

normalised to body weight (BW). Follow-up MRI was completed on 32 participants 5 years post-ACLR. Early patellofemoral OA was defined as the presence of a patellofemoral cartilage lesion, assessed with the validated MRI OA Knee Score (MOAKS) by an experienced musculoskeletal radiologist with established reliability. Generalised linear models (Poisson family) assessed the relationship between peak patellofemoral joint force (BW) and prevalent early patellofemoral OA at 1 year and worsening patellofemoral OA (i.e., developing a new or more severe cartilage lesion) between 1 and 5 years adjusted for sex and age. **Results:** At 1 year following ACLR, 14 (30%) participants had early patellofemoral OA. Of these, 8 (57%) and 6 (43%) had isolated patellofemoral OA and combined patellofemoral/tibiofemoral OA, respectively. There were no differences in characteristics for participants who did and did not have MRI at 5 years. Participants with a lower peak patellofemoral joint contact force were more likely to have early patellofemoral OA at 1 year (prevalence ratio: 1.37, 95%CI 1.02–1.85). Of the 31 participants with 5-year follow-up data, 9 (28%) displayed worsening patellofemoral OA. A lower peak patellofemoral joint contact force at 1 year increased the risk of worsening patellofemoral OA up to 5 years (risk ratio: 1.54, 95%CI 1.13–2.11). Sensitivity analyses additionally adjusting for the presence of early tibiofemoral OA did not alter results. **Conclusions:** Young adults following ACLR who underload their patellofemoral joint during a hopping task are at high risk of early patellofemoral OA onset and progression within the first 5-years after ACLR. For every one unit (i.e., body weight) decrease in peak patellofemoral joint contact force, the risk of incident or progressive early patellofemoral OA increases ~50%. These findings challenge traditional thinking that joint overloading drives post-traumatic OA and provides new targets for OA prevention. Early identification of individuals at high risk of early-onset OA may allow novel treatments with potential to change the trajectory of OA to be designed and tested. It is possible that treatments designed to change unloading tendencies in certain individuals might mitigate/slow patellofemoral OA onset and progression.

#### 14 POTENTIAL SURROGATE OUTCOMES FOR INCIDENT KNEE OSTEOARTHRITIS AMONG OVERWEIGHT AND OBESE WOMEN

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**Purpose:** Experts in the field of OA suggested that a shift in research focus towards the early disease stage is needed; here joint damage might still be reversible, pain is not chronic, and physical functioning is not heavily impaired. Studying incident knee OA among patients with early-stage disease requires very long follow-up when established measures of knee OA, e.g. Kellgren & Lawrence (KL) grade  $\geq 2$  or the ACR-criteria, are used. Validated surrogate outcomes of established knee OA, can boost the research on new disease- and symptom-modifying treatments within the 'window of opportunity' of early-stage knee OA. The current study aimed to evaluate the performance of the short-term change (2.5 years) of several clinical and imaging markers as surrogate outcomes for long-term (6.5 years) clinical knee OA development, among high-risk women with overweight and obesity.

**Methods:** Data of the PROOF study were used. In PROOF, 407 women (aged 50 - 60 years, BMI  $\geq 27$  kg/m<sup>2</sup>, and free of clinical knee OA) were recruited and followed for 6.5 years. At baseline, 2.5 years, and 6.5 years, questionnaires (demographics, knee symptoms, WOMAC scores), and standardized semi-flexed PA radiography (osteophytes, joint space width, and medial alignment angle) and multi-sequential MRIs (semi-quantitative scores using MOAKS) were obtained. For all pre-specified potential surrogate outcome, first the 2.5 years progression (i.e. worsening) was determined and compared to the 2.5 years incidence of clinical knee OA, using the combined ACR-criteria (i.e. pain on most days of the last month, definite osteophyte on radiography, and  $\geq 1$  out of age >50, morning stiffness <30 minutes, crepitus). Published measures of the Minimal Clinically Important Difference (MCID) were used to determine the number of knees with progression based on knee pain severity (NRS), WOMAC pain, WOMAC stiffness, WOMAC function, and medial and lateral joint space narrowing. For osteophytes scored on radiographs, progression  $\geq 1$  grade on the 0–4 scale, excluding progression from 0 to 1, was used to determine short-term progression. For MOAKS features (bone marrow lesions, cartilage defects, osteophytes, meniscal pathologies, and meniscal extrusion), published definitions by Runhaar et al (2014) were used to define progression. MOAKS features were stratified for medial/lateral and tibiofemoral/patellofemoral

