

Predictive factors for new onset or progression of knee osteoarthritis one year after trauma: MRI follow-up in general practice

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Abstract

Objective To prospectively evaluate prognostic factors for new onset or progression of degenerative change on follow-up MRI one year after knee trauma and the association with clinical outcome.

Methods Within a prospective observational cohort study in general practice, we studied a subgroup of 117 patients with acute knee trauma (mean age 41 years, 43% women). Degenerative change was scored on MRI at baseline and after one year follow-up. Multivariate logistic regression

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analysis was performed to evaluate prognostic factors for new onset or progressive degenerative change on follow-up MRI. Association between new or progressive degeneration and clinical outcome after one year was assessed.

Results On follow-up MRI 15% of patients with pre-existing knee osteoarthritis showed progression and 26% of patients demonstrated new degenerative change. The only statistically significant prognostic variable in the multivariate analysis was bone marrow oedema on initial MRI (OR 5.29 (95% CI 1.64–17.1), $p=0.005$). A significant association between new or progressive degenerative change and clinical outcome was found ($p=0.003$).

Conclusion Bone marrow oedema on MRI for acute knee injury is strongly predictive of new onset or progression of degenerative change of the femorotibial joint on follow-up MRI one year after trauma, which is reflected in clinical outcome.

Keywords Knee injury · Osteoarthritis · MRI · Follow-up · Clinical outcome

Introduction

Osteoarthritis (OA) of the knee is a common cause of functional impairment and pain in the general population. Although the pathogenesis and aetiology of OA has not been fully understood, it is regarded as a generalised degenerative process involving all tissues of the affected joint [1]. Besides demographic factors such as age and sex, obesity and knee trauma are established risk factors for the development of OA of the knee [2–4]. With a reported incidence of 5.3 per 1000 patients annually, traumatic knee injury is a frequently encountered condition in general practice [5].

Meniscal lesions and anterior cruciate ligament (ACL) injuries constitute a large proportion of traumatic knee injury, and evidence exists that traumatic meniscal lesions are associated with progression of knee osteoarthritis [6, 7]. ACL injuries most commonly occur in young- to middle-aged physically active people, and in a previous study it was found that approximately 50% of this population develop OA of the knee 10–20 years after the injury [8]. It has also been suggested that bone marrow oedema is a risk factor for structural deterioration and progression of knee OA [9, 10].

Detection of early OA changes in the knee by radiographs alone is limited and the correlation between radiographic findings and clinical symptoms is poor [11–13]. With magnetic resonance imaging (MRI) it is possible to separately evaluate bone, cartilage, ligaments, meniscus and soft tissue abnormalities, allowing an in-depth whole organ assessment rather than an indirect radiographic projection of intra-articular damage. Therefore, MRI has been advocated

as the best currently available imaging technique for the detection of early osteoarthritic changes [6, 14, 15].

The extent to which traumatic knee abnormalities predict the development of OA within the first years after trauma has only been sparsely documented. We performed a study in the general practice population to prospectively evaluate prognostic factors, including initial MRI findings, for new onset or progression of OA of the femorotibial joint, assessed by follow-up MRI one year after trauma, and to evaluate the association with clinical outcome.

Materials and methods

Patient selection and study design

We performed a subgroup study within the HONEUR knee cohort, a prospective observational cohort study in general practice, in which patients were included if they consulted their general practitioner for the first time because of acute or chronic knee complaints. The study design of this general cohort, in which a total of 1068 patients were included, has been described in detail by Heintjes et al. [16]. The subgroup under investigation in the present study consisted of consecutively included patients aged 18 to 65 years who were consulting their general practitioners because of an acute knee trauma within the preceding 5 weeks from March 2002 until October 2003 [17]. Patients were excluded in the case of severe injury requiring immediate hospital referral, if a fracture was demonstrated in those referred for conventional radiography, or if there were contra-indications for MRI. The study was approved by the institutional review board of the Maasstad Ziekenhuis, Rotterdam, The Netherlands, and written informed consent was obtained from each patient.

