 10-camera Vicon motion capture system (Vantage V5, VICON, Oxford, UK) sampling at 200Hz. Synchronous kinetic data will be collected at 2000Hz by two force platforms (Bertec, Columbus, OH). Testing orders between DVJ, running, and stair ambulation will be randomized and the randomized order will be carried forward through all sessions for a given participant. Participants will be fitted with spandex shorts, tight fitting shirts, and regular athletic shoes. Then, 36 retro-reflective markers will be placed on specific bony landmarks of the trunk, hips, knees, and ankles/feet to capture biomechanical data using a custom marker set.[61] Once markers are placed, a static calibration trial will be captured with the participant standing in anatomical

position to define the hip, knee and ankle joint centers. Five successful trials of each biomechanical task described below will be completed following adequate practice trials.

Drop Vertical Jump: Participants will stand on top of a 30cm box placed half of their height away from the force platforms. Participants will drop forward onto the forceplates, land with one limb on each plate and perform an immediate maximal vertical jump, again landing with one foot on each forceplate.[45] A trial will be repeated if: 1) the foot does not land entirely on the forceplate and 2) the movement is not continuously performed.

Running: Participants will run at a velocity of 4.0m/s ±5%, stepping onto forceplates.[62] Running speed was selected for consistency with previous literature.[62] Running velocity will be determined by measuring the time it takes for participants to cover 10m, which will be marked on the floor using tape. Time spent between 2.38s (4.2m/s) to 2.63s (3.8m/s) to travel 10m will be a successful trial. A trial will be repeated if: 1) running speed is not between 3.8-4.2m/s and 2) the foot does not land entirely on the forceplate.

Stair Ambulation: Participants will ascend and descend a series of four 20cm high steps. The painful limb will contact the first and third steps, respectively.[57]

Femoral cartilage measures will be performed using a LOGIQe Ultrasound system (General Electric, Fairfield, CT, USA) with 12MHz linear probe. Femoral cartilage was chosen as retropatellar cartilage cannot be viewed on ultrasound. Participants will be seated on a treatment table with their back against a wall and knee positioned to 140°, 110°, and 90° of flexion using a manual goniometer.[39] The probe will be placed transversely in line with the medial and lateral femoral condyles just above the patella. The probe will be rotated to maximize cartilage reflection.[39,63] A transparent grid will be placed on the

ultrasound machine's computer screen to center the intercondylar notch and enhance reproducibility.[39] Three images will be collected per knee flexion angle.

Clinical measures

Single-Leg Triple Hop Test will quantify hop distance during three consecutive hops. This test will be performed 3 times for maximal distance.[58] Distance will be recorded from the start line to the location of the participant's heel following completion of the third hop using a standard tape measure. Distances will be normalized to participant limb length (supine distance between anterior superior iliac spine and medial malleolus) and averaged for statistical analysis.

Quadriceps and hamstring strength will be assessed concentrically (60°/s) using a Biodex isokinetic dynamometer. Participants will be secured in the chair by straps around the torso and hips. Participants will sit with the hip in 85° of flexion and the knee at 90° at rest and with the knee joint center aligned with the fulcrum of the dynamometer. Participants will complete 3 submaximal practice trials each followed by 10s rest. Next, participants will perform a single set of 5 repetitions of knee extension and flexion for maximal effort. Peak knee extension and flexion strength will be extracted and averaged across the 5 trials then normalized to participant body mass (Nm/kg).[64] Verbal and visual feedback will be provided to encourage maximal effort.

Hip abduction and external rotation strength will be assessed using a hand-held dynamometer.[59] Hip abduction isometric strength will be assessed with participants in a side-lying position. A strap will be placed 5.08cm above the iliac crest to stabilize the trunk.[59] Participants will maintain approximately 10° hip abduction at the beginning. The dynamometer will be placed over the lateral femoral condyle and participants will

gradually increase the muscle contraction and hold at maximal effort for 5s.[59] Hip external rotation strength will be performed with participants sitting on the edge of a table with hips and knees flexed to 90°. The dynamometer will be placed 5.08cm proximal to the medial malleolus.[59] Participants will be asked to gradually increase the resistance and hold the maximum resistance for 5s. For each task, participants will be given one submaximal practice trial and perform 3 maximal effort trials. A 15s rest will be given between trials and peak values from each trial will be recorded.

