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# Knee osteoarthritis in traumatic knee symptoms in general practice: 6-year cohort study

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#### ABSTRACT

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Pim AJ Luijsterburg; p.luijsterburg@erasmusmc.nl **Aim:** To identify degenerative knee abnormalities using MRI and radiography 6 years after knee trauma, their relation with persistent knee symptoms and baseline prognostic factors.

Methods: Adults (18-65 years) with incident traumatic knee symptoms visiting their general practitioner were followed up for 6 years and underwent baseline MRI and 6-year follow-up MRI and radiography. Logistic regression was used to analyse associations between various degenerative abnormalities on 6-year MRI and radiography, persistent knee symptoms and baseline prognostic factors for knee osteoarthritis (OA) on 6-year MRI. **Results:** On 6-year radiography, 60% of patients showed no OA, 28% showed OA with Kellgren&Lawrence (K&L) grade 1 and 13% showed with K&L grade 2. On 6-year MRI, 55% of patients showed cartilage defect(s), 45% showed osteophyte (s), 36% showed subchondral cyst(s), 40% showed bone marrow oedema, 21% showed meniscal subluxation, 83% showed meniscal degeneration, 11% showed effusion and 11% showed a Baker's cyst. Of these, most were significantly related with 6-year radiographic K&L grade, while only lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation were significantly related with persistent knee symptoms. 32% of patients showed new onset or progressive knee OA on 6-year MRI, for which age, history of non-traumatic knee symptoms and bone marrow oedema at baseline were independent prognostic factors.

**Conclusions:** Degenerative knee abnormalities on MRI are related to the K&L score; however, not all abnormalities are reflected in clinical outcome. Age, history of non-traumatic knee symptoms and bone marrow oedema predict knee OA 6 years after knee trauma, present in 32% of the patients.

#### INTRODUCTION

The incidence of traumatic knee symptoms in Dutch general practice is  $\sim 5.3$  per 1000 patients per year.<sup>1</sup> Our earlier study showed that 17% of these patients reported persistent knee symptoms at 1-year follow-up.<sup>2</sup> Because knee trauma is a risk factor for knee

#### What are the new findings?

- Degenerative knee abnormalities on MRI are related to osteoarthritis (OA) on X-ray.
- Age, history of non-traumatic knee symptoms and bone marrow oedema on MRI predict knee OA 6 years after knee trauma.

## How might it impact on clinical practice in the near future?

Clinicians should be aware of the occurrence of knee OA in patients after knee trauma, and check for a history of non-traumatic knee symptoms and bone marrow oedema on initial MRI.

osteoarthritis  $(OA)^{3-6}$  and knee OA is a chronic disorder with a major burden,<sup>7</sup> knowledge on prognostic factors for knee OA in patients with traumatic knee symptoms could be helpful to diminish this burden of knee OA in these patients in the future.

From primary care, one study showed progression of knee OA in 15% of the patients with existing knee OA, new degenerative changes in 26% of the patients with no knee OA at baseline.<sup>8</sup> From secondary care, there is evidence that about 50% of patients with a traumatic meniscal lesion or an anterior cruciate ligament lesion develop knee OA at a younger age than expected.<sup>9</sup> Bone marrow oedema may also be a risk factor for structural deterioration and progression of knee OA in secondary care.<sup>10</sup>

Research on developing knee OA in patients with traumatic knee symptoms is complicated because it is difficult to diagnose knee OA in an early stage.<sup>12</sup> MRI is the best available technique for the detection of early osteoarthritic changes.<sup>13</sup> Although a consensus-based definition for OA has been published, it has not yet been validated.<sup>14</sup>



This study assessed the (1) frequency of degenerative knee abnormalities in these patients on radiography and MRI at 6-year follow-up, (2) the relationship between findings on MRI and radiography, (3) their correlation with persistent knee symptoms at 6-year follow-up and (4) their relationship with prognostic factors at baseline (including MRI findings).

#### METHOD

#### **Design and patients**

The present study is a part of a prospective, observational cohort study in which 1068 consecutive patients visiting their general practitioner (GP) with a new episode of knee symptoms followed up for 6 years.<sup>15</sup> New knee symptoms were defined as episodes of symptoms presented to the GP for the first time. Traumatic knee symptoms were defined as those caused by a sudden impact.

