Traumatic and Non-traumatic Knee Complaints in General Practice

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Traumatic and Non-traumatic Knee Complaints in General Practice

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in de huisartsenpraktijk

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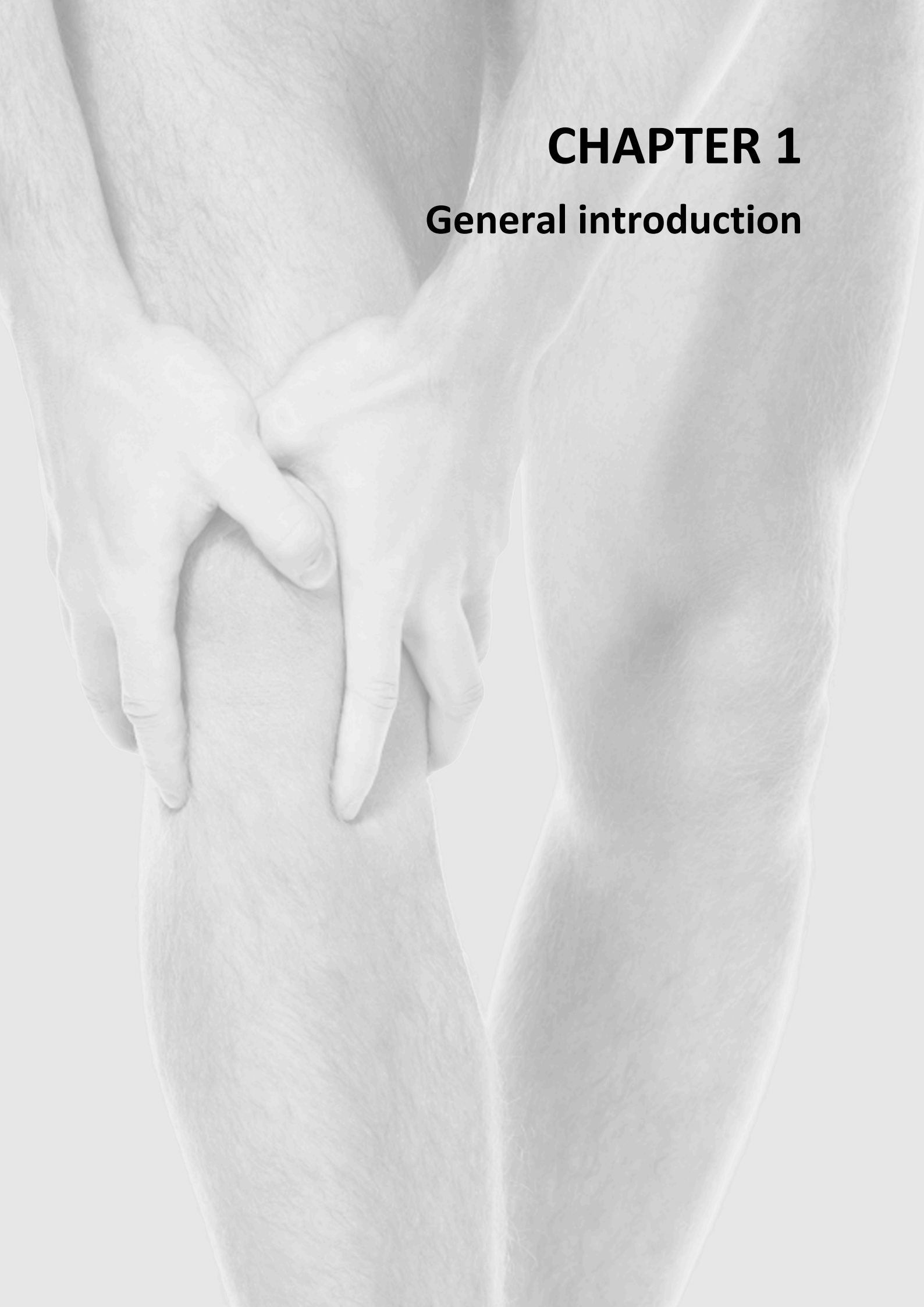