Patient reported outcomes

Participants will be asked to fill out PROs (AKPS, KOOS, KOOS-PF, VAS) before and after the intervention, and for follow-ups (1-, 2- and 4-weeks post-intervention). PROs will be assessed up to one month post-intervention as previous research suggests PRO improvements last up to 1 month.[30] **AKPS** has 13 questions asking the individual's functional capacity in different exercises.[65] Its validity is reported to be 0.92 and consistency between measures was 0.98.[66] With high

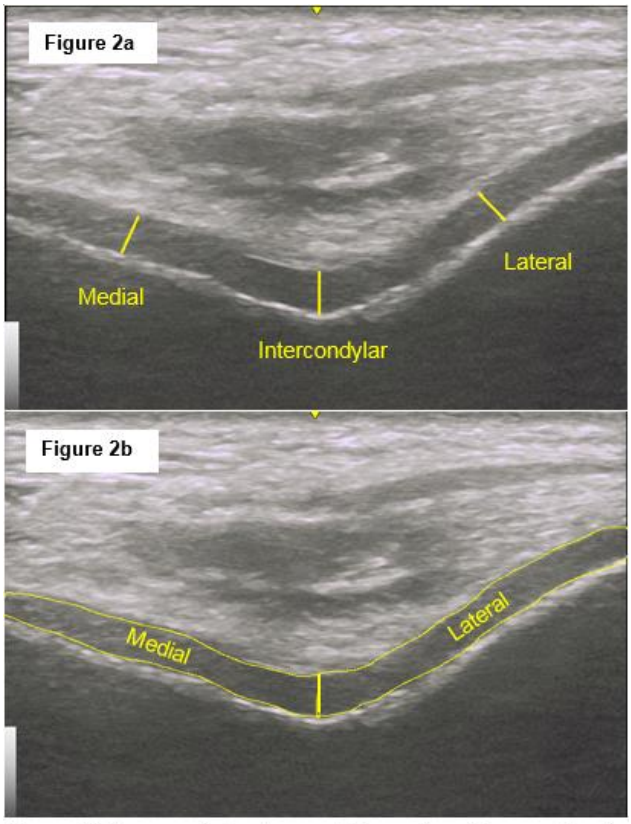


Figure 2. Representative image of femoral cartilage captured in our laboratory. Perpendicular line will be drawn to measure cartilage thickness at mid-point of medial and lateral femur and intercondylar notch (2a). Segmentation of medial and lateral cartilage (2b).

validity and reliability, AKPS is considered a gold standard PRO in evaluating the severity of PFP. Additionally, minimal detectable change (MDC) is 13.[67]

KOOS was developed from a knee osteoarthritis-spe0cific questionnaire (Western Ontario McMaster Universities Osteoarthritis Index) to evaluate function in patients who had knee injuries and are at risk of posttraumatic osteoarthritis. This questionnaire tests two different subscales for activities of daily life (ADL) and sports so that it can cover a wide variety of patients with different physical activity levels. From its creation, its reliability was between 0.75 to 0.93 in subscales.[68] MDC range for pain is 6-6.1, symptoms is 5-8.5, ADL is 5.8-12, and lastly quality of life is 7-7.2.[69]

KOOS-PF was recently developed as a PFP-specific subscale of KOOS. It showed good internal consistency with Cronbach's α of 0.86 and test-retest reliability 0.86.[70] Validity compared with AKPS using correlation was 0.74 and it showed statistically significant score difference between healthy individuals and individuals with moderate knee pain ($p<0.001$).[70]

VAS is a continuous scale which uses a 10cm straight line.[71] A score of 0 means no pain and 10 means the worst possible pain.[71] Spearman correlation between usual pain with VAS and AKPS showed strongest association ($\rho=0.74$) and secondly, between worst pain in VAS and AKPS ($\rho=0.62$).[72]

Data Preparation and Reduction

Biomechanical data processing

All kinematic and ground reaction force data will be filtered using a 4th order, zero lag, low pass Butterworth filter with cutoff frequency of 14.5 Hz.[45] All collected motion data will be processed to obtain joint angles and moments using Visual3D software (C-Motion,

