A clinical study focusing Evaluation and treatment of acute and chronic cartilage injuries of the knee

Asbjørn Årøen (asbjørn.aroen@medisin.uio.no)
University of Oslo: Universitetet i Oslo

Stian Kjennvold
University of Oslo: Universitetet i Oslo

Study Protocol

Keywords: Articular Cartilage Inquires, Bone Marrow Derived Stem Cells, Chondral Fractures, Detached Fragment Removal

DOI: https://doi.org/10.21203/rs.3.rs-359828/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Treatment of articular cartilage injuries have been a challenge for orthopedic surgeons for decades. The following study protocol add knowledge about ongoing research in the field and outline the ongoing long-term follow-up on the transplantation of bone marrow derived stem cells in a clinical trial with 10 years follow-up. The study protocol describes a method to save chondral fractures, which in the past frequently treated with removal of the detached fragments.

2. Background

Focal chondral defects of the knee are common [1,2], especially in young and active adults. The hyaline cartilage of joints has limited potential to heal and localized disruption of this surface have been shown to impair quality of life similar to patients scheduled for knee replacement [3]. The patients are however 30 years younger. It is now well established that hyaline cartilage lesions lead to early onset osteoarthritis [4,5]. Knee replacement is not an acceptable or appropriate option for these patients, and the orthopedic community has therefore tried to find a way to repair or regenerate knee cartilage in an effort to restore knee function and postpone the need for arthroplasty. Treatment of symptomatic chondral injuries in the knee is therefore of importance to the patients as well as society.

Several improvements in cartilage restoration techniques have been developed over the last decades, but none have so far proved to be superior to others in properly conducted randomized trials [6]. Current surgical strategies range from simple debridement or microfracture to chondrocyte implantation (ACI) and stem cell therapy (MSC). However, all methods have their shortcomings, and no conclusion have be made on optimal treatment of this injury [7].

Cartilage has no blood supply, and it has been a widely accepted that once injured, cartilage doesn't heal. This view has been challenged lately, by the introduction of small fixation devices that makes fixation of the loose chondral fragment possible in acute injuries. This is the only known method that preserves the originally hyaline cartilage. However, this technique is only described in a few very small case series of 1-3 patients and the functional outcome of this treatment is poorly established [8-15]. Furthermore, the most commonly used arthroscopic classification system for cartilage lesions (ICRS) has never been properly validated [16,17]. Thus, decision-making, treatment planning, evaluation and comparison of research results is even more challenging.

Ahus is heading The Norwegian Cartilage Project (NCP), a multicenter nationwide project that conducts clinical trials on the treatment of chronic cartilage lesions. The current project will complement the NCP, by looking at the treatment of acute chondral fractures, an injury that is underrepresented in cartilage research. As such, the current project is the next logical step in the cartilage research conducted at Ahus, and will affirm Ahus as a significant cartilage research institution. Ahus serves as the main hospital for a large population and we treat a significant number of cartilage injuries. Through this PhD project,
comprised of three studies, we aim to fill current knowledge gaps and to continue the search for optimal treatment of cartilage injuries by:

1. Retrospectively determining the clinical outcome in a cohort of 12 patients with an acute chondral fracture treated with re-fixation of the fragment in our hospital. (Study 1)

2. Investigating the reliability of the most widely used classification system for focal cartilage lesions of the knee. (Study 2)

3. Determining whether the use of recorded images influence the precision of evaluating cartilage injuries as compared to arthroscopy. (Study 2)

4. Conducting long term follow up of 72 patients with a symptomatic cartilage lesion included in a RCT to compare Autologous Chondrocyte Implantation (ACI) with Mesenchymal Stem Cell implantation (MSC). (Study 3)

