Is good muscle function a protective factor for early signs of knee osteoarthritis after anterior cruciate ligament reconstruction? The SHIELD cohort study protocol

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SUMMARY

Introduction: Knee injury history and increased joint load, respectively, are major risk factors for the development of knee osteoarthritis (OA). Lower extremity muscle function, such as knee muscle strength, influence joint load and may be important for the onset of knee OA. However, the role of muscle function as a possible modifiable protective mechanism for the development of OA after anterior cruciate ligament reconstruction (ACLR) is not clear.

Methods and analysis: In this prospective cohort study, 100 patients (50% women, 18–35 years) with ACLR will be recruited from Skåne University Hospital, Sweden and Oslo University Hospital, Norway. They will be assessed with a comprehensive test battery of muscle function including muscle strength, muscle activation, hop performance, and postural orientation as well as patient-reported outcomes, one year (baseline) and three years (follow-up) after ACLR. Primary predictor will be knee extension strength, primary outcome will be patient-reported knee pain (Knee Injury and Osteoarthritis Outcome Score, subscale pain) and secondary outcomes include compositional MRI (T2 mapping) and turnover of cartilage and bone biomarkers. Separate linear regression model will be used to elucidate the influence of each baseline muscle function variable on the outcomes at follow-up, adjusted for baseline values. Twenty non-injured individuals will also be assessed with MRI. This study is approved by The Regional Ethical Review Board in Lund (Sweden) and Oslo (Norway).

Discussion: This study may have important clinical implications for using muscle function to screen for risk of early-onset knee OA and for optimizing exercise therapy after knee injury.

1. Introduction

An anterior cruciate ligament (ACL) injury is commonly associated with long-term functional limitations [1–4]. In addition, it is well established that a history of knee injury is a major risk factor for the development of knee osteoarthritis (OA). A recent systematic review and meta-analysis found that a previous ACL injury was associated with a four to six-fold increased risk of developing knee OA two to 22 years post knee injury [5].

OA develops slowly. Follow-up of approximately 5–10 years is required to detect radiographic features indicative of OA such as joint space narrowing and osteophytes, i.e., features found relatively late in the disease process [6], indicating that radiography is not useful for early detection of OA [7,8]. Early detection of the disease is important as this

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may permit early intervention, such as load management by appropriate exercise programs, before the biomechanical derangement becomes too severe. Patient-reported pain may be used as a marker of future significant knee pain and early symptomatic knee OA in patients with ACL injury [9,10] and has also been reported to be related to features of tibiofemoral OA, such as joint space narrowing and cartilage thickness [9,11,12]. Magnetic resonance imaging (MRI) techniques, such as T2 relaxation time (a measure of water content and biochemical composition) is another promising technique that seems sensitive for detecting cartilage degeneration early (two – three years) in the disease process [13,14]. T2 is reported to be higher in the involved knee 6–24 months after injury compared to both healthy controls [15] and to the contra-lateral knee [16]. Furthermore, increased knee adduction moment [17], worse self-reported activity of daily living [16] and lower knee muscle strength [18] seem to be associated with higher T2. Thus, T2 may be a clinically important measure of early knee OA after knee injury. Molecular biomarkers may also be used to identify early OA in these patients and several biomarker candidates are under validation [19–21].

Knee joint load is suggested to be a contributing factor for knee OA development and progression [22–25]. Sensorimotor function, such as muscle strength and muscle activation patterns, factors that are modifiable by training, influences the magnitude of joint load and may, thus, play an important role for the onset of knee OA [26]. Knee muscle weakness has been reported to be associated with an increased risk of developing radiographic and symptomatic knee OA in individuals without previous knee joint injury [27], whereas the evidence for such association in individuals with a knee injury is inconclusive [27,28]. A recent systematic review reported conflicting results of other measures of muscle function than knee muscle strength, such as hop performance, as contributing factors for radiographic or symptomatic OA development after knee injury [28]. Furthermore, low patient-reported function 2 years after ACLR has also shown to be associated with symptomatic and radiographic knee OA ten years post injury [28]. To our knowledge, there are no studies on the role of muscle function as a possible modifiable protective mechanism for the development of early-stage OA after knee injury, using a comprehensive test battery of muscle function as well as different measures of early knee OA. Such knowledge would help in designing more effective training interventions in the treatment of knee injury and subsequent early-onset OA. Thus, the aim of this prospective cohort study including young people with anterior cruciate ligament reconstruction (ACLR) is to study the association between different measures of muscle function and early future knee OA assessed with MRI, and early detection of OA in biomarker profiles, respectively. In addition, we will investigate the prevalence of early knee OA in individuals 1 and 3 years post ACLR, respectively, compared to non-injured controls.