Patients were eligible for the present study if they were aged 18–65 years, had consulted their GP with traumatic knee symptoms within 5 weeks after the trauma and signed informed consent for an MRI of their knee. Exclusion criteria were knee symptoms that required urgent medical attention (eg, fractures), patients with malignancies, neurological disorders or systematic musculoskeletal diseases (eg, rheumatoid arthritis), as well as patients with insufficient understanding of the Dutch language.

#### **Data collection**

Patients filled out a questionnaire at baseline, and at 1-year and 6-year follow-up. The questionnaires provided data on demographics, on knee symptoms (eg, knee pain assessed on an 11-point [0=no pain and 10=unbearable pain] numeric rating scale (NRS), and knee pain and function assessed with the Lysholm Knee Scoring Scale)<sup>16-18</sup> and on treatment. For the Lysholm score, higher scores represent better function/outcome.

In addition, the questionnaires at 1-year and 6-year follow-up also provided data on experienced recovery measured on a 7-point Likert scale (ranging from 'completely recovered' to 'worse than ever').

Persistent knee symptoms were defined as knee symptoms that were 'slightly improved', 'not changed', 'slightly worsened', 'much worsened' or 'worse than ever'.

Clinically important recovery was defined as knee symptoms that were 'completely recovered' or 'much improved'.

A standardised physical examination was carried out by a trained physiotherapist at baseline and at 1-year follow-up; this consisted of inspection (alignment and joint effusion), palpation (temperature, collateral ligaments and joint line tenderness), assessment of joint effusion, passive range of motion in flexion and extension, meniscal tests and knee stability tests.<sup>19 20</sup>

MRI of the knee was performed within 3–6 weeks of the trauma and was repeated after 6 years. At baseline, a

1.0 T whole-body MRI unit was used, whereas at 6-year follow-up, MRI was performed on a 1.5 T whole-body MRI scanner. In both examinations, we used a dedicated knee coil and an MRI protocol that consisted of sagittal T1, T2 and proton density-weighted fast spin-echo sequences, coronal T2\*-weighted gradient echo and fat-suppressed T2-weighted fast spin-echo sequences, and an axial proton density-weighted fast spin-echo sequence.

The initial and follow-up MRI examinations were independently evaluated by two radiologists for the presence of degenerative abnormalities of the femorotibial joint of the index knee, according to the Knee Osteoarthritis Scoring System (KOSS).<sup>21</sup>

In case of discrepancies, consensus was reached through discussion. We defined OA of the femorotibial joint of the index knee on MRI according to the definition described by Hunter *et al.*<sup>14</sup> In addition to degenerative abnormalities, we also assessed the presence of ligamentous lesions, meniscal lesions and bone marrow oedema on MRI.

To reflect clinical practice, the reports and the images of the initial MRI examination were available when evaluating the follow-up MRI. In this observational cohort study, the treating GP was not informed of the MRI findings unless the findings required immediate treatment.

At 6-year follow-up only, an anterior posterior radiograph of the index knee was made. To assess radiographic knee OA at 6-year follow-up, two trained readers independently scored the radiograph for OA according to the classical K&L grading (0–4) system,<sup>22</sup> unaware of the clinical status of the patients.

#### Statistical analysis

ORs were used to calculate the association between the various degenerative abnormalities on the 6-year MRI and the 6-year K&L score. ORs were also used to calculate the relation between the various degenerative abnormalities on the 6-year MRI and persistent knee symptoms at 6-year follow-up.

Univariate logistic regression analysis was performed to determine which baseline variables from history taking and MRI are associated with new onset knee OA or progression of existing knee OA seen on the 6-year MRI. The baseline variables used as eligible prognostic factors for the univariate analysis were based on literature<sup>23</sup> and clinical relevance. The eligible factors were divided into three domains: patient characteristics, complaint characteristics and MRI findings. Imputation of missing data was carried out by multiple imputation, creating a total of five imputed databases.<sup>24–26</sup>

The factors of each domain showing a univariate association with knee OA seen on the 6-year MRI in at least 3 of 5 imputed databases ( $p \le 0.20$ ) were analysed in a multivariable (backward) logistic regression model (entry 0.10, removal 0.20). If a factor of one domain was selected in at least 3 of 5 imputed databases in the multivariate analysis, it was included in the final model (enter method).

Analyses were performed with SPSS V.17.02 (SPSS, Chicago, Illinois, USA).