5. Determining the long term natural history of focal cartilage defects of the knee. (Study 3)

2.1 Needs description

**Study 1:** Because of the limited healing potential of hyaline cartilage, treatment of acute chondral injuries has traditionally been limited to arthroscopic removal of the loose fragment. However, the development of new fixation devices such as meniscus arrows and chondral darts has permitted the surgeon to re-fixate the chondral fragment. This surgical technique could prove to be the only treatment option preserving the patients own hyaline cartilage, which in turn could vastly improve the prognosis for patients with acute isolated chondral trauma. Describing the surgical technique and examining the results of this treatment is therefore of interest to anyone involved in treating cartilage injuries, and will make them more aware of this option. As this is a new technique, we owe it to our patients and ourselves to critically and systematically evaluate the results in a scientific manner to determine the indication, limitations and expected outcome after this treatment. Although this is a case cohort with a limited number of patients, our study will comprise the largest case series to date, and the findings will pave way for further improvement in the surgical management of these difficult knee injuries.
| Authors                  | Fixation Method                                           | No. of Cases | Follow-up | Outcome          |
|-------------------------|-----------------------------------------------------------|--------------|-----------|------------------|
| Maletius et al (1994)   | Fibrin sealant and polydioxanone pins                     | 2            | Unknown   | Partial healing  |
| Nakamura et al (2004)   | Bioabsorbable pins                                        | 1            | 2y9mo     | Successful repair|
| Uchida et al (2012)     | Bioabsorbable pins                                        | 3            | 2y        | 1 of 3 reoperated|
| Chan et al (2014)       | Bioabsorbable suture anchors, absorbable suture, bone fixation nails | 1            | 1y        | Successful repair|
| Nakayama et al (2014)   | Autograft bone pegs                                       | 1            | 26mo      | Successful repair|
| Chung et al (2014)      | Bioabsorbable suture anchors                              | 1            | 1y        | Successful repair|
| Morris et al (2016)     | Poly L-Lactic Acid Chondral darts                         | 1            | 1y        | Successful repair|
| Siparsky et al (2017)   | Chondral darts and Tissel fibrin glue                     | 3            | 1y        | Successful repair|

Table 1. Published case series on refixation of chondral fragments [8-15]

**Study 2:** A common classification system facilitates decision-making and evaluation as well as comparison of research. Determining the reliability of the ICRS grading system is an important methodological evaluation. Both research and clinical decisions are based on this classification of cartilage lesions, but we do not know if it works as intended. This might influence the way we describe and treat the different types of cartilage injuries in the future. Evaluating the use of recorded images has not been done before and will be important to clinical researchers, as this is a constant source of discussion in arthroscopic studies. The validation of video-classification of cartilage injuries will explore the possibility for the use of telemedicine in diagnostic purposes, which can be very useful and might both improve and speed up the diagnosis of cartilage injuries.

**Study 3:** The natural history of a conservatively treated symptomatic cartilage lesion is not well described or understood. We know now that physical therapy and focused knee rehabilitation improve clinical outcome without surgery [18]. But the long-term outcome is yet to be described. In a RCT conducted by our research group including 72 patients with a focal cartilage lesion, 46 patients improved during the preoperative rehabilitation to such a degree that they ended up declining surgery. Evaluation of the long term clinical and radiological outcome in these patients, and comparing the results with the 26 patients who underwent surgery, will provide important knowledge regarding the natural history of focal cartilage injuries.
Since Caplan and others managed to differentiate so-called stem cells into various tissues (muscle, cartilage, bone) in vitro in the 1980s and 1990s, there has been a tremendous interest and optimism regarding mesenchymal stem cells (MSC) derived from bone marrow [20]. Parallel to this development, Brittberg and colleagues developed the autologous cartilage implantation (ACI) technique where the patients’ cartilage cells were cultured and re-implanted in the cartilage defect in an attempt to repair the cartilage defect with hyaline-type cartilage [21]. If MSC could produce a hyaline cartilage repair tissue over the lesion to the same degree as the clinically well established ACI technique, the method would be considerably less costly and would involve only one surgery rather than two. Our group therefore randomized the remaining 26 patients from the above mentioned RCT to either autologous chondrocyte implantation (ACI) or implantation of MSC derived from bone marrow. We will conduct a five to seven year follow up of these patients, which will explore the potential of MSC derived from bone marrow to heal a cartilage injury. This is the first conducted human clinical trial on this topic, and therefore much warranted to move the field forward.