2. Methods and analysis

This is a prospective cohort study adhering to the STROBE guidelines (http://www.strobe-statement.org). The study is registered on Clinical-Trials.gov (NCT03473873).

2.1. Participant and setting

Patients will be consecutively recruited from the Department of Orthopedics, Skåne University Hospital, Sweden (main site) and the Department of Orthopedics, Oslo University Hospital, Oslo, Norway. The majority of patients (approx. 70%) will be included in Sweden. The study is approved by The Regional Ethical Review Board in Lund, Sweden (Dnr D: 2016/1128). Inclusion criteria: i) one year (between 10 and 16 month) after ACLR, with or without associated injuries to other structures of the knee (e.g., collateral ligament(s), meniscal injury), ii) age 18–35 years. Exclusion criteria: i) previous serious injury or surgery to either knee (e.g., ACL tear, meniscal tear), ii) diseases or disorders overriding the knee condition (e.g., neurological disease), iii) contra-indicators for MRI, iv) not understanding the languages of interest (any Scandinavian language or English). Possible confounders to record at the assessments include: i) additional surgery to the index knee between the time point of ACLR and inclusion and/or during follow-up, ii) serious injury to the index knee (e.g., giving-way episode(s)) resulting in pain and/or swelling and requiring inpatient or outpatient health care between the time point of ACLR and inclusion and/or during follow-up. Demographics (e.g., age, sex, BMI, heredity) and other patient-reported outcomes will be collected at baseline and at follow-up (See Table 1 for full details). As a sample of convenience, 20 age- and sex-matched non-knee injured individuals will be recruited among students in Lund, Sweden. With the exception that these individuals should be free from ACL injuries to both knees, the inclusion/exclusion criteria will be the same for this cohort as for the patient cohort.

2.2. Assessments

All predictors and outcomes will be assessed at 1 year (baseline) and at 3 years (follow-up) after ACLR. Primary predictor is knee extension muscle strength at baseline. Secondary predictors are knee flexion, hip, and trunk muscle strength, hop performance, postural orientation and patient-reported outcomes (except patient-reported pain) at baseline. Exploratory predictor is muscle activation pattern at baseline. Main outcome is the Knee Injury and Osteoarthritis Outcomes Score (KOOS), subscale pain at follow-up. Secondary outcome is T2 (MRI) and biomarker profiles at follow-up (full description of predictors and outcomes are outlined below and in Tables 1 and 2). One physical therapist researcher will perform all functional assessments in Lund and another physical therapist researcher will perform all functional assessments in Oslo. The researchers will give standardized verbal instructions and an inter-rater reliability testing has been performed, showing moderate to excellent inter-rater reliability for all functional assessments (ICC, 0.66–1.0) (See Appendix A for detailed description of the reliability assessment).

The participants are told to wear shorts and t-shirt. Strength tests will be performed without shoes whereas the postural orientation tasks and hop tests will be performed with training shoes. In an effort to minimize bias related to learning effects of the injured leg, the right leg will be tested first (irrespective of whether the right or left leg is injured). This will be applied for all assessments except for isokinetic knee strength for which the non-injured leg will be tested first, according to the standard procedure for Biodex assessments.

2.3. Predictors

2.3.1. Knee strength

Isokinetic concentric muscle strength tests during knee extension and flexion will be measured at 60°/sec with a dynamometer (Biodex Medical Systems, Shirley, New York). Four trial repetitions will be performed with submaximal effort, followed by a 1-min rest. Five test repetitions will then be performed and recorded. Peak torque (Nm) and normalized peak torque (Nm/kg) for knee extension and flexion will be recorded [29].

2.3.2. Hip and trunk strength

Isometric peak force (N) of hip external rotation, abduction, and extension, and trunk, will be measured with a hand held dynamometer (Power Track II Commander Echo, JTECH Medical, Salt Lake City, Utah, USA) as described [30]. During all assessments, a belt will be used to fixate the dynamometer and the participant will be encouraged to push against the dynamometer as much as they can. The leverage (m) will be measured from the joint axis of rotation to the point of application of the force transducer for each test. Each test will be repeated three times and each contraction will be maintained for 5 s with approximately 15 s of rest in between contractions. The peak value of the three trials in Newton meter, normalized for body weight (Nm/kg), will be used in the analysis.
2.3.3. Hop performance

Two reliable hop tests, the single-leg hop for distance and the side-hop, will be performed as described [31]. The participants will perform three to five practice trials followed by three maximum approved trials for the single-leg hop test for distance. The hop distance is measured in centimeters from the toe at the push-off to the heel at the landing position. The side hop will be performed once on each leg and the participants will be instructed to jump as many times as possible, landing outside two tape strips 40 cm apart, during a period of 30 s.