Germantown, MD). Specifically, lower limb joint centers will be defined in accordance with our previous work.[73-75] Joint rotations will be calculated using a Cardan rotation sequence[76-78] and expressed relative to each participant's neutral position.[79] Synchronous 3D ground reaction force data will be filtered using the same parameters as kinematic data and submitted to a standard inverse dynamics analysis.[80] Segment inertial parameter estimates will be derived from anthropometric data from Dempster.[81] Kinetic data will be normalized to body mass and height (Nm/kg*m) and expressed as external moments, or moments acting on or about the body. For example, an external knee flexion moment acts to generate a knee flexion rotation.

Cartilage image processing

All collected femoral cartilage ultrasound images will be processed using ImageJ software (National Institutes of Health, Bethesda, MD, USA). Cartilage thickness (mm) will be assessed at the mid-point of medial and lateral femur and intercondylar notch by drawing a perpendicular line between synovial and osteochondral interfaces **(Figure 2a)**.[39] Cartilage CSA and echo intensity will be analyzed by segmenting the cartilage to medial and lateral using the intercondylar notch as a reference **(Figure 2b)**. CSA will be recorded as (mm^2) and echo intensity will be analyzed by obtaining mean gray-scale value of each segmented pixel. The echo intensity will vary from 0 (black) to 255 (white). The lower the value (the more black the image), the greater the water content present in the area. CSA analysis will provide a more complete understanding of cartilage size across the whole surface to complement the focal cartilage thickness measures. All obtained values will be used to calculate a percentage change score to determine the cartilaginous response to physical loads.

$$\text{percent change} = \left(\frac{\text{meanpost} - \text{meanpre}}{\text{meanpre}}\right) * 100$$

Interventions

The strengthening intervention **(Table 1)** was developed based on a previous large (n=199), multi-center hip, core and knee musculature strengthening treatment provided to patients with PFP.[52] The feedback motion retraining protocol was developed using running[29] and jump-landing studies.[82] All intervention groups will complete 6 sessions of their respective interventions over a 2 week period (3x/week). This duration of intervention was selected because 6 sessions represents a common number of visits for PFP in rehabilitation clinics and patients with PFP start to experience pain alleviation after 6 sessions.[52,83]

The **ST** group, particularly, will be modifying intensity by increasing knee flexion angle during single legged squats, adding lunges and adding step down exercises. Extra resistance during exercises will be applied using TheraBand (Hygenic Corp, Akron, OH) and the addition of resistance will be determined by the primary investigator based on his clinical expertise in treating patients with PFP, accounting for patient feedback, joint pain, swelling, symptoms and participants' ability to complete 10 repetitions of a given exercise (i.e., if a participant cannot complete 10 repetitions, the exercise intensity will not be progressed in the following session). For week 1, ST exercises will be non-weight-bearing exercises targeting hip and knee muscles then progress to light intensity weight-bearing exercises. Lastly, double leg balancing on Airex pad (Airex AG, Sins, Switzerland) will be completed by participants. Week 2 exercises will include hip and core musculature strengthening exercises and single-limb intensive exercises.

The **FB** group participants will initially be provided with scripted verbal cueing information including: 1) "move with your knees apart with your kneecaps pointing straight ahead" and 2) "squeeze your buttocks". Along with scripted information, participants will be provided with initial instructions in front of a full-body mirror to visualize their movement. If needed, participants will be instructed to widen their stance or keep their toe pointed outwards as necessary. Successful performance of a movement will be considered a movement goal and participants will be encouraged to repeat the successful movement. Participants will receive additional verbal feedback during each training session if they demonstrate faulty hip and knee movements. Faulty movements are defined as subjects showing knock-kneed position or toe-in stance and will be identified subjectively by the intervention provider. Length of movement time will be continuously increased over the first 3 sessions and then capped at a maximum of 18 minutes for last three sessions **(Figure 3)**.[29] Time used for feedback will increase for first 3 sessions and then be gradually reduced for the remaining sessions to all participants to internalize their cues.[84] During the feedback reduction period, participants will be given feedback at the beginning of a session regarding their movements in the previous session.[29]