3. Hypotheses, Aims And Objectives

**Study 1: Re-fixation of acute chondral fractures:**

**Aim:** To measure the clinical and radiological (MRI) results after acute fixation of chondral fractures and describe the surgical procedure.

**H0:** There is no difference between the injured and non-injured knee two years after surgery as measured by a validated hop-test.

**Study 2: Reliability of the ICRS classification system:**

**Aim:** To quantify both the inter- and intra-rater reliability of the ICRS classification system for cartilage lesions in the knee between different knee surgeons. This will provide us with a quantitative measure on how trustworthy this commonly used classification system is. In addition, we will investigate whether the use of recorded images will affect the reliability of the classification system. This is important to ascertain the appropriateness of the methodology in cartilage research in general.

**H0:** There is no difference in the reliability of the ICRS classification between surgeons who classified the lesions in theatre and surgeons who classified the lesions watching a standardized recorded video.

**Study 3: Long term follow up of the ACI vs MSC trial:**

**Aim:** To compare the long term clinical and radiological results between the two surgical groups, and the conservatively treated group. To describe the natural history of cartilage lesions in the 46 patients who did not undergo surgery.

**H0:** No difference in knee function between groups
**H1:** Patients not undergoing surgery have worse knee score (Lysholm /KOOS) compared to patients undergoing cartilage surgery

### 4. Project Methodology

The present PhD project will consist of both prospective and retrospective studies. One study is a methodological evaluation of the most commonly used classification system for cartilage lesions. The two others are clinical and radiological evaluation of patients treated for cartilage lesions, with either fixation of the acute chondral injuries or cell therapies (chondrocyte implantation or stem cell therapy) for chronic defects. The combination of studies should ensure adequate methodological diversity in the PhD.

#### 4.1. Project arrangements, method selection and analyses

**Study 1: Re-fixation of acute chondral fractures**

We have performed re-fixation of chondral fragments using meniscal arrows in a small number of patients with acute injury. The aim of this study is to evaluate the degree of union of these chondral fractures as well as assess the postoperative clinical function and patient reported outcome. The resulting article will also serve as a description of the surgical technique.

This study is a retrospective cohort study since all the patients have already been operated. Inclusion criteria include patients older than 16 years at the time of clinical evaluation who have previously undergone an acute fixation of an isolated chondral fracture of the knee with meniscal arrows at our hospital. The patients will be identified from our internal medical record system and will be invited to a designated follow-up clinic at our institution. The only exclusion criterion is patients declining participation. A combination of clinical parameters, questionnaires and radiological examination will be used for follow up.

- To assess clinical function the patients will perform a validated single leg hop test [19] and range of motion (ROM) will be measured with a goniometer. Patients will also provide information about return to work, to physical activity and to sport. Complications or reoperations will be registered. A standard visual analogue scale will be used to quantify pain. Standardized radiographs (in Synflex frame) of both knees will be performed to look for signs of osteoarthritis according to Kellgren Lawrence grading. Magnetic Resonance Imaging will be used to assess the healing of the defect and the quality of the cartilage by T2 mapping and the following patient reported outcome measures (PROMs) will be completed by the patients:
  - **KOOS score:** to assess the patient's perception of their own knee and associated problems as well as map changes induced by treatment. It assesses five domains; pain, symptoms, activity of daily living, sport and recreational function and knee-related quality of life
  - **Tegner score:** Will be used to map the level of physical activity.
Lysholm score: A condition-specific outcome score containing eight domains; limp, locking, pain, stair-climbing, use of support, instability, swelling and squatting.