2.3.4. Postural orientation

The test battery consists of 5 functional tasks; single-limb mini squat (SLMS), stair descending (SD), forward lunge (FL), single-leg hop for distance (SLHD) and side hop (SH); tasks ranging from resembling daily

Table 1

Demographics and patient-reported outcomes to be collected at baseline and at follow-up.

| Demographics         | Baseline | Follow-up |
|----------------------|----------|-----------|
|                      | ACLR     | Controls  |
|                      | patients | patients  |
| Sex                  | X        | X         |
| Age (years)          | X        | X         |
| Height (cm)          | X        | X         |
| Body mass (kg)       | X        | X         |
| Primary sport        | X        | X         |
| years in primary sport | X      | X         |
| Injured knee (left/right) | X     | X         |
| Date of injury       | X        | X         |
| Date of reconstruction | X      | X         |
| Graft type           | X        | X         |
| Injury situation     | X        | X         |
| Contact/non-contact injury | X   | X         |

Table 2

Predictors and outcomes at baseline and follow up.

| Predictors at baseline and follow-up for ACLR patients | Data collection instrument |
|-------------------------------------------------------|---------------------------|
| **Primary predictor**                                 | Isokinetic strength (Nm/kg) (Biodex) |
| Knee extensor muscle strength                         | Hop performance (side-hop (n), SLHD (cm)), Postural orientation errors (movement quality scoring) |
| **Secondary predictors**                              | Isokinetic knee flexion strength (Biodex), isotropic hip and trunk muscle strength (handheld dynamometer) |
| Performance-based measures                            | Questionnaires: KOOS subscales (except pain), SF-36, Tegner activity scale, ACL-RSI, ACL-QoL, Global knee function (NRS 1-10), PSS-10 |
| Muscle strength                                       | Muscle activation pattern of the hip, trunk and knee during the SLHD (electromyography) |
| Patient-reported function                              | Muscle activation pattern of the hip, trunk and knee during the SLHD (electromyography) |
| **Exploratory predictor**                             | Muscle activation pattern of the hip, trunk and knee during the SLHD (electromyography) |

| Outcomes at baseline and follow-up for ACLR patients and controls | Data collection instrument |
|-------------------------------------------------------------------|---------------------------|
| **Primary outcome**                                               | Questionnaire: KOOS subscale pain |
| Patient-reported outcome                                          | T2 mapping (MRI) |
| **Secondary outcomes**                                            | Blood samples of venous blood to assess specific biomarkers: COMP and ARGS-aggrecan, NTX-I, TRAP5b and cytokines |
| Quantitative assessment of cartilage morphology                   | SLHD = single-leg hop for distance, KOOS = knee osteoarthritis outcome score, ACL-RSI = ACL Return to Sport after Injury Scale, ACL-QoL = ACL Quality of Life, SACQ = Self-administered Comorbidity Questionnaire, PSS-10 = Perceived Stress Scale, MRI = magnetic resonance imaging, ARGS-aggrecan = ARGS neoepitope of aggrecan, COMP = Cartilage oligomeric matrix protein, NTX-I = N-terminal type I collagen cross-linked telopeptide, TRAP5b = tartrate-resistant acid phosphatase Sb. |

a Data collection in Lund only.
to more demanding activities [32]. The tasks will be video-recorded from a frontal view for later assessment of the patient’s postural orientation. The videos can be viewed several times and/or in slow motion if needed. Between 2 and 6 segment-specific postural orientation errors (POEs) will be observed and scored for each task on a 4-point ordinal scale from 0 to 3 where 0 = good postural orientation, i.e., represents no signs of POEs, 1 = "fair", represents signs of POEs, 2 = "poor", represents clear signs of POEs and 3 = "very poor", represents when the execution of the test does not have any similarities to the intended task. The total POE score across all and within tasks and segment-specific POEs will be used in the analysis. High inter-rater reliability has been reported for this test battery in patients with ACL injury [32].