MRI technique and interpretation

Magnetic resonance imaging was performed within 3 to 6 weeks of trauma and repeated after approximately 1 year follow-up. For both examinations, we applied the same technique and pulse sequences, using a 1.0 Tesla whole-body MRI unit and a dedicated knee coil. The imaging protocol 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 evaluated for the presence of degenerative abnormalities of the femorotibial joint. For this purpose, we used the items of the Knee Osteoarthritis Scoring System (KOSS) [18]. To grade the severity of OA we used the Kellgren and

Lawrence scoring system, which was originally developed for grading osteoarthritic change on conventional radiography [19] (Table 1). In addition to degenerative abnormalities including meniscal lesions and bone marrow oedema, we assessed the presence of ligamentous lesions on the initial MRI. Findings were documented on a standardised report form.

Two independent readers (one senior radiology resident (SB) and one experienced musculoskeletal radiologist (DV)) evaluated the initial MRI examination. In the case of discrepancies, consensus was reached through discussion. The follow-up MRI examinations were assessed by three independent readers (two senior radiology residents (EHGO and IMK) and one experienced musculoskeletal radiologist (JHH)). In the case of discrepancies the majority opinion was used for analysis.

To reflect clinical practice, both the reports and the images of the initial MRI examination were available on follow-up MRI evaluation. In this observational cohort study, the treating general practitioner was not informed of the findings on the initial MRI unless findings required immediate treatment. Hence, the treatment strategy was not influenced by the MRI findings. If a patient was referred to a medical specialist, the initial MRI report was provided on request, so as to avoid unnecessary repetition of an MRI examination.

Self-reported questionnaires

Self-reported questionnaires were completed at baseline and 12 months after trauma. On the questionnaires, we recorded a pain score measured on an 11-point numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain) [20], the

Lysholm knee function score [21], recurrence, level of sports activities, referral to a medical specialist, and whether an operation had been performed. At 12 months we also scored perceived recovery as rated by the patient and measured on a 7-point Likert scale, ranging from ‘completely recovered’ to ‘worse than ever’. Both the initial and follow-up MRI readers were blinded to the reported scores on the questionnaires.

Data analysis

Univariate and multivariate binary logistic regression analysis was performed using SPSS 11.0 for Windows. As the binary outcome, we defined any increase on the Kellgren and Lawrence scale on follow-up MRI compared with initial MRI. Therefore, this could either be new degenerative change in a previously unaffected knee or deterioration of pre-existing osteoarthritis.

We analysed the following independent variables: age (both continuous and dichotomised at age 50 years), sex, physique as measured by body weight and body mass index (both continuous and dichotomised at 25 and 30 kg/m²), sports injury as the setting of knee trauma, baseline pain score measured by the 11-point numeric rating scale (continuous and dichotomised at 6 points or higher), Lysholm knee function score (continuous and dichotomised at 50 points). The prognostic value of the following knee lesions on initial MRI was also evaluated: meniscal lesion (degenerative, tear, or combined; lateral and medial meniscus analysed separately or in combination), anterior cruciate ligament rupture (partial, total, or combined), bone marrow oedema in the distal femur or proximal tibia (medial and lateral femorotibial joint compartments analysed separately

Table 1 Cross-tabulation of femorotibial Kellgren and Lawrence score on initial versus follow-up MRI

		Kellgren and Lawrence score on initial MRI					Total
		Grade 0 (normal)	Grade 1	Grade 2	Grade 3	Grade 4	
Kellgren and Lawrence score on follow-up MRI	Grade 0 (normal)	62	–	–	–	–	62
	Grade 1	18	16	–	–	–	34
	Grade 2	4	1	5	–	–	10
	Grade 3	–	2	–	4	–	6
	Grade 4	–	–	–	2	3	5
	Total	84	19	5	6	3	117