CHAPTER 1

General introduction

General introduction

General practitioners (GPs) are frequently consulted by patients with various types of knee complaints. The incidence of these knee complaints presented in Dutch general practice is about 13.7 per 1000 registered patients per year with a prevalence of 19.0 per 1000 patients per year.[1] About 80% of these knee complaints are of non-traumatic origin.[2] The most common non-traumatic diagnosis varies with age; adolescents and young adults suffer mostly from patellofemoral pain syndrome, jumper's knee (knee extensor tendinitis) or Osgood-Schlatter disease, while adults suffer mostly from bursitis, tendinitis or osteoarthritis (OA).[3,4] Traumatic knee complaints include contusion, distortion, collateral ligament lesion, cruciate lesion, meniscal tear, patella-luxation and fractures.[2] In spite of the finding that knee complaints are a common disorder in general practice, clinical evidence on the management of this subject in general practice is scarce. To improve the management of knee complaints in general practice, evidence is needed on diagnosis, long-term natural course and prognostic factors for persistent knee complaints and the development of knee OA. Therefore, we performed a prospective observational cohort study (the HONEUR knee cohort) with a six-year follow-up, aimed to assess the natural course of knee complaints and to study prognostic factors for persistent knee complaints in general practice.

HONEUR knee cohort

The HONEUR knee cohort is a prospective, observational cohort study established by the Department of General Practice of Erasmus Medical Center Rotterdam.[5] The follow-up period was initially one year; however, because of the high percentage of patients with persistent knee complaints at one-year follow-up, the follow-up was extended to six years with permission of the local Medical Ethical Committee.[5-7] Forty GPs in the southwest of the Netherlands participated in this study and represented a total population of about 84,000 persons.[5] In total, 1068 consecutive patients (aged 12 years and older) who visited their GP with a new episode of traumatic or non-traumatic knee complaints were enrolled in the study. New episodes of knee complaints were defined as episodes of complaints presented to the GP for the first time. Recurrent symptoms for which the GP was not consulted within the past three months were also considered as a new episode of complaints. Traumatic knee complaints were defined as those caused by a sudden impact or wrong movement within one year before consulting their GP; all other knee complaints were considered as non-traumatic knee complaints.

The 1068 patients participating in this study were divided in three main groups (groups 1-3), and one subsequent subgroup (group 3a) based on age and type of knee complaints:

- Group 1: Adolescents and young adults, aged 12 to 35 years, with non-traumatic knee complaints, n=191

- Group 2: Adults, aged 35 years and older, with non-traumatic knee complaints, n=549
- Group 3: Adolescents and adults, aged 12 years and older, with traumatic knee complaints, n=328
    - Group 3a: Adults, aged 18 to 65 years, with traumatic knee complaints who participated in an additional MRI study, n=134

Diagnostic value of history taking and physical examination in traumatic knee patients

The GP tries to get an impression of the nature and severity of the knee injury when a patient with a traumatic knee complaint presents in primary care.[2] This is important to establish a good working diagnosis, to decide on subsequent management and to provide the patient with appropriate information about their knee complaint. Although MRI of the knee is an excellent method for diagnosing internal knee lesions, in Dutch general practice this diagnostic tool is generally not immediately used for patients with traumatic knee complaints.[2,8,9] Therefore, the GP has to mainly rely on history taking and physical examination to arrive at a working diagnosis in these patients.[2] Some knowledge on the diagnostic value of history taking and physical examination in patients with traumatic knee complaints is available; however, this knowledge is mostly based on patients in a secondary care setting, who are not directly comparable with patients seen in primary care.[9-13] Wagemakers et al. reported on the diagnostic value of history taking and physical examination of meniscal lesions and anterior cruciate lesions (ACL) of the knee in the subgroup of adults with traumatic knee complaints of the HONEUR knee cohort who underwent an additional MRI of their knee (group 3a). They concluded that GPs can screen for ACL lesions using history taking and physical examination, and that history taking has some diagnostic value for detecting meniscal tears whereas physical examination has no additional diagnostic value in diagnosing meniscal tears.[14,15] In addition, in this thesis we describe the diagnostic value of history taking and physical examination for medial collateral ligament lesions of the knee in this same subgroup of the HONEUR knee cohort (group 3a). In this subgroup we also investigate the diagnostic value of history taking and physical examination for intra-articular effusion of the knee, because it is reported that this condition is an important sign of intra-articular lesion of the knee.[16]