EQ-5D: A generic measure of health status that provides a simple descriptive profile used in the clinical evaluation of health care.

Study 2: Reliability of the ICRS classification system

The purpose of this study is to assess the reliability of the International Cartilage Repair Society classification system for assessment of focal cartilage injuries in the knee. We also aim to evaluate whether the use of recorded images influences the grading or reliability. The study is designed as a Cohort study/prospective validation study.

The inclusion will take place at Akershus University Hospital, which has an extensive orthopedic outpatient surgery activity. Patients will be recruited from a consecutive cohort of patients scheduled to arthroscopy for various random knee complaints; e.g. diagnostic arthroscopy, restorative procedures like ACL reconstruction and cartilage surgery or meniscal tear treatment.

Inclusion criteria are:

- Patients scheduled for knee arthroscopy at the outpatient clinic or in The Norwegian Cartilage Project
- Age 18 (Closed epiphysis) - 50 years
- Informed consent

Exclusion criteria are:

- Osteoarthritis assessed on preoperative standing radiographs or by per-operative arthroscopy
- Rheumatoid arthritis, Mb Bechtrew, Psoriatic arthritis, Chondrocalsinosis, tumors, former/ongoing joint infection or other generalized disease that might affect joint cartilage
- Former reconstructive cartilage surgery
- Knee joint contracture or deformity that might impair assessment of all 6 articulating surfaces

As Årøen et al. [1] showed in 993 consecutive arthroscopies, articular cartilage pathology can be expected to be found in 66%, and a localized cartilage defect in 20% of the knees. A localized full-thickness cartilage lesion (ICRS grade 3 and 4) was found in 11% of knees scheduled for arthroscopy. A total of 100 patients in the cohort should therefore give a representative spectrum of macroscopic cartilage appearance, from good to poor. We also plan to include patients referred for inclusion in the ongoing Norwegian Cartilage Project in which patients with symptomatic focal cartilage lesions are randomized into different treatment groups. This will ensure the inclusion of enough grade 3 and 4 lesions which are the least common.

The knees of all patients eligible for the study will be systematically assessed and photos and video of all 6 articulating surfaces (patella-trochlea compartment, tibia and femur in both lateral and medial
compartments) will be taken in a standardized manner, before any debridement or restorative procedures are conducted. The video is then stored in a secured database for later assessment. Pre-planned procedures will not be affected by inclusion in this study. Experienced surgeons, to ensure good quality photos and video, will perform the arthroscopic procedures.

A panel of orthopedic surgeons, both experienced knee surgeons and orthopedic residents, will then assess the arthroscopic pictures and video, scoring each knee according to the ICRS classification. Prior to assessment both scoring systems will be reviewed in detail with all participants. Scoring is then repeated after a 3-month interval. The photo documentation will be anonymized prior to assessment. The order of presentation will be altered for the second assessment to prevent any recall bias among the raters.

One of the main objections against this method of testing reliability has been that grading lesions using recorded images will deprive the raters of the tactile sense used during arthroscopy and thus cause the lesions to be graded differently than they would be by the performing surgeon. To investigate whether the grading of lesions with the use of recorded images differ from the grading done by the surgeon during the arthroscopic procedure, we also aim to have two groups of raters at the initial evaluation. One group will grade the lesions while performing the arthroscopic procedure. The other group will be doing the initial grading using recorded images only. Both groups will use recorded images for the follow-up evaluation. This will enable us to evaluate whether the use of recorded images influences grading and reliability.

Reliability tests assess the overall consistency of a measure, in this case the ICRS-score. A measure is said to be highly reliable if it produces similar results under consistent conditions. The interclass correlation coefficient (ICC) will be used to assess the inter-, and intra-observer reliability of each scoring system. The ICC represents the consistency, or conformity, of measurements made by observers measuring the same quantity. A level of > 0.75 is considered to be excellent reliability, and values between 0.4 and 0.75 represents fair to good reliability.