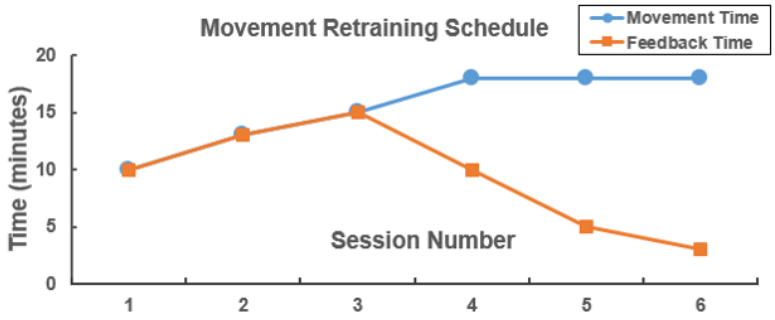


Figure 3. The movement retraining schedule: Over the first three visits, movement time and feedback time is increased from 10 minutes to 15 minutes. Over the last three visits, movement time is increased to 18 minutes while feedback is faded to 3 minutes

The **STFB** group will complete the same exercises as the ST group. However, in addition to those strengthening exercises, participants will be provided with visual feedback using a full-body size mirror during the intervention. Participants will be verbally instructed to keep their knees apart during the movement. Verbal feedback will be provided if any abnormal movement is detected at the end of each exercise movement. Examples of verbal feedback include: 1) "keep your knees apart with your kneecaps pointing straight ahead" and 2) "squeeze your buttocks".[47] Amount of feedback will be increased for first three sessions and decreased gradually for last three sessions **(Figure 4)**.

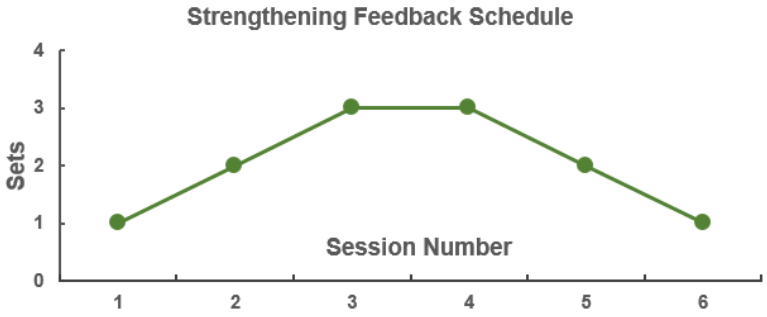


Figure 4. The strengthening feedback schedule: Over the first three visits, sets with feedback will be increased. Over the last three visits, sets with feedback will be decreased.

The **CT** group will not receive any physical interventions.

Power Analysis

No previous investigation has directly compared outcomes of interest in patients with PFP. Therefore, our sample size is estimated from data of cartilage thickness and echo intensity differences between controls and those with PFP. Power calculations were conducted using G*Power 3.1.9.2 (Univ. Dusseldorf, Dept. of Psychology) with $\alpha<0.05$ and power (1-β) set at 0.80. Sample size estimates and power calculations for the proposed experiment were determined using: differences in echo intensity between Patients with PFP and healthy controls (140° echo intensity, effect size=1.11) from preliminary data indicating a sample size of n=14 per group is needed to determine group differences. Our

estimate of 14 participants per group is in line with previous research in patients with PFP[29] [85] and ultrasonographic cartilage studies[39] that all observed significant differences in their outcome measures. Thus, we are confident that we will observe significant differences in motion, cartilage thickness measures, lower extremity muscle strength, SLTHT, and PROs with 14 participants per group. However, to account for potential drop-out, 15 participants per group will be recruited and enrolled.