Natural six-year course and prognostic factors for persistent knee complaints

Information on the natural course and prognosis of knee complaints is important for GPs, because it can help to provide the patient with more valid information about their prognosis and to make a more appropriate choice regarding treatment and/or referral. For patients this information is also important for reasons of ‘knowing for the sake of knowing’ and ‘planning of future activity’.[17] However, information on the natural course and prognosis of knee complaints of patients presenting in general practice is scarce.

Although some information is available on the one to three year course[18-21] many patients have knee complaints for a longer period of time. Belo et al. reported on the one-year natural course and prognostic factors for persistent knee complaints for adults with non-traumatic knee complaints of the HONEUR knee cohort (group 2). They concluded that symptom characteristics were the strongest predictors of persisting knee symptoms at one-year follow-up and that physical examination has no added value.[6] Wagemakers et al. reported on the one-year natural course and prognostic factors for persistent knee complaints for the subgroup of adults with traumatic knee complaints of the HONEUR knee cohort who underwent an additional MRI of their knee (group 3a). They concluded that the vast majority of patients report clinically relevant recovery at one-year follow-up and that there is no clear difference in outcomes between patients with meniscal tears or ligament lesions and patients without these diagnoses.[7] Additionally, in this thesis we investigate the six-year natural course and prognostic factors for an unfavourable outcome for the group of adults with non-traumatic knee complaints of the HONEUR knee cohort (group 2). We also examine the one and six year natural course and prognostic factors for persistent knee complaints for the other main groups of the HONEUR knee cohort (groups 1 and 3).

Osteoarthritis of the knee

OA of the knee is a common disorder among patients with knee complaints, especially in older patients.[22] Moreover, it is well known that patients with a traumatic knee complaint have an increased risk of developing OA of the knee at a younger age, probably 10-20 years after onset of the injury.[23] OA of the knee is a chronic disorder with a major burden for both the patient and for society.[24] Predicting which patients with knee complaints will develop chronic complaints due to knee OA may encourage the development and testing of interventions for knee OA in an early stage and, hopefully, may diminish this burden. Currently, however, it is difficult to diagnose knee OA in an early stage in general practice, because an X-ray of the knee shows abnormalities only at a later (more developed) stage and is not very consistent with clinical symptoms.[25] Therefore, because an X-ray of the knee is not recommended in general practice for the diagnosis of knee OA, diagnosis is still based on history taking and physical examination.[3] Although the American College of Rheumatology has established criteria for OA of the knee (clinical ACR criteria), these criteria were mainly developed for scientific research and to distinguish OA from rheumatoid arthritis.[26] Moreover, these criteria are not considered appropriate for diagnosing OA of the knee in general practice.[27] Belo et al. reported on the prognostic value of the clinical ACR criteria for persisting knee complaints and increase of disability in the group of adults with non-traumatic knee complaints of the HONEUR knee cohort (group 2). They concluded that the clinical ACR criteria of knee OA had no prognostic value for predicting persisting knee complaints or an increase of disability at one-year of follow-up in adults with non-traumatic knee complaints in general practice.[28] Koster et al.

reported on the predictive factors for new onset or progression of knee OA one year after trauma in the subgroup of adults with traumatic knee complaints of the HONEUR knee cohort who underwent an additional MRI of their knee (group 3a). They concluded that bone marrow oedema on baseline MRI was strongly predictive of new onset or progression of degenerative change of the femorotibial joint on follow-up MRI one year after trauma and that this was also reflected in clinical outcome.[29] Additionally, in this thesis we investigate the presence of knee OA at six-year follow-up and the prognostic factors in the group of adults with non-traumatic knee complaints (group 2) and in the subgroup of adults with traumatic knee complaints of the HONEUR knee cohort who received an additional MRI (group 3a).