**Study 3: Long term follow up of the ACI vs MSC trial:**

Cohort study to investigate the long term clinical and radiological results from a RCT with 72 included patients previously conducted by our research group. All patients included underwent a standardized physical therapy prehabilitation program prior to surgery. 46 of the patients improved to such extent that they no longer wanted the operation. The remaining 26 patients were randomized into two treatment groups, 13 in each group. Although the number of surgically treated patients in this RCT is limited, it is to the best of our knowledge the only study comparing ACI with MSC. The short term results are currently being analyzed, but the effect of the prehabilitation program has been published [18]. The cohort has also been used to describe the presence of specific urinary biomarkers of cartilage degeneration [22]. The aim in the long term follow-up is to compare the outcome between the conservatively and surgically treated groups, which will also elucidate the natural history of appropriately rehabilitated conservatively treated injuries. We will also evaluate the long term clinical and radiological outcome of ACI and MSC.
Cartilage lesions have been of interest to surgeons for several decades, and numerous surgical methods have been developed. However, the natural history of a symptomatic lesion is not well described or understood. We know now that physical therapy and focused knee rehabilitation improve clinical outcome without surgery [18]. But the long term outcome is yet to be described. To evaluate the long term clinical and radiological outcome from these patients, and compare the results with the 26 patients who underwent cartilage surgery, will provide important knowledge regarding the natural history of focal cartilage injuries.

To assess clinical function the patients will perform a validated single leg hop test [19] and range of motion (ROM) will be measured with a goniometer. Patients will also provide information about return to work, to physical activity and to sport. Complications or reoperations will be registered. A standard visual analogue scale will be used to quantify pain. Standardized radiographs (in Synflex frame) of both knees will be performed to look for signs of osteoarthritis according to Kellgren-Lawerence grading. Magnetic Resonance Imaging with T2 mapping will be used to assess the healing of the defect and the quality of the cartilage. We will collect both blood- and urinary samples to look for specific biomarkers for cartilage injury or degeneration. Data from the cohort has already been used to describe the presence of cartilage specific biomarkers in urine (22). In addition the following PROMs will be completed by the patients:

- **KOOS score**: to assess the patient's perception of their own knee and associated problems as well as map changes induced by treatment. It assesses five domains; pain, symptoms, activity of daily living, sport and recreational function and knee-related quality of life
- **Tegner score**: Will be used to map the level of physical activity.
- **Lysholm score**: A condition-specific outcome score containing eight domains; limp, locking, pain, stair-climbing, use of support, instability, swelling and squatting.
- **EQ-5D**: A generic measure of health status that provides a simple descriptive profile used in the clinical evaluation of health care.

### 4.2. Participants, organization and collaborations

The PhD will be conducted at Ahus and will be a further addition to the solid group of PhDs from the orthopedic department. Main supervisor: Asbjørn Aarøen PhD, MD Professor and Consultant at and Project Manager for the Norwegian Cartilage Project and co-supervisor Rune Bruhn Jakobsen MD, PhD Akershus University Hospital, Orthopedic department

The project participants are all part of the Oslo Sports Trauma Research Centre (OSTRC) which is a regional research network working in injury prevention and treatment. We have also established collaboration with the Norwegian Cartilage Project (NCP) which is a nationwide multicenter scientific collaboration with an aim to improve the management of chondral damage to the knee. This established research network will ensure collaboration across national institutions and will ensure the inclusion of enough patients for our ICRS validation study and contribute to the quality of our research. Conducting
these studies parallel to the Norwegian Cartilage Project will ensure steady inclusion and progress as cartilage injuries nationwide are referred to Ahus in this period.