Table presents number of patients

Kellgren and Lawrence Score:

Grade 0: no degenerative abnormalities

Grade 1: minimal osteophyte of unknown significance

Grade 2: osteophytes without joint space narrowing

Grade 3: moderate joint space narrowing

Grade 4: severe joint space narrowing with sclerosis of subchondral bone

and combined). As there were relatively few total PCL and collateral ligament ruptures, we combined these lesions as a total ACL rupture, resulting in a combined variable indicating any total rupture of either cruciate of the collateral ligament. In the univariate analysis, we regarded variables as statistically significant with a *p* value of less than 0.10. In the multivariate analysis, we used a statistically significant threshold of a *p* value of 0.05.

We missed data on sports injury in 6 patients. As the association with a sports injury was strongly correlated with age and sex, we used these variables in a logistic regression analysis to impute the missing data on sports injury. Data on baseline pain score and Lysholm knee function score were missing in 3 patients, the pain score and perceived recovery data after 12 months' follow-up were lacking in 7 and 1 patients respectively. We imputed these data with the mean values of the other patients, as it has been demonstrated that imputation of missing data reduces the risk of bias and is preferable over complete case analysis [22, 23].

Sixteen patients underwent surgery during follow-up. As this study was not aimed at therapy, the exact type of surgical or arthroscopic procedures was not known in every operated patient. To explore the possible effect of surgery on the result of the analysis, we performed a sensitivity analysis from which the operated patients were excluded.

Perceived recovery measured on the self-reported questionnaire at 12 months' follow-up was regarded as an indicator of clinical outcome. The expected course of recovery one year after knee trauma was complete recovery or at least strong improvement. Following dichotomisation of this variable into complete recovery or strong improvement versus some improvement, unchanged or deteriorated, we analysed the association between OA progression on the Kellgren and Lawrence score and the clinical outcome using Fisher's exact test.

Results

One hundred and thirty-four patients were included and underwent MRI at baseline. Seventeen patients were not followed up because they refused participation or because they had moved and we were unable to contact them. Thus, follow-up MRI was performed in 117 patients (67 male, 50 female; mean age 41 years, standard deviation 12.2 years, range 18–63 years). The mean time between MRI examinations was 403 days (standard deviation 57.8 days, range 315–675 days). A flow diagram indicating the selection of subjects and the flow of patients through the study is presented in Fig. 1.

A cross-tabulation of the Kellgren and Lawrence score on initial versus follow-up MRI is listed in Table 1. At one year follow-up, a total of 27 knees showed an increase on the Kellgren and Lawrence scale; 22 of these were initially

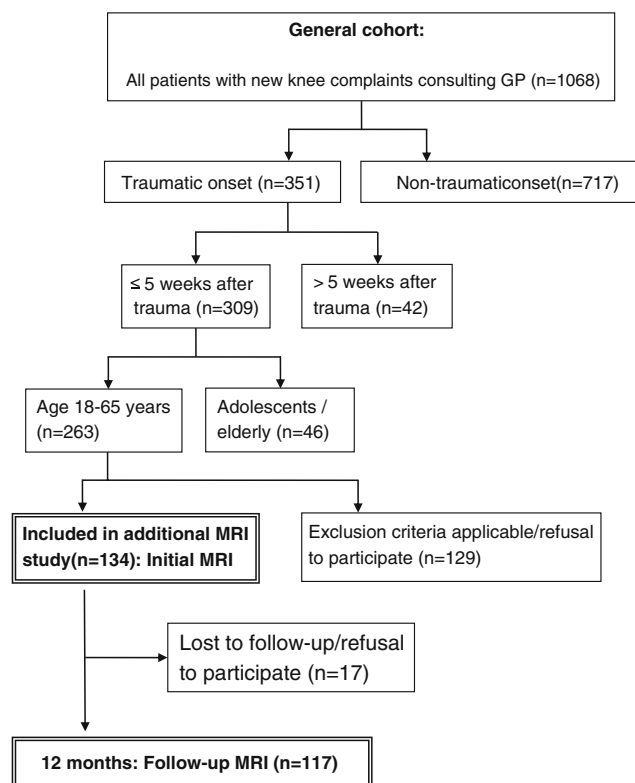


Fig. 1 Flow diagram indicating the selection of subjects and the flow of patients through the study

normal. Five patients demonstrated deterioration of pre-existing degenerative change.