Contents of this thesis

Chapter 2 describes the diagnostic value of history taking and physical examination in assessing medial collateral ligament lesions of the knee in traumatic knee patients in general practice.

Chapter 3 addresses the diagnostic value of history taking and physical examination in assessing effusion of the knee in traumatic knee patients in general practice.

Chapter 4 describes the one and six-year course and prognostic factors for persistent knee complaints of adolescents and young adults with non-traumatic knee complaints in general practice.

Chapter 5 presents the six-year course and prognostic factors for persistent knee complaints of adults with non-traumatic knee complaints in general practice.

Chapter 6 examines the one and six-year course and prognostic factors for persistent knee complaints of adolescents and adults with traumatic knee complaints in general practice.

Chapter 7 describes the presence of knee OA at six-year follow-up and prognostic factors in adults with non-traumatic knee complaints in general practice.

Chapter 8 explores the presence of knee OA at six-year follow-up and prognostic factors in adults with traumatic knee complaints in general practice who received an additional MRI.

Chapter 9 discusses the main findings of the previous chapters, reflects on the study limitations, and examines their implications for daily practice and future research.

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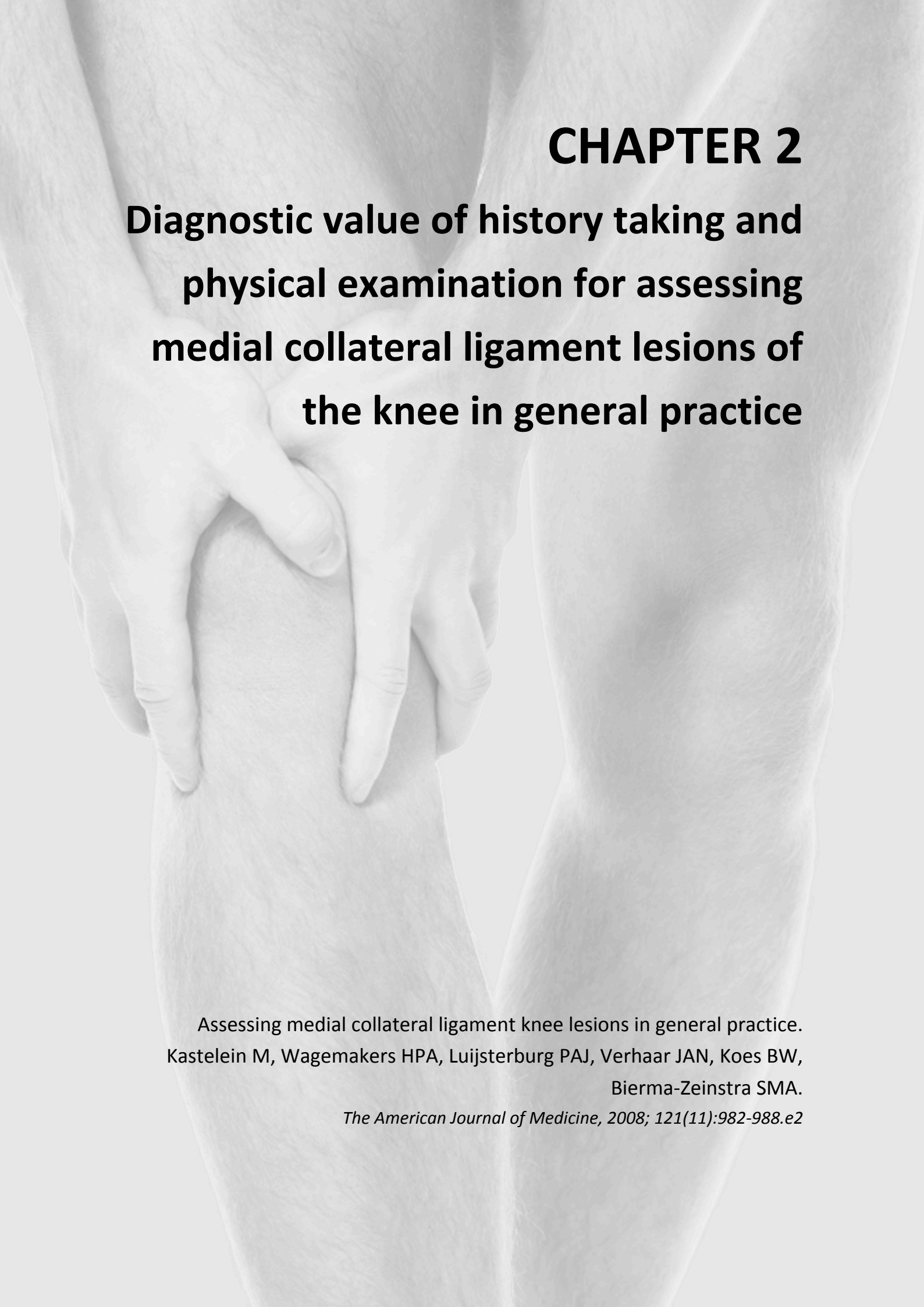