2.3.5. Patient-reported outcomes

Data for the following valid questionnaires will be collected and managed using an electronic data capture tool (REDCap) [33] (Lund) or using paper questionnaires (Oslo); The Short-Form 36 [34] will be used for assessment of perceived generic health. For patient-reported knee specific function, the KOOS (all subscales except pain) [35], Global knee function: Numeric Rating Scale (1–10 were 1 = worst and 10 = best) [36] and the ACL Quality of Life [37] will be used. The Tegner activity scale [38] will be used to assess pre-injury and current activity level and the ACL Return to Sport after Injury Scale [39] will be used to evaluate psychological readiness for returning to sport after injury. In addition, the participants will answer a questionnaire regarding their pre-injury activity, if they plan to return/have returned to the same activity or different activity level as well as time point of return (if any). Finally, the Perceived stress scale - 10 [40] will be used for perceived stress.

2.3.6. Muscle activation pattern

For the patients recruited in Lund, muscle activation patterns for the following muscles will be recorded during the landing phase of the single-leg hop for distance, using a wireless electromyographic system (Desktop DTS, Noraxon U.S.A. Inc, Scottsdale, Arizona, USA); Gluteus maximus, Gluteus medius, Semitendinosus, Biceps femoris, Vastus medialis, Medial gastrocnemius and Iliocostalis. The maximum voluntary contraction (MVC) for each muscle will be calculated from the maximum value of three repetitions, synchronously collected with the torque data described above.

2.4. Outcomes

2.4.1. Patient-reported outcome

The valid, patient-reported KOOS [35] subscale pain, scored on a 0 (worst) to 100 (best) scale will be used as a marker of symptomatic OA. In addition to the continuous measure of KOOS pain, a cut-off of will be used, where a score of ≤72 on the KOOS pain subscale will represent symptomatic knee OA and a score of >72 will represent no symptomatic knee OA, according to that previously described [9,10]. This particular cut-off is based on the normal mean (92.3 ± 10.0) KOOS pain score in an athletic population with a history of knee ligament injury and represents two standard deviations below the mean [41].

2.4.2. MR imaging

Compositional MRI of cartilage quality will be performed using T2 mapping using a 1.5 T scanner.

2.4.3. MR image acquisition

Subjects will be positioned in a supine position with their feet first in a 1.5 T MRI scanner (AvantoFit, Siemens Healthcare, Erlangen, Germany) and the injured knee placed in a knee coil (TxRx 15 Ch Knee, Siemens, Erlangen, Germany). After localizer sequences, four 2D proton density weighted turbo spin echo sequences will be acquired for scoring and clinical evaluation with: 1) sagittal orientation and no fat suppression, and 2–4) sagittal, transversal and coronal orientations with fat suppression. For T2 mapping, two sagittal slices positioned in the central part of each of the medial and lateral tibiofemoral cartilage compartments, respectively, will be acquired in a single, interleaved acquisition using a 2D multi echo spin echo sequence with 12 echoes. Finally, a sagittal T1 weighted 3D VIBE (Volumetric Interpolated Breath Hold Examination) sequence will be acquired for segmentation of the bone. Imaging parameters for each sequence are summarized in Table 3.

2.4.4. Analysis and ROI definition

T2 maps will be calculated online at the scanner from the acquired multi echo spin echo images using a built-in application (MapIt). Using the ImageJ software (Rasband, W.S., ImageJ, U. S. National Institutes of Health, Bethesda, Maryland, USA, https://imagej.nih.gov/ij/, 1997–2018.), regions of interest (ROIs) will be defined covering the superficial half and the deep half of the cartilage in each of the medial and lateral weight-bearing femoral and tibial cartilages respectively, resulting in a total of eight ROIs per subject MR exam. Although the articular cartilage is generally divided into three layers, distinction beyond a superficial and deep ROI will not be possible here, due to the limited spatial resolution of the MR image. The femoral ROIs will cover a region from the middle of the tibial plateau (regarding anterior-posterior position) to the posterior horn of the meniscus. The tibial ROIs includes the central 1/3 of the tibial cartilage in the sagittal plane (Fig. 1). ROIs will be defined in the shortest TE (TE = 10 ms) image and the position of each ROI will then be copied to the corresponding T2 map for evaluation of T2.

All ROIs will be drawn by a single reader (AC), but the ROIs of a subgroup of 15 subjects will also be drawn by an additional reader (PP), and a second time by AC, for investigation of the inter- and intra-rater reliability, respectively, using the Intra-class Correlation Coefficient (ICC) [42]. Results will be presented as the mean T2 within each ROI, i.e., the deep and superficial regions of the femoral and tibial cartilages, respectively.