The results of the univariate logistic regression analysis are presented in Table 2. Age above 50 years, body mass index greater than 25 kg/m², and the presence of bone marrow oedema on initial MRI (both for medial and lateral compartments separately and combined) were significant predictors of increased Kellgren and Lawrence score after one year follow-up. We included age above 50 years, body mass index greater than 25 kg/m², and bone marrow oedema (medial and lateral compartments combined) in the multivariate logistic regression analysis. Although age and body mass index both were no longer statistically significant when controlling for bone marrow oedema (OR 1.51 (95% CI 0.56–4.12), *p*=0.42 and OR 2.07 (95% CI 0.75–5.73), *p*=0.16 respectively), we kept these variables in the model, as these are established risk factors for osteoarthritis. Thus, in the final multivariate model medial and/or lateral femorotibial bone marrow oedema on initial MRI was the only statistically significant predictor of increased Kellgren and Lawrence score on follow-up MRI after one year (OR 5.29 (95% CI 1.64–17.1), *p*=0.005).

In the sensitivity analysis of 101 conservatively treated patients excluding the 16 patients who had undergone surgery during follow-up, we identified the same statistically significant variables in univariate logistic regression analysis

Table 2 Results of the univariate logistic regression analysis

Covariate	Frequency in study population of 117 patients (percentage) ^a	Odds ratio (95% confidence interval)	<i>p</i> value
Age (continuous)	41.0 years (12.2, 18–63) ^a	1.03/yr (0.99–1.07)	0.10
Age >50 years	30 (26)	2.57 (1.02–6.44)	0.04
Male sex	67 (57)	0.74 (0.30–1.78)	0.50
Body weight	82.6 kg (15.6, 40–129) ^a	1.01/kg (0.98–1.04)	0.41
Body mass index (continuous)	26.3 kg/m ² (4.1, 17–40) ^a	1.07 (0.97–1.19)	0.18
Body mass index >25 kg/m ²	69 (59)	2.39 (0.92–6.21)	0.07
Body mass index >30 kg/m ²	20 (17)	1.55 (0.53–4.53)	0.42
Sports injury ^b	59 (50)	1.08 (0.46–2.55)	0.87
Baseline pain score continuous ^c	4.6 (2.3, 0–10) ^a	1.01 (0.84–1.22)	0.92
Baseline pain score >6 points ^c	44 (38)	0.79 (0.32–1.94)	0.60
Baseline Lysholm score continuous ^c	65.1 (18.8, 16–100) ^a	0.99 (0.97–1.01)	0.25
Baseline Lysholm score >50 ^c	88 (75)	0.72 (0.28–1.89)	0.51
Lesions on initial MRI			
Total ACL rupture	12 (10)	1.13 (0.28–4.49)	0.87
Total or partial ACL rupture	21 (18)	1.90 (0.68–5.33)	0.22
Total cruciate or collateral ligament rupture	14 (12)	2.05 (0.62–6.73)	0.24
Lateral meniscal tear	24 (21)	0.85 (0.28–2.54)	0.77
Lateral meniscus degenerative lesion or tear	47 (40)	0.84 (0.35–2.05)	0.71
Medial meniscal tear	32 (27)	1.82 (0.73–4.55)	0.20
Medial meniscus degenerative lesion or tear	91 (78)	1.34 (0.45–3.97)	0.60
Lateral or medial meniscal tear	43 (37)	1.52 (0.64–3.65)	0.35
Lateral or medial meniscus degenerative lesion or tear	95 (81)	1.03 (0.34–3.09)	0.97
Bone marrow oedema in lateral compartment	45 (39)	3.06 (1.26–7.42)	0.01
Bone marrow oedema in medial compartment	53 (45)	3.14 (1.27–7.77)	0.01
Bone marrow oedema in lateral or medial compartment	67 (57)	6.01 (1.92–18.8)	0.002