CHAPTER 2

Diagnostic value of history taking and physical examination for assessing medial collateral ligament lesions of the knee in general practice

Assessing medial collateral ligament knee lesions in general practice.
Kastelein M, Wagemakers HPA, Luijsterburg PAJ, Verhaar JAN, Koes BW, Bierma-Zeinstra SMA.
The American Journal of Medicine, 2008; 121(11):982-988.e2

Abstract

Objective: To assess the diagnostic value of history taking and physical examination of medial collateral ligament (MCL) lesions after a knee injury presenting in general practice.

Methods: Patients aged 18 to 65 years with a traumatic knee injury who consulted their general practitioner within 5 weeks after trauma filled out a questionnaire, underwent a standardized physical examination and underwent a magnetic resonance imaging (MRI) scan. Logistic regression analysis was used to test possible associations between determinants from history taking/physical examination and MCL lesions. The diagnostic value of history taking and physical examination was determined for those variables indicating an association ($p<0.15$) with MCL lesions and was assessed by sensitivity, specificity, predictive value and likelihood ratios.

Results: Of the 134 patients included in this study, 35 had an MCL lesion seen on MRI. From history taking the determinants "trauma by external force to leg" and "rotational trauma" showed an association with MCL lesion after multivariate analysis ($p<0.15$). From physical examination "pain valgus stress 30^{o}" and "laxity valgus stress 30^{o}" showed an association ($p<0.15$). Isolated determinants from history taking and physical examination showed some diagnostic value; the likelihood ratio positive (LR+) was 2.0 for "trauma by external force to leg" and for "pain valgus stress 30^{o}" 2.3. Adding "pain valgus stress 30^{o}" and "laxity valgus stress 30^{o}" from physical examination to history taking improved the diagnostic value to a LR+ of 6.4.

Conclusion: MCL lesions are frequently seen in patients with traumatic knee injury. History taking has a diagnostic value, while adding physical examination increase the diagnostic value.

Introduction

General practitioners (GPs) are frequently consulted by patients who have sustained a traumatic knee injury. The incidence of these injuries (excluding fractures) reported in Dutch general practice is about 5.3 per 1000 patients per year.[1] The medial collateral ligament (MCL) is important for knee joint stability.[2] A rupture of the MCL, due to trauma, is reported frequently: 25.7% of patients in primary care have a partial lesion and 0.7% have a complete lesion.[3]

In the Dutch healthcare system, the GP plays a key role as a gatekeeper. After history and physical examination the GP decides on a wait-and-see policy, initiates conservative treatment or considers referral for further diagnostic imaging or secondary care. About 25% of all patients with traumatic knee injuries in the Netherlands is referred to secondary care.[4]