2.4.5. Biomarker profiles

Blood samples of venous blood will be collected to assess molecular biomarkers of cartilage and bone turnover in serum [43]. Specific biomarkers including, but not limited to, cartilage markers cartilage oligomeric matrix protein (COMP; ELISA based immunoassay from BioVendor) and ARGS-aggrecan (ARGS neoepitope of aggrecan; in-house

| Table 3 | Image acquisition parameters for the proton-density weighted turbo-spin echo (PDW TSE), multi-echo spin echo (MESE) and T1 Weighted Volumetric Interpolated Breath Hold Examination (3D T1W VIBE) sequences. |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sequence | PDW TSE | PDW TSE | PDW TSE | PDW TSE | MESE | T1W VIBE |
| Orientation | Sagittal | Sagittal | Coronal | Transversal | Sagittal | Sagittal |
| 20/3D | 2D | 2D | 2D | 2D | 2D | 3D |
| Fat suppression | None | Fat | Fat | Fat | None | Water excitation |
| Echo time (ms) | 41 | 45 | 37 | 38 | 10–120 | 6 |
| Repetition time (ms)* | 3000 | 4550 | 3000 | 3760 | 2360 | 14 |
| Flip angle | 10 | 11 | 5 | 5 | 12 |
| Field of view (mm²) | 160×160 | 170×170 | 150×150 | 160×160 | 145×160 | 150×150 |
| Voxel size (mm³) | 0.4×0.4×3 | 0.5×0.5×3 | 0.5×0.5×3 | 0.4×0.4×3 | 0.3×0.3×0.6 |

* May vary slightly as the number of slices will be adjusted for coverage in each case.
immunoassay based on Meso Scale Discovery platform (MSD), and bone markers N-terminal type I collagen cross-linked telopeptide (NTX-I; ELISA based immunoassay from Osteomark) and tartrate-resistant acid phosphatase 5b (TRAP5b; ELISA based immunoassay from Quidel) will be analysed in batch mode \[44–47\]. Possibly, inflammatory biomarkers (including C-reactive protein, tumour necrosis factor-α, interleukin-6; e.g. using MSD multiplex immunoassays) will be analysed in batch mode to obtain complementary data \[48,49\].

2.5. Statistical analysis

For descriptive purposes, the mean (SD), or median (quartiles), at baseline and follow-up assessments will be used as appropriate. Separate linear regression models will be used to elucidate the influence of the absolute values of each predictor on the absolute value on primary, secondary and exploratory outcomes in cross-sectional analyses and on the absolute value as well as change in primary, secondary and exploratory outcomes in longitudinal analysis, adjusted for baseline values and possible confounders (e.g., age and associated injuries). In addition, logistic regression analysis will be used to elucidate the influence of each predictor on significant knee pain (KOOS pain $\leq 72$ vs $> 72$). Assuming a clinically relevant correlation of 0.30 between knee extension strength and self-reported pain \[50\], we need 84 patients with 80% power at the 5% significance level. Based on this calculation, we will include 100 patients including an approximate drop-out of 15%. For explorative purposes, an analysis of covariance (ANCOVA) will be used to investigate differences in the presence of early knee OA between the 100 patients with ACLR and twenty sex and age matched non-injured individuals, adjusting for activity level.

3. Discussion

To our knowledge, our study will be the first to investigate the role of different measures of muscle function as possible protective factors for possible markers of early OA development including patient-reported pain, MRI, and biomarkers in patients with ACLR. There is today no consensus regarding the definition of early symptomatic OA in younger individuals with a history of knee injury \[10\]. Several different models, such as a cut-off of 72 on the KOOS pain subscale, the minimally clinical reported difference (KOOS pain) and a combination of different cut-offs of the different KOOS subscales have been proposed \[10\]. In this study, we chose the cut-off of 72 on the KOOS pain subscale since this measure is reported to be related to cartilage loss \[11\] as well as knee pain in patients with ACL injury \[9\]. Furthermore, we will include both advanced measures of muscle function (isometric muscle strength assessed with a Biodex) and those that are easily administered in clinical research and in the clinical setting (performance-based measures). If muscle function will be a protective factor for possible markers of early OA, this will have important clinical implications for using muscle function as screening for knee OA at an early stage of the disease, and for optimizing muscle function in the treatment of knee injury. Further studies may determine whether exercise aimed at improving important aspects of muscle function may prevent, or slow the progression of, early signs of knee OA. By addressing muscle function as a modifiable factor to prevent, or slow the progression of, knee OA, this project ultimately has the potential to influence clinical management at an early stage of this chronic disease, and reduce the personal and societal burden of this increasing health problem.