#### RESULTS

#### Study population

Table 1 shows the baseline characteristics of the 134 patients included in the study. Their mean age was 40.3 (SD 12.2) years and 55.2% was men. MRI of the knee was normal in 15 patients (11.2%). At baseline, the mean knee pain severity on the NRS was 4.8 (SD 2.4) and the mean Lysholm knee function score was 63.7 (SD 19.8).

After 6 years, 78 patients (58.2%) were still available for follow-up (table 1). The patients lost to follow-up showed no differences compared with those available at 6-year follow-up regarding baseline variables. Reasons for no longer participating at 6-year follow-up were lack of time and/or lack of interest (n=18, 32.1%), and being untraceable due to change of address and/or telephone number (n=27, 48.2%); in addition, 2 patients (3.6%) had died during the follow-up period and for 9 patients (16.1%) no reason was available.

#### **Clinical outcome**

At 6-year follow-up, 26 (33.3%) of the 78 available patients reported persistent knee symptoms; these 26 patients reported a mean knee pain severity of 3.7 (SD 2.0) and a mean Lysholm knee score of 68.4 (SD 16.9).

None of the diagnoses on baseline MRI (table 1) was significantly associated with persistent knee symptoms at 6-year follow-up (data not shown).

Having persistent knee symptoms at 1-year follow-up was significantly associated with reported persistent knee symptoms at 6-year follow-up (OR 5.54, 95% CI 1.44 to 20.32).

During the 6-year follow-up, 11 (14.1%) of the 78 patients underwent surgery of the knee; of these 11 patients, 6 (54.5%) reported persistent knee symptoms at 6-year follow-up.

#### Degenerative abnormalities of the knee

The K&L score for knee OA on the 6-year radiograph is shown in table 2. Of the 47 available patients, 28 (59.6%) showed no radiographic knee OA (grade 0), 13 (27.7%) showed grade 1 knee OA and 6 patients (12.8%) showed grade 2 knee OA. There were no patients with advanced stage OA (K&L grade 3 or 4).

The degenerative abnormalities on the 6-year MRI (based on the KOSS scoring system) are also reported in table 2. Of the 47 patients, 26 (55.3%) showed cartilage defect(s), 21 (44.7%) osteophyte(s), 17 (36.2%) subchondral cyst(s), 19 (40.4%) bone marrow oedema, 10 (21.3%) meniscal subluxation, 39 (83.0%) meniscal degeneration, 5 (10.6%) joint effusion and 5 patients (10.6%) showed a Baker's cyst. These degenerative changes on the 6-year MRI were significantly more frequently reported in the medial than in the lateral compartment of the femorotibial joint (table 2).

Most of the degenerative abnormalities on the 6-year MRI showed a significant relation with the K&L score on the 6-year radiograph. Only lateral subchondral cyst, lateral bone marrow oedema, medial meniscal degeneration, effusion and Baker's cyst were not significantly related (table 2). Only a few of the degenerative abnormalities on the 6-year MRI (ie, lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation)

Table 1         Baseline characteristics of the total group of patients and those available at 6-year follow-up						
Baseline characteristic	All included patients at baseline (n=134)	Available at 6-year follow-up (n=78)	Agreed to 6-year MRI and radiography (n=47)			
General						
Age in years, mean±SD	40.3±12.2	41.6±11.2	43.7±10.5			
Male, n (%)	74 (55.2)	38 (48.8)	23 (48.9)			
Diagnosis on MRI						
No lesion or effusion, n (%)	15 (11.2)	8 (10.3)	3 (6.4)			
Contusion (effusion with no ligament or meniscal lesion), n (%)	37 (27.6)	16 (20.5)	9 (19.1)			
Medial collateral ligament lesion, n (%)	35 (26.1)	24 (30.8)	17 (36.2)			
Lateral collateral ligament lesion, n (%)	8 (6.0)	6 (7.7)	4 (8.5)			
Anterior cruciate ligament lesion, n (%)	28 (20.9)	20 (25.6)	12 (25.5)			
Posterior cruciate ligament lesion, n (%)	6 (4.5)	2 (2.6)	1 (2.1)			
Meniscal tear	47 (35.1)	29 (37.2)	17 (36.2)			
Knee symptoms						
Sport activity as cause, n (%)	61 (45.5)	34 (43.6)	20 (42.6)			
Knee pain NRS (0–10), mean±SD	4.8±2.4	4.6±2.5	4.7±2.4			
Lysholm knee function score (0–100), mean±SD	63.7±19.8	62.2±20.7	61.3±21.2			