Statistical Analysis

Demographic (age, height, body mass) and descriptive (IPAQ-SF) data will be compared between groups at baseline using one-way ANOVAs. We will conduct 4x3 repeated measures ANOVA (RMANOVA) to allow within and between groups (STFB, ST, FB, and CT) comparisons at three time points (before the intervention and immediately and 1 week post-intervention) in laboratory (Specific Aim 1) and clinical measures (Specific Aim 2) and 4x5 RMANOVA for PROs (Specific Aim 3) for five time points (pre-, immediately post-intervention, 1-, 2-, and 4-weeks post-intervention). Tukey's post hoc tests will be used to identify specific differences in the event of significant interactions or group or time main effects. For all statistical procedures, alpha will be <0.05. To measure magnitude of changes, Cohen's d effect size and 95% confidence intervals (CIs) will be calculated.[86] For all outcome measures, an intention-to-treat analysis will be conducted as necessary.

ANTICIPATED OUTCOMES

Specific Aim 1

Our hypothesis for Aim 1 is that STFB group will demonstrate greater improvements in biomechanics and cartilage health compared to ST, FB, and CT groups. Patients with

PFP perform repeated dynamic valgus (hip adduction and internal rotation) during weight bearing activities.[87] This faulty movement applies lateral force on the patella causing derailment of the patella and increases compressive force to the lateral knee cartilage.[17,44] Thus, valgus collapse is thought to exacerbate PFP symptoms and reduce cartilage thickness.[44] It has been previously established that strengthening the hip musculature to mitigate valgus collapse in patients with PFP will improve strength in the targeted muscles.[27] However, biomechanical improvements have not followed these strength gains.[27] Conversely, interventions providing feedback of movement technique can improve biomechanics without concurrent increases in muscle strength.[29]

We anticipate finding a greater reduction of hip adduction and internal rotation angles in STFB group compared to all other groups immediately after the intervention and at 1-week follow up. This improvement in biomechanics has the potential to mitigate cartilage health by unloading the lateral knee compartments. Thus, we anticipate the STFB group will experience less femoral cartilage deformation after the intervention and that this finding will continue 1-week after the intervention. This observation would provide evidence that improving biomechanics using evidence-based intervention (STFB) in patients with PFP will superiorly mitigate cartilage health compared to standard of care treatments. These findings will have the potential to translate to other patient populations with similar impairments and aberrant biomechanics (e.g., patients after anterior cruciate ligament reconstruction).

Specific Aim 2

We hypothesized that STFB group will have greater lower extremity strength gains and improved SLTHT distance compared to other groups at all time points (immediate and 1-

week follow up). Patients with PFP have less quadriceps[88], hip abductor[87] and external rotator strength[59] compared to pain-free individuals. It is established that isolated hip strengthening in patients with PFP yields hip strength improvements.[85] However, we anticipate finding greater lower extremity strength improvement and SLTHT distance in STFB since we are optimizing delivery of exercises using feedback, which is reported to yield greater muscular improvement.[89] Better strength improvement with STFB will give greater SLTHT distance improvement compared to other groups at all time points.[90]

Specific Aim 3

We hypothesized STFB intervention will superiorly improve all patient-reported outcomes (AKPS, KOOS, KOOS-PF, and VAS) immediately and at 1-, 2-, and 4-week follow-up. Since STFB should demonstrate greater improvement in biomechanics and strength, we anticipate the STFB group will report better subjective outcomes (PROs) and the residual benefit will last up to 4 weeks. Further, the improvement in PROs in the STFB group will be greater than in all other groups at all time points. This hypothesis is supported by previous research demonstrating increased hip strength (e.g., hip abductor and hip external rotator) is associated with decreased pain (VAS) and improved function (AKPS) after intervention.[52,91]

Taken together these findings may be applied to future intervention protocols. By improving lower extremity musculature strength and reducing dynamic valgus through STFB, patients with PFP will be able to experience better cartilage health during weight bearing activities. It is expected that because both biomechanics and strength will be improved that the benefits will last longer than conventional treatments targeting either strength or biomechanical impairments. Lastly, this improved cartilaginous health will lead

to better perceived function and less pain. These improvements will contribute to the slowing the progression to PFOA in patients with PFP. This investigation has great potential in improving the delivery of physical intervention from clinicians and other healthcare professionals to patients with PFP which will lead to not only a reduction of pain symptom but also improvement of cartilage health. Future studies will compare the effectiveness of other types of interventions commonly used in treating patients with PFP (e.g., foot orthoses, patellar taping and bracing, electrical therapy, and combined physical interventions) on cartilage health and biomechanics in these patients using methods in the current proposed study.[25]