compartments, where appropriate. Potential surrogate outcomes showing progression  $\geq 10\%$  of the knees after 2.5 years were further analyzed for their association with the incidence of clinical knee OA after 6.5 years, using Generalized Estimating Equations to account for repeated measures within persons. Only for WOMAC pain, stiffness and function scores, a simple logistic regression was used, as these measures were obtained at a person-level. For all potential surrogate markers showing a significant association with incident clinical knee OA, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

**Results:** 470 knees from 238 women were free of clinical knee OA at baseline and had long-term OA incidence measures available (mean age 55.8  $\pm$  3.1 years and mean BMI 31.8  $\pm$  3.8 kg/m<sup>2</sup>). After 2.5 and 6.5 years, incidence of clinical knee OA was 7% and 11% respectively. Table 1 presents the progression of the selected potential surrogate outcomes at 2.5 years and their association to incident clinical knee OA after 6.5 years. Ten potential surrogate outcomes had short-term progression in  $\geq 10\%$  of the knees. Of these, only the progression of medial tibiofemoral osteophytes on MRI (OR 2.2 [95% CI 1.1–4.6]) and pain severity (2.9 [95% CI 1.5–5.5]) were significantly associated to incident clinical knee OA. Both measures had low sensitivity and PPV (22%–28%), and high specificity and NPV (90%–91%).

**Conclusions:** Among a high-risk population of overweight/obese women free of clinical knee OA, both the progression of medial tibiofemoral osteophytes on MRI and of knee pain severity fulfill the basic requirements of a surrogate outcome; their short-term change was significantly associated to long-term OA development. The next step to validate these potential surrogate outcomes would be to show in an RCT that the long-term preventive effects of a treatment (i.e. less OA incidence) are captured by the short-term change in these surrogate outcomes. If so, future trials can evaluate their preventive effect more efficiently by evaluating the short-term change in these surrogate outcomes only.

Table 1. Short-term (2.5 years) progression of potential surrogate outcomes and their association to incident clinical knee OA after 6.5 years.

Potential surrogate outcome	2.5 years progression	Incident clinical knee OA	Sensitivity / specificity	PPV / NPV
<b>Radiography markers</b>				
JSN medial	2%	-		
JSN lateral	0%	-		
Alignment angle	22%	1.4 (95% CI 0.8-2.6)		
Osteophytes	3%	-		
<b>MRI markers</b>				
<b>BML</b>				
PF	24%	1.0 (95% CI 0.5-2.0)		
TF medial	8%	-		
TF lateral	7%	-		
<b>Cartilage defects</b>				
PF	24%	1.2 (95% CI 0.6-2.5)		
TF medial	8%	-		
TF lateral	6%	-		
<b>Osteophytes</b>				
PF	7%	-		
TF medial	10%	2.2 (95% CI 1.1-4.6)	22% (95% CI 12-36) / 91% (95% CI 88-94)	24% (95% CI 13-39) / 90% (95% CI 87-93)
TF lateral	5%	-		
<b>Meniscal pathologies</b>				
Medial	19%	1.5 (95% CI 0.7-2.4)		
Lateral	9%	-		
<b>Meniscal extrusion</b>				
Medial	18%	1.5 (95% CI 0.6-2.6)		
Lateral	3%	-		
<b>Clinical markers</b>				
<b>Chronic pain</b>				
Pain severity	11%	2.9 (95% CI 1.5-5.5)	27% (95% CI 16-43) / 91% (95% CI 88-94)	28% (95% CI 17-43) / 90% (95% CI 88-93)
<b>WOMAC</b>				
WOMAC pain	20%	1.7 (95% CI 0.8-3.8)		
WOMAC stiffness	22%	1.5 (95% CI 0.7-3.2)		
WOMAC function	15%	1.2 (95% CI 0.5-3.1)		