		K&L score on 6-year radiograph				Persistent knee
		Grade 0	Grade 1	Grade 2	K&L score (grade 0 vs 1	symptoms OR
		(n=28) n (%)	(n=13) n (%)	(n=6) n (%)	and 2) OR (95% CI)	(95% CI)
Signs of OA on 6-year MRI	Frequenc	y (n=47) n (%)	1			
Chondral defect	26 (55.3)	10 (35.7)	10 (76.9)	6 (100.0)	9.6 (2.2 to 41.1)*	2.3 (0.7 to 8.4)
Medial	22 (46.8)	6 (21.4)	10 (76.9)	6 (100.0)	19.6 (4.2 to 90.2)*	1.8 (0.5 to 6.0)
Lateral	15 (31.9)	5 (17.9)	5 (38.5)	5 (83.3)	5.1 (1.4 to 19.2)*	5.4 (1.4 to 20.3)*
Osteophytes†	21 (44.7)	7 (25.0)	8 (61.5)	6 (100.0)	8.4 (2.2 to 31.8)*	3.0 (0.9 to 10.6)
Medial	19 (40.4)	5 (17.9)	8 (61.5)	6 (100.0)	12.9 (3.2 to 52.6)*	4.1 (1.1 to 14.6)*
Lateral	13 (27.7)	4 (14.3)	4 (30.8)	5 (83.3)	5.4 (1.3 to 21.7)*	2.1 (0.6 to 7.7)
Subchondral cyst	17 (36.2)	5 (17.9)	7 (53.8)	5 (83.3)	7.9 (2.1 to 30.2)*	1.6 (0.5 to 5.7)
Medial	11 (23.4)	2 (7.1)	5 (38.5)	4 (66.7)	11.7 (2.1 to 63.8)*	1.9 (0.5 to 7.5)
Lateral	7 (14.9)	3 (10.7)	3 (23.1)	1 (16.7)	2.2 (0.4 to 11.3)	1.6 (0.3 to 8.0)
Bone marrow oedema	19 (40.4)	7 (25.0)	8 (61.5)	4 (66.7)	5.1 (1.5 to 18.2)*	1.8 (0.5 to 6.2)
Medial	14 (29.8)	4 (14.3)	6 (46.2)	4 (66.7)	6.6 (1.7 to 26.8)*	1.7 (0.5 to 6.3)
Lateral	7 (14.9)	3 (10.7)	3 (23.1)	1 (16.7)	2.2 (0.4 to 11.3)	3.1 (0.6 to 16.1)
Meniscal subluxation‡	10 (21.3)	2 (7.1)	3 (23.1)	5 (83.3)	9.5 (1.7 to 51.9)*	7.3 (1.5 to 34.1)*
Medial	10 (21.3)	2 (7.1)	3 (23.1)	5 (83.3)	9.5 (1.7 to 51.9)*	7.3 (1.5 to 34.1)*
Lateral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Meniscal degeneration‡	39 (83.0)	21 (75.0)	12 (92.3)	6 (100.0)	6.0 (0.7 to -53.5)	4.4 (0.5 to 39.2)
Medial	32 (68.1)	17 (60.7)	11 (84.6)	4 (66.7)	2.4 (0.6 to 9.3)	1.0 (0.3 to 3.8)
Lateral	18 (38.3)	6 (21.4)	7 (53.8)	5 (83.3)	6.3 (1.7 to 23.0)*	3.1 (0.9 to 11.0)
Effusion‡	5 (10.6)	2 (7.1)	2 (15.4)	1 (16.7)	2.4 (0.4 to 16.2)	1.3 (0.2 to 8.9)
Baker's cyst	5 (10.6)	4 (14.2)	1 (7.7)	0 (0.0)	_	2.0 (0.1 to 34.2)
Knee OA on 6-year MRI§	17 (36.2)	3 (10.7)	8 (61.5)	6 (100.0)	23.3 (4.8 to 112)*	3.7 (1.0 to 13.2)*

\* p≤0.05.

 $\dot{z}$  minimal osteophytes or  $\geq 1$  moderate or severe osteophyte(s) in the lateral or medial compartment of the femorotibial joint.