Authors’ contribution

All authors contributed to the conception and design of this study as well as the writing of this study protocol. All authors read and approved the final version of this manuscript.

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Declaration of competing interest

The authors declare no competing interest.

Appendix A. Assessment of inter-rater reliability

Methods

An inter-rater reliability assessment between the two testers in Sweden and Norway was performed in November 2017. Ten healthy individuals without previous knee injury performed all muscle strength tests, single-leg hop for distance and the side-hop as described in the study protocol. A 5-min warm-up on a stationary bike was performed prior to the tests. The tests were performed twice with 30 min of rest between tests. Two minimize bias relating to learning effects, half of the participants were assessed by one of the testers on their first testing session and the other half were assessed by the second tester on their first testing session.
A moderate to excellent inter-rater reliability were found for all assessments (ICC2 0.66–1.0) (Table A1).

Table A1
ICC values of the muscle strength measures and hop tests.

| Test                                    | ICC2   |
|-----------------------------------------|--------|
| Hip external rotation peak torque (hhd) | 0.931  |
| Hip extension peak torque (hhd)         | 0.666  |
| Hip abduction peak torque (hhd)         | 0.759  |
| Side-bridge peak torque (hhd)           | 0.726  |
| Knee extension peak torque (biodes)     | 0.849  |
| Knee flexion peak torque (biodex)       | 0.838  |
| SLHD (cm)                               | 1.0    |
| Side-hop (n)                            | 0.994  |

ICC = intra-class correlation coefficient, hhd = hand-held dynamometer.
SLHD = single-leg hop for distance, cm = centimeter, n = number of repetitions.