APPENDIX D: MID-ATLANTIC ATHLETIC TRAINERS' ASSOCIATION RESEARCH GRANT

1. Research Problem

Patellofemoral pain (PFP) is an overuse condition associated with increased pain and compressive forces on the cartilage lining of the posterior surface of the patella. PFP is frequently observed in physically active individuals and its symptoms are aggravated during daily and athletic activities. PFP is one of the most common knee injuries treated by sports medicine clinicians, accounting for approximately 1/3 of all knee injuries.[92] Patients with PFP often experience difficulty with work and daily and physical activities due to the aggravation of pain associated with movement. Recent evidence suggests that prolonged symptoms of PFP may contribute to the development of patellofemoral osteoarthritis.[8,9] Progressing to the level of osteoarthritis will further compromise the general health of the patient while also increasing national healthcare costs.

Plain radiography remains the gold standard for diagnosing osteoarthritis; however, changes likely occur in the articular cartilage before radiographic evidence of osteoarthritis can be observed on x-ray. Magnetic resonance imaging (MRI) has also been used previously to measure changes in cartilage thickness in patients with osteoarthritis and PFP. Farrokhi et al., for example, used MRI on patients with PFP and healthy controls finding 14% less cartilage thickness in individuals with PFP at baseline.[36] Additionally, individuals with PFP exhibited greater femoral cartilage deformation after a single session of weighted 50 deep knee bends.[36] While useful, MRI is a costly and sometimes impractical imaging tool. Diagnostic ultrasound is a valid imaging tool[38,39] that may aid in assessing femoral cartilage thickness before radiography would detect changes in joint integrity and at a lower cost than MRI. Recently, investigators have

utilized diagnostic ultrasound to measure cartilage thickness changes after a variety of physical activities in healthy adults, finding a significantly decreased thickness after 30 minutes of walking or running compared to a control condition.[39] It remains unknown if these same ultrasound techniques can be applied to assess cartilage thickness in patients with PFP and how various athletic activities known to exacerbate PFP symptoms (e.g., running, strength training, and plyometric activity) acutely influence cartilage thickness. It is our belief that patients with PFP will show greater reduction of patellofemoral cartilage after activities known to exacerbate symptoms when compared to healthy populations. Understanding the influence of common athletic activities on cartilage thickness in patients with PFP is vital to the development of strategies to reduce symptoms and combat PFP. Thus, the goal of this project is to determine if patients with PFP experience greater reductions in cartilage thickness after a single bout of 30 minutes of running, strength training and plyometric exercises when compared with healthy populations.

Specific Aim 1: To determine if joint loading changes cartilage thickness in patients with PFP compared to healthy adults.

Hypothesis 1.1: Participants with PFP will demonstrate greater reduction of cartilage thickness after running compared to healthy adults.

Hypothesis 1.2: Participants with PFP will demonstrate greater reduction of cartilage thickness after strength training compared to healthy adults.

Hypothesis 1.3: Participants with PFP will demonstrate greater reduction of cartilage thickness after plyometric activities compared to healthy adults.

Specific Aim 2: To determine if changes in patient reported outcomes as a result of joint loading are associated with changes in cartilage thickness.

Hypothesis 2.1: Participants with PFP will demonstrate greater reduction of self-reported function on both the Anterior Knee Pain Scale (AKPS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) compared to healthy adults following all joint loading conditions.

Hypothesis 2.2: Lower scores on the AKPS and KOOS will be associated with greater reductions in cartilage thickness in patients with PFP.

2. Significance of the Proposed Research

Over 2 million individuals in the United States were diagnosed with PFP between 2007-2011.[3] Not only is the incidence of PFP high, but the authors observed a steady increase of cases throughout the period of the epidemiological study.[3] In addition to symptoms and disability experienced by patients with PFP, these individuals are at increased risk of developing patellofemoral osteoarthritis.[3,8] Due to the high prevalence of PFP and its linkage to patellofemoral osteoarthritis, greater understanding of the disorder and improved treatment strategies are necessary to optimize quality of life and long-term health in these patients.