‡Moderate and severe.

§Definition according to Hunter et al.

K&L score, Kellgren & Lawrence score; KOSS, Knee Osteoarthritis Scoring System; OA, osteoarthritis.

had a significant relation with the self-reported persistent knee symptoms at 6-year follow-up (table 2).

At 6-year follow-up of the 47 patients, knee OA on MRI (according to the definition of Hunter *et al*)<sup>14</sup> was present in 17 patients (36.2%) and showed a strong significant relationship with the K&L score on the 6-year radiograph (OR 23.3, 95% CI 4.8 to 112). A significant relationship was also found with the reported persistent knee symptoms (table 2).

Table 3 presents a cross-tabulation of knee OA at baseline versus 6-year MRI. Of the 17 patients with knee OA at 6-year follow-up, 12 (25.5%) showed new onset knee OA on 6-year MRI, 3 (6.4%) showed progression of existing knee OA, and 2 patients (4.3%) with existing knee OA showed no progression on 6-year MRI. Therefore, of the 42 patients with no knee OA at baseline, 12 (28.6%) showed new knee OA at 6-year follow-up and, of the five patients with existing knee OA at baseline, 3 (60.0%) showed progression.

#### **Prognostic factors**

Table 4 presents the pooled univariable associations between baseline characteristics and new onset knee OA or progression of existing knee OA at 6-year MRI.  
 Table 3
 Cross-tabulation of knee OA at baseline versus the 6-year MRI

		Knee OA on baseline MRI		
		No	Yes	Total
Knee OA on	No	30	_	30
6-year MRI	Yes, new knee OA	12	_	12
	Yes, stable existing knee OA	-	2	2
	Yes, progression existing knee OA	-	3	3
	Total	42	5	47

The patient characteristics age and female gender showed an association with progression or new onset knee OA at the 6-year follow-up ( $p \le 0.20$ ). From the mechanism and symptom characteristics, trauma during sports, limitation during daily function and history of non-traumatic knee symptoms were associated ( $p \le 0.20$ ).

From the baseline MRI findings, cartilage defect, osteophytes, bone marrow oedema and meniscal degeneration were associated ( $p \le 0.20$ ).

 Table 4
 Univariable association between baseline characteristics and knee osteoarthritis (new or progression) on the 6-year MRI

	Univariable 6 year (n=47)			
Variable	Pooled OR	Pooled 95% Cl	Pooled Sig	
Patient characteristics				
Age	1.10	1.02 to 1.18	0.01*	
Female gender	2.57	0.71 to 9.26	0.15*	
Body mass index	1.03	0.87 to 1.23	0.71	
Mechanism and symptom characteristics				
Trauma during sport	0.23	0.06 to 0.98	0.05*	
Pain (11-point scale)	1.16	0.89 to 1.53	0.28	
Limitation and pain during daily function (Lysholm <80)	5.48	0.63 to 48.0	0.13*	
Instability of the knee (Lysholm)	0.49	0.12 to 1.93	0.31	
History of traumatic knee symptoms	1.04	0.28 to 3.87	0.95	
History of non-traumatic knee symptoms	4.26	1.09 to 16.7	0.04*	
MRI findings				
Any lesion	0.56	0.14 to 2.19	0.40	
Anterior cruciate ligament tear	0.64	0.15 to 2.81	0.55	
Medial collateral ligament lesion	1.27	0.36 to 4.51	0.71	
Meniscal tear	1.27	0.36 to 4.51	0.71	
Chondral defect	2.70	0.64 to 11.4	0.18*	
Osteophytes	10.0	1.71 to 58.4	0.01*	
Bone marrow oedema	3.11	0.73 to 13.2	0.12*	
Meniscal degeneration	0.38	0.10 to 1.49	0.17*	

 Table 5
 Multivariable association between baseline characteristics and knee osteoarthritis (new or progression) on the 6-year MRI

	Multivariable 6 year (n=47)			
Variable	Pooled OR	Pooled 95% Cl	Pooled Sig	
Age	1.15	1.02 to 1.29	0.02	
History of non-traumatic knee symptoms	10.56	1.14 to 97.8	0.04	
Bone marrow oedema	6.89	0.83 to 57.3	0.07	

Table 5 presents the pooled multivariable associations between baseline characteristics and new onset knee OA or progression of existing knee OA at 6-year MRI. Age (p=0.02), history of non-traumatic knee symptoms (p=0.04) and bone marrow oedema (p=0.07) were independently related with progression or new onset knee OA at 6-year MRI.