References

[1] E. Tengman, L. Brax Olefsson, K.G. Nilsson, Y. Tegner, L. Lundgren, C.K. Häger, Anterior cruciate ligament injury after more than 20 years: 1. Physical activity level and knee function, Scand. J. Med. Sci. Sports 24 (6) (2014) e491–500.
[2] J.L. Whitaker, L.J. Woodhouse, A. Nettel-Aguirre, C.A. Emery, Outcomes associated with early post-traumatic osteoarthritis and other negative health consequences 3–10 years following knee joint injury in youth sport, Osteoarthritis Cartilage 23 (7) (2015) 1122–1127.
[3] E. Ågeberg, R. Thomee, C. Neeter, K.G. Sillernagel, E.M. Roos, Muscle strength and functional performance in patients with anterior cruciate ligament injury treated with training and surgical reconstruction or training only: a two to five-year follow-up, Arthritis Rheum. 59 (12) (2008) 1773–1779.
[4] E. Tengman, L. Brax Olefsson, A.K. Stemdotter, K.G. Nilsson, C.K. Häger, Anterior cruciate ligament injury after more than 20 years: 2. Concentric and eccentric knee muscle strength, Scand. J. Med. Sci. Sports 24 (6) (2014) e501–509.
[5] E. Poulsen, G.H. Goncalves, A. Bricca, E.M. Roos, J.B. Thorlund, C.B. Juhl, Knee osteoarthritis risk is increased 4-6 fold after knee injury - a systematic review and meta-analysis, Br. J. Sports Med. 53 (23) (2019) 1454-1465.
[6] R.A. Magnussen, A.A. Mansour, J.L. Carey, P. Spindler, Meniscus status at anterior cruciate ligament reconstruction associated with radiographic signs of osteoarthritis, Osteoarthritis Cartilage 22 (5) (2014) 1024.
[7] E. Tengman, L. Brax Olofsson, K.G. Nilsson, Y. Tegner, L. Lundgren, C.K. Häger, Anterior cruciate ligament injury and knee osteoarthritis: data from the osteoarthritis initiative, Osteoarthritis Cartilage 21 (9) (2013) 1768–1777.
[8] J.T. Andrish, R.G. Marx, S.I. Macias-Hernandez, A. Miranda-Duarte, I. Ramirez-Mora, S. Cortes-Gonzalez, J.D. Morenza-Alba, A. Olascaga-Gomez, R. Coronado-Zarco, L. Soria-Bastida Mde, T.J. Nava-Bringas, E. Cruz-Medina, Knee muscle strength correlates with joint cartilage T2 relaxation time in young participants with risk factors for osteoarthritis, Clin. Rheumatol. 35 (8) (2016) 887–892.
[9] M.S. Harkey, B.A. Luc, Y.M. Golightly, A.C. Thomas, J.B. Driban, A.C. Hackney, B. Piotroskin, Osteoarthritis-related biomarkers following anterior cruciate ligament injury and knee osteoarthritis reconstruction: a systematic review, Osteoarthritis Cartilage 23 (1) (2015) 1–12.
[10] W.E. van Spil, L.A. Sliagga, Osteoarthritis year in review 2019: biomarkers (biochemical markers), Osteoarthritis Cartilage 28 (3) (2020) 296–315.
[11] L.J. Wang, N. Zeng, Z.P. Yan, J.T. Li, G.X. Ni, Post-traumatic osteoarthritis following ACL injury, Arthritis Res. Ther. 22 (1) (2020) 57.
[12] M.R. Maly, S.M. Acker, S. Totterman, J. Tames-Peña, P.W. Stratford, J.P. Callaghan, J.D. Adachi, K.A. Beattie, Knee adduction moment relates to medial femoral and tibial cartilage morphology in clinical knee osteoarthritis, J. Biomech. 48 (12) (2015) 3495–3501.
[13] M.W. Creaby, Y. Wang, K.L. Bennell, R.S. Hinman, B.R. Metcalf, K.A. Bowles, F.M. Cicuttini, Dynamic knee loading is related to cartilage defects and tibial plateau bone area in medial knee osteoarthritis, Osteoarthritis Cartilage 18 (11) (2010) 1380–1385.
[14] K.L. Bennell, K.A. Bowles, Y. Wang, F. Cicuttini, M. Davies-Tuck, R.S. Hinman, Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis, Ann. Rheum. Dis. 70 (10) (2011) 1770–1774.
[15] T. Miyazaki, M. Wada, H. Kawahara, M. Sato, H. Baba, S. Shimada, Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis, Ann. Rheum. Dis. 61 (7) (2002) 617–622.
[16] K.L. Bennell, T.V. Wrigley, M.A. Hunt, B.W. Lim, R.S. Hinman, Update on the role of muscle in the genesis and management of knee osteoarthritis, Rheum. Dis. Clin. N. Am. 39 (1) (2013) 145–176.
[17] B.E. Oiestad, C.B. Juhl, J. Itzen, J.B. Thorlund, Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis, Osteoarthritis Cartilage 23 (2) (2015) 171–177.
[18] M.M. Lie, M.A. Risberg, K. Storheim, L. Enghebretsen, B.E. Oiestad, What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? An updated systematic review, Br. J. Sports Med. 53 (18) (2019) 1162–1167.
[19] J.B. de Araujo Ribeiro Alvares, R. Rodrigues, R. de Azevedo Franke, B.G. da Silva, R. Pinto, M.A. Vaz, B.M. Baroni, Inter-machine reliability of the Biodex and Cybex isokinetic dynamometers for knee flexor/extensor isometric, concentric and eccentric tests, Phys. Ther. Sport 16 (1) (2015) 59–65.
[20] J.I. Kemp, A.G. Schache, M. Makdissi, K.J. Sims, K.M. Crossley, Greater understanding of normal hip physical function may guide clinicians in providing targeted rehabilitation programs, J. Sci. Med. Sport 16 (4) (2013) 292–296.
[21] J. Nae, M.W. Creaby, G. Nilsson, K.M. Crossley, Muscle strength, Scand. J. Med. Sci. Sports 24 (6) (2014) e501–e509.
[22] J.B. de Araujo Ribeiro Alvares, R. Rodrigues, R. de Azevedo Franke, B.G. da Silva, R. Pinto, M.A. Vaz, B.M. Baroni, Inter-machine reliability of the Biodex and Cybex isokinetic dynamometers for knee flexor/extensor isometric, concentric and eccentric tests, Phys. Ther. Sport 16 (1) (2015) 59–65.
[23] J.I. Kemp, A.G. Schache, M. Makdissi, K.J. Sims, K.M. Crossley, Greater understanding of normal hip physical function may guide clinicians in providing targeted rehabilitation programs, J. Sci. Med. Sport 16 (4) (2013) 292–296.
[24] J.B. de Araujo Ribeiro Alvares, R. Rodrigues, R. de Azevedo Franke, B.G. da Silva, R. Pinto, M.A. Vaz, B.M. Baroni, Inter-machine reliability of the Biodex and Cybex isokinetic dynamometers for knee flexor/extensor isometric, concentric and eccentric tests, Phys. Ther. Sport 16 (1) (2015) 59–65.
[25] J.I. Kemp, A.G. Schache, M. Makdissi, K.J. Sims, K.M. Crossley, Greater understanding of normal hip physical function may guide clinicians in providing targeted rehabilitation programs, J. Sci. Med. Sport 16 (4) (2013) 292–296.
[33] P.A. Harris, R. Taylor, R. Thielke, J. Payne, N. Gonzalez, J.G. Conde, Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support, J. Biomed. Inf. 42 (2) (2009) 377–381.