Careful history taking and physical examination should help the GP making a clinical diagnosis in knee injury.[5] However, the diagnostic value of history taking and physical examination is often questioned by clinicians.[6,7] Four systematic reviews summarized available knowledge on this issue.[8-11] However, most studies reported on meniscus and cruciate lesions.[8-10] Only Solomon et al.[11] reported about MCL lesions. They concluded that there were no data available to determine the accuracy of physical examination of the MCL.[11] One comparative studies has looked at the diagnostic value of physical examination at MCL lesions.[12] Rasenberg et al.[12] concluded that there is a very high degree of agreement between the results in grading acute MCL injuries with magnetic resonance imaging (MRI) and an instrumented valgus-varus laxity tester.[12] However, the conclusion from this study[12] is based on patients presenting of a secondary care setting. There are no studies available concerning patients with traumatic lesions of the knee in primary care. The likelihood of actual lesions of the knee in secondary care settings is expected to be higher, because the selection of patients has already taken place in primary care.

The present study aims to determine the diagnostic value of items from history taking and physical examination for detecting MCL lesions in primary care, for isolated determinants as well as combinations of determinants.

Methods

Design

The present prospective, observational cohort study is part of the research network HONEUR (40 GPs) established by the department of General Practice of Erasmus Medical Center Rotterdam.[13] New complaints were defined as episodes of complaints presented to the GP for the first time.

Patients were eligible for the present study if they were aged 18 to 65 years and had consulted their GP for a traumatic knee complaint within 5 weeks after the initial trauma.

Patients with MRI contraindications (pregnancy, metal implants or a pacemaker) were excluded.

The study protocol was approved by the Medical Ethics committees of the Erasmus Medical Center Rotterdam and of the Medical Center Rijnmond Zuid.

Data collection

Patients filled out a self-report questionnaire and an appointment was made for the MRI study. A standardized physical examination was carried out immediately after the MRI study by a trained physical therapist; this time sequence was chosen to avoid physical examination of missed fractures. The physical therapist was blinded to the MRI results, as was the radiologist to the results of the physical examination and questionnaire. Neither the patient nor the GP was informed about the outcome of the MRI or physical examination to avoid transmitting results or influencing the behavior of the patient or the GP.

The baseline questionnaire[13] collected data including age, gender, socio-economic status, history of previous knee injuries and/or operations, present symptoms, mechanism of injury, level of activity in work, household, study, sports and the Lysholm knee score.[14]

Physical examination[13] of both knees consisted of inspection (alignment and joint effusion[15]), palpation (temperature, collateral ligaments and joint line tenderness[15]), assessment of effusion,[15,16] passive range of motion in flexion and extension[15,16] and the valgus stress test in 0° and 30° flexion.[17] Other stability tests and meniscal tests, as the anterior drawer test[17] and MCMurray test,[18] also are performed, but were not used for analysis in the present study.

MRI was selected as the reference test because it is a highly accurate diagnostic tool for detecting MCL lesions.[2] In the present study MRI was scheduled 3 to 6 weeks after the initial trauma using a 1.0 Tesla General Electric device (GE Healthcare, Buckinghamshire, UK); acute symptoms (such as effusion or hemoarthros) will likely be reduced while MCL lesions are still present.[19] Detailed information about the MRI procedure is reported elsewhere.[3]

Patient outcome was defined as presence or absence of an MCL lesion as seen on MRI. Two radiologists classified the MRI scans independently from one another. In case of disagreement, the findings were discussed until consensus was reached.

Statistical analysis

Descriptive statistics were used to present the results of the MRI. Univariate logistic regression analysis (SPSS, version 11.0; SPSS Inc., Chicago, III) was used to determine the association of separate determinants from history taking and physical examination with MCL lesions, expressed as odds ratios (OR). Determinants showing a univariate association ($p<0.15$) with an MCL lesion were analysed in a multivariate logistic regression

analysis (Backward Wald method, entry 0.10, removal 0.20) to eliminate redundant variables. Separate analyses were performed for history taking and physical examination. Finally, the remaining determinants (p<0.15) were analysed together (using the Enter method) to compose a diagnostic model for MCL lesions. Based on the relatively small sample size, we choose the arbitrary P-value of 0.15 for the univariate logistic regression analysis to be included in the multivariate model in order to create some stability of this multivariate model.