4.3. Funding

Project duration is estimated to 6 years. Our research group has previously received internal strategic funding that has been used for video recording equipment for use in the ICRS validation study. Internal strategic funding from Ahus for 2017 (NOK 100.000) has been used to initiate the follow up of chondral fractures. We have received NOK 218.000 from Sophies Minde for 2019 which will be used to start the Stem Cell Study follow up. For 2020 our project has been granted NOK 500.000 in additional internal strategic funding to ensure further progress.

4.4. Plan for activities, visibility and dissemination

The plan is to complete the PhD within the 6 years outlined. The first study on Chondral fractures will start 01.01.19 with inclusion and data collection estimated within the first half of 2020. Data processing and publication within 01.01.20 The other two studies are planned for submission by 2023 and 2025 respectively. Publication is expected 3 to 6 months after first submission. A thesis is expected to be defended by 2026. Progress will be ensured by regular meetings between the PhD candidate and the supervisors as well as presentations in the research group Oslo Sports Trauma Research Centre (OSTRC).

The results will be published in a peer reviewed orthopedic journal, as well as presented to the orthopedic community at scientific meetings. According to University of Oslo recommendations, preference will be given to open access, high impact journals. So far, the project has been presented at the Norwegian Orthopedic Society’s annual autumn congress, OSTRC’s Kleivstua congress, Orthopedeic Research Seminars at Ahus as well as morning meetings in the orthopedic department. The study protocol has received favourable feedback from national as well as international reviewers present.

4.5 Plan for implementation

It is of paramount importance that surgical methods are evaluated scientifically before new procedures are introduced into clinical practice. Anecdotal and single case reports indicate that fixation of chondral fractures by meniscal arrows is an improvement from the traditional debridement and removal of the fragment, however little evaluation exists in the literature. Our study will comprise the largest case series to date, and the findings will pave way for further improvement in the surgical management of these difficult knee injuries.

A universally accepted classification system is mandatory in decision-making regarding treatment planning, evaluation and comparison of research results. Assessment of the reliability of the ICRS classification system is the first important step towards such standardization in the evaluation of cartilage injury. Evaluating the influence of recorded images is important knowledge for the clinicians and researchers evaluating chondral lesions as this could potentially allow for remote diagnostics or research.
Comparing the long term outcome of the patients treated with MSC or ACI will explore the potential of mesenchymal stem cells derived from bone marrow to heal a cartilage injury. This is the first conducted human clinical trial on this topic, and may influence the choice of treatment in chronic cartilage injuries worldwide.

5. User Involvement

Akershus University Hospital has a well-functioning general service-user panel, which, among other duties, judges the need for user involvement in new research projects and assists in providing it. The user-panel consists of patient representatives, health professionals, policy makers and healthcare administrators. The panel will be used to discuss the strategic direction of our research as well as more detailed planning and dissemination of our research projects. This process will ensure the appropriate type and level of involvement in the different sub-projects, appointing service-users with topic-specific experience. The PhD candidate will take special care to safeguard the interests of the user. Since the cartilage, lesions are often young and active athletes, our collaboration with OSTRC (Oslo Sports Trauma Research Center) ensures user involvement from the athletes as well as the national sports medicine community.

6. Ethical Considerations

The recruitment of patients will depend on informed written consent. Participants in the studies will not be subjected to any alterations in pre-planned procedures or post-operative rehabilitations. There will be no possible disadvantages for the included patients, except from a calculated elongation of the arthroscopic procedure due to photo/video assessments of about 2-3 minutes. Patients declining to participate in the study will be treated according to the current standard of care at the investigating institution. All three studies are approved by the Regional Ethical Committee of South Eastern Norway, University of Oslo and by the local data protection officer. The MCS vs ACI trial is registered at http://clinicaltrials.gov (ClinicalTrials.gov NCT00885729), and conducted according to Good Clinical Practice (GCP) guidelines.

Authors contribution: Asbjørn Årøen drafted the first version of the protocol that later was revised by Stian Kjennvold in the final round for application for funding by regional grants. The Icrs has approved the reprint of the figure in the protocol.