^a For continuous variables, we report mean (standard deviation, range)

^b 6 missing values were imputed

^c 3 missing values were imputed

(results not tabulated). Similarly, femorotibial bone marrow oedema was the only statistically significant variable in multivariate analysis (OR 5.38 (95% CI 1.67–17.3), *p*=0.005).

A cross-tabulation of perceived recovery versus stable or progressive degenerative change on follow-up MRI is

shown in Table 3. Ninety-seven patients reported complete recovery or strong improvement after 12 months' follow-up, whereas 3 patients experienced some deterioration. Seventeen of the 27 patients with new or progressive osteoarthritic change reported complete recovery or strong improvement in terms of perceived recovery versus 80 of

Table 3 Perceived recovery after 12 months and progression of degenerative change on follow-up MRI

	Perceived recovery					Total
	Complete recovery	Strong improvement	Some improvement	Unchanged	Some deterioration	
Absent or unchanged pre-existing degenerative change	23	57	6	3	1	90
New or progressive degenerative change	7	10	7	1	2	27
Total	30	67	13	4	3	117

No patients selected the categories strong deterioration or worse than ever

Table displays number of patients

the 90 patients with absent or unchanged OA. There was a statistically significant association between new or progressive osteoarthritic change on follow-up MRI and perceived recovery (Fisher's exact test p value 0.003).

Discussion

We evaluated prognostic factors, including initial MRI findings after knee trauma, for new onset or progression of OA of the femorotibial joint, as assessed by follow-up MRI after one year. Unlike previously published studies on this subject, we conducted this study in the general practice population as most patients with traumatic knee injury are managed in a primary care setting in our country. In the univariate logistic regression analysis, higher age (>50 years), higher body mass index (>25 kg/m²), and bone marrow oedema were associated with new or progressive osteoarthritic changes of the femorotibial joint one year after trauma. In multivariate logistic regression analysis, however, only bone marrow oedema was statistically significant and it was found to be a strong predictor. Whereas previously published studies focused on the long-term (2 years and more) risk of developing OA after knee injury, we focused on the risk of developing MRI signs of OA during the first year following trauma [7, 8, 24].

Both higher age and higher body mass index were identified as risk factors for progression of knee osteoarthritis in previous case control studies and population based studies [2, 4, 25]. Although we only found this association in univariate logistic regression analysis, we kept these variables in the model, as these are established risk factors for osteoarthritis. It is possible that the number of patients was too small to demonstrate significance. Apparently bone marrow oedema is more important in the onset or progression of knee osteoarthritis than the other two risk factors.

Our findings are consistent with other reports on bone marrow oedema. In the Pond-Nuki dog model of OA, bone marrow lesions were considered a very early sign of OA [10]. In a longitudinal study by Felson et al. bone marrow oedema was suggested to be a powerful predictor of disease progression in non-traumatically injured patients with symptomatic OA of the knee [9]. Kubota et al. recently found a relationship between bone marrow abnormalities and the progression of knee OA [26].

Histopathologically, bone marrow oedema after traumatic knee injury (also referred to as bone bruise) is thought to be the result of microfractures and haemorrhage in the subcortical trabecular bone. Bone bruise-related cartilage changes are reported to be the result of chondrocyte degeneration with proteoglycan loss [27]. As damage to the articular cartilage is thought to be an important factor in the development of OA,

this may explain the relationship between traumatic bone marrow oedema and early progression of OA.