#### DISCUSSION

### Degenerative abnormalities on 6-year MRI and radiography

We found that most of the degenerative abnormalities on the 6-year MRI (according to the KOSS scoring system) were significantly related with the K&L score on the 6-year radiograph. Only a few of the degenerative abnormalities on the 6-year MRI, that is, lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation, were significantly related with patients' reported persistent knee symptoms at 6-year follow-up. These results are largely in accordance with similar reports.<sup>27–30</sup> The main difference between our study and earlier studies is that we made a distinction between degenerative abnormalities in the medial and lateral knee compartment, because, in our population, degenerative abnormalities of the medial femorotibial joint compartment were more common than those of the lateral compartment.

#### Knee OA on the 6-year MRI and related prognostic factors

In this study, 32.0% of the patients showed new onset knee OA or progression of existing knee OA on the MRI, 6 years after trauma. This percentage is somewhat higher compared with our 1-year results, where 23.1% of the patients showed new onset knee OA or progression of existing knee OA on 1-year MRI.<sup>8</sup> This also means that in about 70% of the patients with new onset knee OA or progression of existing knee OA at 6-year follow-up, this was already present at 1-year follow-up.

Therefore, the majority of patients appears to develop within the first year after knee trauma a new onset knee OA or progression of existing knee OA.

#### **Open Access**

#### Strengths and limitations

The present study has several limitations. Only a small number of patients were eventually investigated because a relatively large percentage was lost to follow-up. Also, only about 60% of the patients available at 6-year follow-up were willing to undergo a radiograph and MRI of their knee. However, patients lost to follow-up and patients not willing to undergo additional radiography and MRI of their knee did not appear to be a selected group of patients.

Although the definition we used for knee OA on MRI (according to Hunter *et al*)<sup>14</sup> has not been validated, it appears to be the best available definition at this moment. In our data set, the definition showed a strong relationship with the K&L score on 6-year follow-up.

#### **Comparison with existing literature**

In the present study, age, history of non-traumatic knee symptoms and bone marrow oedema on baseline MRI were independently related with progression or new onset knee OA 6 years after knee trauma. This concurs with other reports, in which age and bone marrow oedema were also prognostic factors for the onset or progression of knee OA.<sup>3 4 8-11</sup>

It is noteworthy that, in the present study, no relationship was found between body mass index (BMI) and progressive or new onset knee OA, despite BMI is an established risk factor for knee OA.<sup>3</sup> 4 <sup>9</sup> <sup>31</sup> This relationship was also absent in our 1-year follow-up study on the development of knee OA.<sup>8</sup> Also, we found no significant association between meniscal lesions/cruciate ligament lesions and progression or new knee OA, whereas other studies have suggested that these lesions are related with knee OA.<sup>9</sup> <sup>32</sup> <sup>33</sup>

This might be explained by our small sample size (and resulting lack of power), and our primary care setting where severity of traumatic knee symptoms is expected to be lower than in studies performed in secondary care.

#### Implications for research and/or practice

Clinicians need to be aware of the occurrence of knee OA in patients after knee trauma, and check for a history of non-traumatic knee symptoms and bone marrow oedema on initial MRI. Additional studies are needed to confirm our results and to investigate how to prevent the development of new knee OA or progression of existing knee OA in these high-risk patients.

#### CONCLUSIONS

Degenerative knee abnormalities on MRI are related to the K&L score; however, not all abnormalities are reflected in clinical outcome. Age, history of non-traumatic knee symptoms and bone marrow oedema predict knee OA 6 years after knee trauma, present in 32% of the patients.

**Contributors** BWK, SMAB-Z and EHGO substantially contributed to conception and design of the study. MK, PAJL, IMK, DV and EHGO were involved in acquisition of data. MK, PAJL, EHGO and SMAB-Z were involved

in the analysis and interpretation of data and in drafting the manuscript. All authors revised the draft manuscript critically and have read and approved the final manuscript.

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Competing interests None declared.

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**Data sharing statement** Patients did not give informed consent for data sharing, but the data are anonymised and the risk of identification is low. Data from the trial may be available from the corresponding author at p. luijsterburg@erasmusmc.nl, subject to agreement about the use of the data.

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