#### 15 EARLY MENISCAL SURGERY OR EXERCISE THERAPY AND EDUCATION WITH THE OPTION OF LATER SURGERY IN YOUNG ADULTS: A RANDOMIZED CONTROLLED TRIAL

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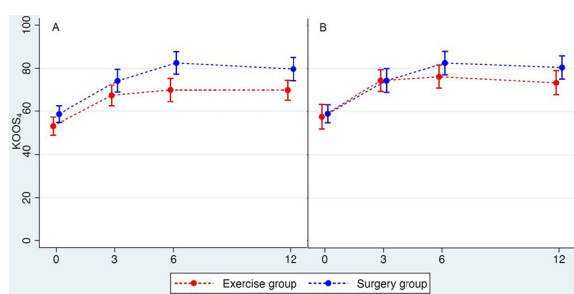
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**Purpose:** Knee injury, including meniscal tear, is a major risk factor for developing osteoarthritis. Although surgery is a common treatment of meniscal tears, no randomized controlled trials (RCTs) have compared surgery with non-surgical alternatives in young adults with a meniscal tear. We aimed to determine whether a strategy of early meniscal surgery was superior to a strategy of exercise and education with the option of surgery later in young adults with a meniscal tear in terms of pain, function, and quality of life.

**Methods:** This was a pragmatic, parallel-group, multicenter, RCT recruiting young adults (18–40 years) with MRI-verified meniscal tears eligible for meniscal surgery from seven Danish hospitals between January 26, 2017 through to December 4, 2019 (ClinicalTrials.gov NCT02995551). Primary endpoint was at 12 months with additional follow-ups at 3 and 6 months. Patients were randomized (1:1, by central study coordinator, stratified by hospital and sex) to surgery (partial meniscectomy or meniscal repair) or a strategy of 12-weeks supervised exercise therapy (two 60–90-minute sessions weekly) and 30–45min of patient education with the option of surgery later if needed. The primary outcome was difference in change from baseline to 12 months in the mean score of four Knee Injury and Osteoarthritis Outcome Score subscales, covering pain, symptoms, function in sport and recreation, and quality of life (KOOS<sub>4</sub> scale: 0 (worst) to 100 (best)). Intention-to-treat and per-protocol analysis were conducted. Per-protocol analysis excluded patients randomized to exercise therapy but participating in <18 of 24 exercise sessions or crossing over to surgery, and patients not having surgery in the surgery group.

**Results:** Out of the 121 young adults enrolled (mean age 29.7 years, 28% women, 60 allocated to surgery group), 107 patients (88%) completed the 12-month follow-up, 16 (26%) from the exercise group had meniscal surgery, while 8 (13%) from the surgery group did not have surgery. In total, 36 (59%) patients attended 18 or more of 24 exercise sessions. Both treatment groups experienced clinically relevant improvements (10 points or more on KOOS<sub>4</sub>). The intention-to-treat analysis did not demonstrate a statistically significant difference in change between groups from baseline to 12 months in KOOS<sub>4</sub> (19.2 vs. 16.4 in surgery vs. exercise group; adjusted mean difference, 5.4 [95% CI, -0.7 to 11.4]; Figure 1A), with similar results in the per-protocol analysis (Figure 1B). No difference in serious adverse events was observed (4 in surgery vs. 7 in exercise group,  $p=0.40$ ).

**Conclusions:** In a group of young, active adults with meniscal tears, our results suggest that a strategy of early meniscal surgery was not superior to a strategy of exercise and education with the option of later surgery. Both groups experienced clinically relevant improvements and one in four patients from the exercise group underwent surgery, suggesting that both treatment strategies could be viable and effective options in clinical practice. Our study therefore highlights that decisions on treatment of meniscal tears in young adults should include patient preferences and values.