[34] C.A. McHorney, J.E. Ware Jr., A.E. Raczek, The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs, Med. Care 31 (3) (1993) 247–263.

[35] N.J. Collins, C.A. Prinsen, R. Christensen, E.M. Bartels, C.B. Terwee, E.M. Roos, Knee Injury and Osteoarthritis Outcome Score (KOOS): systematic review and meta-analysis of measurement properties, Osteoarthritis Cartilage 24 (8) (2016) 1317–1325.

[36] A. Williamson, B. Hoggart, Pain: a review of three commonly used pain rating scales, J. Clin. Nurs. 14 (7) (2005) 798–804.

[37] N. Mohtadi, Development and validation of the quality of life outcome measure (questionnaire) for chronic anterior cruciate ligament deficiency, Am. J. Sports Med. 26 (3) (1998) 350–359.

[38] Y. Tegner, J. Lysholm, Rating systems in the evaluation of knee ligament injuries, Clin. Orthop. Relat. Res. 198 (1985) 43–49.

[39] J.J. Gagnier, Y. Shen, H. Huang, Psychometric properties of patient-reported outcome measures for use in patients with anterior cruciate ligament injuries: a systematic review, JBJS Rev 6 (4) (2018) e5.

[40] J.M. Taylor, Psychometric analysis of the ten-item perceived stress scale, Psychol. Assess. 27 (1) (2015) 90–101.

[41] K.L. Cameron, B.S. Thompson, K.Y. Peck, B.D. Owens, S.W. Marshall, S.J. Svoboda, Normative values for the KOOS and WOMAC in a young athletic population: history of knee ligament injury is associated with lower scores, Am. J. Sports Med. 41 (3) (2013) 582–589.

[42] P.E. Shrout, J.L. Fleiss, Intraclass correlations: uses in assessing rater reliability, Psychol. Bull. 86 (2) (1979) 420–428.

[43] D. Heinegard, T. Saxne, The role of the cartilage matrix in osteoarthritis, Nat. Rev. Rheumatol. 7 (1) (2011) 50–56.

[44] B.B. Das, A. Roy, P.P. Rahan, Cartilage oligomeric matrix protein in monitoring and prognostication of osteoarthritis and its utility in drug development, Perspect. Clin. Res. 6 (1) (2015) 4–9.

[45] E. Åhrman, P. Lorenz, K. Holmgren, A.J. Grodzinsk, L.E. Dahlberg, T. Saxne, D. Heinegard, P. Österfeld, Novel cartilage oligomeric matrix protein (COMP) neoepitopes identified in synovial fluids from patients with joint diseases using affinity chromatography and mass spectrometry, J. Biol. Chem. 289 (30) (2014) 20908–20916.

[46] A. Struglics, S. Larsson, A. Pramhed, R. Frobell, P. Sward, Changes in synovial fluid and serum concentrations of cartilage oligomeric matrix protein over 5 years after anterior cruciate ligament rupture: an exploratory analysis in the KANON trial, Osteoarthritis Cartilage 26 (10) (2018) 1351–1358.

[47] S. Larsson, L.S. Lohmander, A. Struglics, An ARGS-aggreca assay for analysis in blood and synovial fluid, Osteoarthritis Cartilage 22 (2) (2014) 242–249.

[48] A. Struglics, S. Larsson, N. Kumahashi, R. Frobell, L.S. Lohmander, Changes in cytokines and aggrecan ARGS neoepitope in synovial fluid and serum and in C-terminal crosslinking telopeptide of type II collagen and N-terminal crosslinking telopeptide of type I collagen in urine over five years after anterior cruciate ligament rupture: an exploratory analysis in the knee anterior cruciate ligament, nonsurgical versus surgical treatment trial, Arthritis Rheum. 67 (7) (2015) 1816–1825.

[49] R. Giordano, K.K. Petersen, H.H. Andersen, O. Simonsen, L. Arendt-Nielsen, Serum inflammatory markers in patients with knee osteoarthritis: a proteomic approach, Clin. J. Pain 36 (4) (2020) 229–237.

[50] V. Flodadottir, E.M. Roos, E. Ageberg, Muscle function is associated with future patient-reported outcomes in young adults with ACL injury, BMJ Open Sport Exerc. Med. 2 (1) (2016).