Our proposed investigation will examine the influence of brief bouts of tasks known to exacerbate symptoms on cartilage thickness to determine if these activities may be contributing to the development of patellofemoral osteoarthritis. Patients with PFP often complain of symptoms during athletic activities such as running, strength training, and plyometric exercise. While all of these activities can be useful in improving strength and

reducing symptoms, they may negatively influence joint health in patients with PFP. Understanding the influence each of these activities has on cartilage thickness can inform future treatment strategies for these patients.

This study is significant because it is a first attempt in evaluating cartilage thickness in patients with PFP after different forms of physical activities. Our results have the potential to shift current treatment paradigms with an immediate impact because diagnostic ultrasound is available in many sports medicine settings. These outcomes may improve rehabilitation approaches and improve quality of life for patients with PFP.

3. Procedures

Research Design

A single-blinded crossover design will be used to achieve our proposed specific aims. The dependent variable will be cartilage thickness. Independent variables will be group (PFP and healthy) and loading condition (running, strength training, plyometric, and control).

Sample Size and Participants

A total of 24 participants will be enrolled in this study (12 with PFP and 12 healthy controls). Based on a previous investigation,[39] it is estimated that to observe differences in femoral cartilage thickness after running with a moderate effect size (α=0.05, 1-β=0.8), we will need to enroll 8 participants per group. Data currently in review for publication from our laboratory suggest that to determine differences between groups in patient reported outcomes with a moderate effect size (α=0.05, 1-β=0.8), we need to enroll 9

participants per group. To account for potential participant dropout, we plan to enroll 12 individuals per group.

All participants will be between the ages of 18-35 years and will be recreationally active, defined as performing at least 30 minutes of physical activity at least 3 times per week. An individual will be considered to have PFP is he/she has: 1) retropatellar pain for 3+ months during at least two of the following activities— prolonged sitting, stair ascent/descent, squatting, hopping, kneeling, running, and jumping; 2) pain with compression of the patella; and 3) pain on palpation on patellar facets.[50] Testing will be performed on the involved limb or the subjectively worse limb if PFP presents bilaterally. Healthy adults will be matched to the PFP group based on age, body mass index, and physical activity level (Tegner activity scale).[93] A matched limb in the healthy group will be used for testing. Exclusion criteria for all participants will be: 1) history of orthopedic injuries, fractures, or surgeries to either limb or the low back with the exception of PFP in the patient group; 2) severe osteochondral defect in either knee; 3) history of cardiovascular, neurological, or balance disorder that precludes safe participation in exercise; and 4) body mass index > 40 kg/m^2.

Instrumentation

A GE LOGIQe (General Electric Co., Fairfield, CT) diagnostic ultrasound machine with a 12MHz linear probe will be used to perform all ultrasound imaging. Patient reported outcomes will be collected using the AKPS and KOOS. The AKPS is a valid and reliable 13 question survey scored from 0-100 with lower scores indicating worse symptoms/function.[67] KOOS contains five subscales related to pain, symptoms, function

during daily living and sports, and quality of life. It is scored from 0-100 with lower scores indicating greater symptoms/dysfunctions.[94]

Overview of the Methods

An overview of study procedures can be found in Figure 1. Once eligible, participants will provide written, informed consent and demographic data and complete patient reported outcomes surveys. The order of conditions will be randomized for all participants by means of a randomization table completed prior to initiation of the study. Each session will be completed at the same time of day and separated by 1 week. All sessions will begin with the participant sitting in a long-sit position on a treatment table with the knees fully extended for 30 minutes to mitigate cartilage compression that occurred walking to the laboratory.[39]

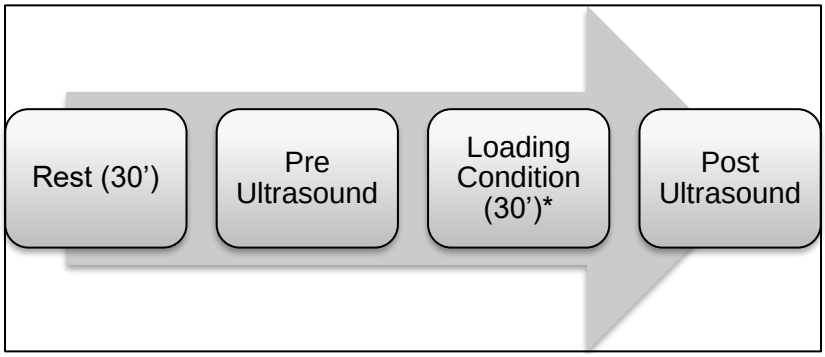


Figure 1. Testing overview. *Indicates conditions: running, strength training, or plyometrics.