7. References

1. Aroen, A., et al., Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med, 2004. 32(1): p. 211-5.

2. Hjelle, K. et al. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy, 2001. 18(7): p. 730-4
3. Heir, S., et al., Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. Am J Sports Med, 2010. 38(2): p. 231-7.

4. Buckwalter et al., Restoration of Injured or Degenerated Articular Cartilage. J Am Acad Orthop Surg, 1994. 2(4): p. 192-201.

5. Loken, S., et al., 6-year follow-up of 84 patients with cartilage defects in the knee. Knee scores improved but recovery was incomplete. Acta Orthop, 2010. 81(5): p. 611-8.

6. Mundi, R et al; Cartilage Restoration of the Knee: A Systematic Review and Meta-analysis of Level 1 Studies. Am J Sports Med. 2016 Jul;44(7):1888-95

7. Jakobsen R. et al. An Analysis of the Quality of Cartilage Repair Studies J Bone Joint Surg Am. 87:2232-2239, 2005. doi:10.2106/JBJS.D.02904

8. Maleisius W et al. Refixation of large chondral fragments on the weight-bearing area of the knee joint: a report of to cases; Arthroscopy 1994 Dec; 10(6): 630-3

9. Nakamura N. et al Healing of a chondral fragment of the knee in an adolescent after internal fixation: a case report J Bone Joint Surg Am. 2004 Dec;86(12): 2741-2746

10. Uchida R, et al. Chondral fragment of the lateral femoral trochlea of the knee in adolescents. Knee. 2012; 19(5):719-723.8.

11. Chan et al. Fixation of chondral fracture of the weight-bearing area of the lateral femoral condyle in an adolescent. Knee Surg Sports Traumatol Arthrosc. 2014 Jun;22(6):1284-7

12. Nakayama H, et al. Bone peg fixation of a large chondral fragment in the weight-bearing portion of the lateral femoral condyle in an adolescent: a case report. J Med Case Rep. 2014; 8:316.

13. Chung et al. Fixation of chondral fracture of the weight-bearing area of the lateral femoral condyle in an adolescent. Knee Surg Sports Traumatol Arthrosc (2014) 22:1284-1287

14. Morris et al. Adolescent Femoral Chondral Fragment Fixation With Poly-L-Lactic Acid Chondral Darts. Orthopedics, 2016 Volume 39. Issue 2: e362-e366

15. Siparsky et al. Open Reduction Internal Fixation of Isolated Chondral Fragments Without Osseous Attachment in the Knee – A case series. Orthop J Sports Med. Mar;5(3): 2325967117696281

16. Spahn, G. et al. Reliability in arthroscopic grading of cartilage lesions: results of a prospective blinded study for evaluation of inter-observer reliability. Arch Orthop Trauma Surg, 2011. 131(3): p. 377-81

17. Fanligan, D et al. Interrater and intrarater Reliability of Arthroscopic Measurements of Articular Cartilage Defects in the Knee. JBJS, Am.21 June 2017Volume 99-Issue 12-p 979-988

18. Wondrasch, B et al. The feasibility of a 3-month active rehabilitation program for patients with knee full-thickness articular cartilage lesions: the Oslo Cartilage Active Rehabilitation and Education Study Orthop Sports Phys Ther. 2013 May;43(5):310-24.

19. Ross MD, Langford B, Whelan PJ; Test-retest reliability of 4 single-leg horizontal hop tests. J Strength Cond Res. 2002;16(4):617–622
20. Caplan et al. Mesenchymal stem cells. Journal of Orthopaedic Research, 1991 (9): p:641-650
21. Brittberg et al. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994 Oct 6;331(14):889-95.
22. Røtterud et al. Relationship between CTX-II and patient characteristics, patient-reported outcome, muscle strength, and rehabilitation in patients with a focal cartilage lesion of the knee: a prospective exploratory cohort study of 48 patients. BMC Musculoskeletal Disorders 2014 15:99