In a previous study, we found that the median healing time of post-traumatic bone bruises in our study group was 42.1 weeks [28]. The present study suggests that although the bone bruise itself is healed within a year, a long-term effect may be initiated by this lesion, i.e. the development of osteoarthritic change of the knee joint.

Our study has several limitations. We only evaluated the femorotibial joint because there were too few patients ($n=4$) with new onset or progressive patellofemoral OA to justify a separate logistic regression analysis. We considered that a pooled analysis of these joints would be meaningless, because the pathogenesis of femorotibial and patellofemoral OA and the effect of trauma is probably different. In recent MRI-based studies on OA, the Whole Organ Magnetic Resonance Imaging Score (WORMS) and Knee Osteoarthritis Scoring System (KOSS) have been used to evaluate the severity of degenerative change [15, 18]. At the time of the baseline MRI performed in our study (2002–2003), these semi-quantitative scoring systems had not been introduced, although the items scored were almost identical to KOSS. For reasons of comparability and to avoid interfering with the prospective study design, we used the KOSS items for the evaluation of progression of OA, but we continued using the adapted Kellgren and Lawrence system for grading OA on the 1-year follow-up MRI [19]. The outcome was defined as any increase on the Kellgren and Lawrence scale. We acknowledge that this refers to a heterogeneous group of patients including those with new onset OA and those with progression of pre-existing osteoarthritic changes. Most patients with progression of OA on MRI, however, had no OA initially, indicating that the results of this study were largely based on patients who developed new onset degenerative change within one year of trauma. Most of these patients developed mild degenerative change of Kellgren and Lawrence grade 1–2 severity. As the contralateral knee was not imaged, we cannot exclude that degeneration as part of the natural history explains part of our findings. Furthermore, which proportion of osteoarthritic change is attributable to trauma is unknown, but whether or not the OA is attributable to the trauma, although interesting pathophysiologically, is clinically less relevant. The important point is that in a patient with knee injury, bone marrow oedema predicts the development of early OA.

We performed our study in the primary care setting, and consequently patients with more severe traumatic knee injuries were not included because they were referred to secondary care immediately. This may explain the relatively limited number of meniscal injuries and cruciate ligament injuries in our patient population, which implied a limited power to demonstrate a statistically significant association between these lesions and early progression of OA. The

true extent to which meniscal damage and cruciate ligament injuries predict early progression of OA may be underestimated in our study, as both types of lesions have been reported to be risk factors for progression of OA [6–8].

As it was not the aim of the study to evaluate treatment for traumatic knee lesions, we did not record in detail what procedure was performed in the operated patients. To explore the consequences of this limitation, we performed a sensitivity analysis excluding the operated patients. The same prognostic factor with a similar odds ratio was found, indicating that the results of the analysis were not influenced by the type of treatment, underscoring the robustness of the model.

We found a significant association between new onset or progression of femorotibial OA at follow-up MRI and clinical outcome as measured by perceived recovery. All patients in our study sustained a knee injury resulting in acute trauma-related symptoms. One year after trauma the expected natural healing course would be complete recovery or at least strong improvement. As the disabling symptoms in the initial stage after trauma are no longer present one year after trauma, a perceived recovery less than “strong improvement” in all likelihood reflects the effect of new onset or progressive OA. In light of our results, this stresses the importance of identifying those patients with bone bruise in the initial stage after trauma and those with no or minor improvement of clinical outcome after trauma, as these patients are at high risk of developing new onset OA. In the future these patients may benefit from the development of treatment strategies targeting bone bruises.

In conclusion, the results of this study demonstrate that bone marrow oedema on initial MRI after knee trauma is a strong predictor, and in multivariable analysis the only predictor, of new onset and progression of knee osteoarthritis on 1-year follow-up MRI, which is reflected in the clinical outcome.

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