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### SPONTANEOUS HEALING OF THE RUPTURED ANTERIOR CRUCIATE LIGAMENT: OBSERVATIONS FROM THE KANON TRIAL

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**Purpose:** Anterior cruciate ligament (ACL) rupture is a strong risk factor for the development of knee osteoarthritis, irrespective of management with ACL reconstruction (ACLR) or rehabilitation alone. Poor long-term physical and psychological outcomes are common. It is often assumed that a ruptured ACL cannot heal without surgery, despite a paucity of studies investigating the potential for a ruptured ACL to heal. It is not known if ACL healing on MRI is associated with restoration of knee function or favorable outcomes. The objectives were to: 1) Report the proportion of participants with 'ACL healing' as visualized on MRI in the first 5 years following acute ACL rupture 2) Describe 2- and 5-year outcomes stratified by ACL healing status and treatment 3) Investigate the relationship between ACL healing, patient-reported sport/recreational function and knee-related quality of life (QOL) at 2 and 5 years following acute ACL injury

**Methods:** This secondary analysis used KANON Trial (ISRCTN84752559) data from participants randomized to rehabilitation and optional delayed ACLR ( $n=54$ ), or early ACLR ( $n=62$ ). The Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) was used to grade ACL healing status (a healed ACL was defined as a normal (grade 0), thickened/high signal but continuous (grade 1) or thinned/elongated but continuous (grade 2) appearance on MRI). Two- and five-year outcomes included the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales (score range 0 to 100 (best)), Tegner Activity Scale, mechanical knee stability (pivot-shift test) and radiographic osteoarthritis (graded according to the Osteoarthritis Research International atlas, equivalent to Grade 2 on the Kellgren Lawrence Scale). The proportion of participants meeting KOOS criteria for patient acceptable symptomatic state (PASS) and treatment failure at 2 years were reported. The relationship between healing status, KOOS-Sports/Rec and KOOS-QOL was explored using mixed linear regression models adjusted for age, sex, smoking, baseline KOOS values, and unmeasured person-specific time-invariant confounding.

**Results:** Using our definition of ACL healing (ACLOAS grade 0–2), 76%, 56% and 58% of participants managed with rehabilitation alone had a healed ACL at 1-, 2- and 5-year follow-ups, respectively. In participants who were managed with rehabilitation alone at 5-year follow-up ( $n=24$ ), 38% had a normal ACL appearance (ACLOAS grade 0) on MRI at 1 year, 30% at 2 years and 33% at 5 years. One in twenty-three (4%) participants who crossed over to delayed ACLR had a normal ACL appearance at any timepoint. Participants with a healed ACL reported high KOOS subscale scores at 2- and 5-year follow-up (Table 1). The proportion of participants with a healed ACL meeting the PASS threshold within a given KOOS subscale ranged from 67 to 93%, and no individuals met the criteria for treatment failure (Table 1). In the other groups, 31 to 61% met the PASS criteria and 0 to 17% met the criteria for treatment failure (Table 1). Tegner Activity Scores were similar between groups at 2 and 5 years. At 2 years, 73% ( $n=11$ ) of the healed ACL group had a mechanically stable knee, compared to 50% ( $n=6$ ) in the non-healed group, 92% ( $n=22$ ) following delayed ACLR and 100% ( $n=60$ ) after early ACLR (Table 1). Two (14%) participants in the healed ACL group had tibiofemoral OA at 5 years, compared to 1 (10%) in the non-healed, 1 (3%) in the delayed ACLR and 9 (15%) in the early ACLR group. One (7%) participant in the healed ACL and 1 (10%) in the non-healed ACL group had patellofemoral OA, compared to 6 (21%) participants in the delayed ACLR and 14 (24%) in the early ACLR group. The estimated between group differences in KOOS subscales suggest better outcomes in the healed group for both subscales at 2 years (mean difference (95% CI) in KOOS Sport/Rec in non-healed: -21.9 (-38.8, -5.0), delayed ACLR: -25.0 (-39.8, -10.1), early ACLR: -18.0 (-31.5, -4.5); mean difference (95% CI) in KOOS QOL in non-healed: -26.9 (-41.7 to -12.1), delayed ACLR: -19.4 (-32.3, -6.4), early ACLR: -13.9 (-25.6, -2.1)). At 5-year follow-up, the 95% CIs exclude the possibility that non-healed, delayed ACLR or early ACLR groups had better KOOS Sport/Rec or QOL scores compared to the