Ultrasound Imaging Identical procedures will be performed before and after the various loading conditions. Participants will sit on a treatment table with their backs against a wall and the test knee flexed to 140°. The ultrasound probe will be placed transversely in line with the femoral condyles above the superior pole of the patella as previously reported.[39] A transparency grid will be secured to the computer screen to improve reproducibility.[39] Three images will be captured.

Loading Conditions For the running condition, participants will run on a treadmill at their self-selected, preferred running speed for 30 minutes. For strength training, participants

will complete a series of exercises designed to mimic a rehabilitation session for patients with PFP. These will include body weight squats, step-downs, and other similar weight-bearing exercises to improve lower extremity muscle strength. Exercises will be completed for 30 minutes. The plyometric condition will be combined with a control condition. Following pre ultrasound, participants will continue resting for 30 minutes in a long-sit position. This control condition will be followed by another ultrasound assessment and then plyometric exercises. Plyometrics will include single- and double-leg landings and drop vertical jumps. Immediately following each loading condition, participants will undergo post ultrasound.

Cartilage Thickness Measurement The investigator assessing cartilage thickness will be blinded to participant group and condition. Ultrasound images will be processed in ImageJ (NIH, Bethesda, MD) as previously described.[39] Cartilage thickness (mm) will be determined at the midpoint of the medial and lateral femoral condyles. A straight line from the osteochondral interface to the synovial space will be drawn to quantify cartilage thickness. Data will be averaged at each time point for each condition.

Data Management and Analysis

Descriptive data will be compared between groups using independent samples t-tests. To address specific aims 1 and 2, change scores for cartilage thickness and patient reported outcomes within each condition will be determined and those change scores will be compared between groups and conditions using 2x4 (group x condition) repeated measures ANOVAs. Tukey *post-hoc* analyses will be used in the presence of significant interactions. Cohen's d effect sizes will be calculated to quantify the magnitude of change in cartilage thickness between conditions (<0.2: weak; 0.21-0.5: small; 0.51-0.8: medium;

and >0.8: large). To address specific aim 2, Pearson's product moment correlations will be performed to determine the association between cartilage thickness and patient reported outcomes separately for the AKPS and KOOS. Alpha levels will be set *a priori* at P<0.05 for all analyses. All statistical analyses will be completed in SPSS (v.21).

Means of Data Reporting

Data will be submitted for presentation at the MAATA 2019 annual meeting as well as other appropriate venues (i.e., NATA, ACSM, etc.). Resulting manuscripts will be prepared for Journal of Athletic Training and other similar journals. Data will also be used to secure additional extramural funding aimed at improving treatment and long-term outcomes for patients with PFP.

4. Proposed Budget

A) Expendable supplies	$35.00
B) Equipment	N/A
C) Salary	N/A
D) Participant honoraria	$1,080.00
E) Data management and analysis	N/A
TOTAL	$1,115.00

Budget Justification

No funds are needed to purchase equipment, pay salary, or provide for data management and analysis for this project.

Expendable Supplies: We are requesting money to purchase 1 container of ultrasound gel ($35/container). Total amount requested for supplies is $35.

Participant Incentives: Because of the time commitment associated with participation in this study, we propose offering a $15 participant incentive per testing session. Each participant will complete 3 testing sessions ($15 x 3 = $45 per participant). We plan to

enroll 24 total participants (24 x $45 = $1080 total for participant incentives). Payment will occur at the conclusion of the final testing session. This payment amount is in line with other investigations in our department.

5. Timeline

Project Timeline (January 2018-December 2018)												
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sept	Oct	Nov	Dec
Participant recruitment												
Data collection												
Data analysis												
Final report												
Abstract/manuscript preparation/ submission												