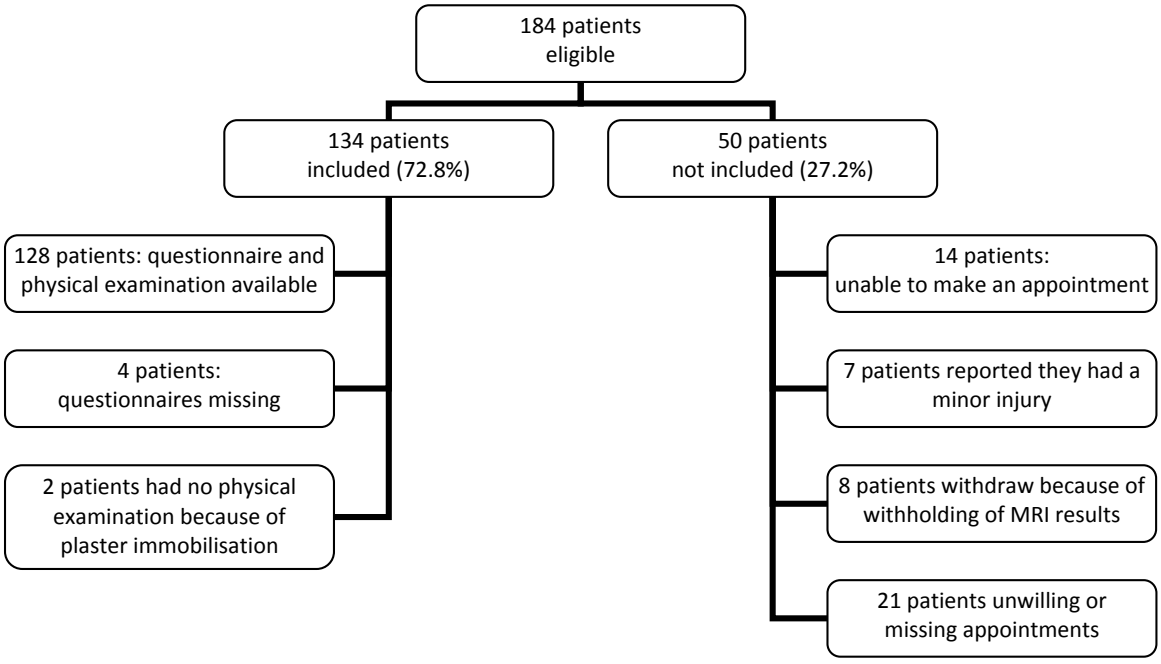
We determined the diagnostic value of the isolated determinants from history taking and physical examination with a statistically significant independent relationship with MCL lesions (p<0.15) by calculating the sensitivity (Se), specificity (Sp), predictive value-positive (PVP) and predictive value-negative (PVN).[20] We also determined the likelihood ratio (LR) for positive (LR+) and negative (LR-) examination.[20] Finally, we combined determinants from the composed diagnostic model for MCL lesions (p<0.15) and determined the diagnostic value of these combinations.

Results

Study population

Of the 184 eligible patients, 134 (73%) were included in the present study (March 2002 to October 2003). Figure 1 shows the flowchart of eligible patients. Reasons for non-participation were unwillingness or missing appointments for the MRI (n=21), no availability of MRI appointment (n=14) and other reasons (n=15). No patient was excluded because of the MRI exclusion criteria.

Figure 1 Flow chart of eligible patients.



No statistically significant (P<0.05) differences were found between the baseline characteristics of the participants and non-participants (Table 1).

Mean age of the participants was 40.2 years (SD 12.2) and a small majority was male (55.2%). Sixty-one patients (45.5%) reported that sport activities were the cause of the sustained knee injury. At baseline, the mean pain severity, measured with a numerical rating scale, was 4.7 (0 = no pain to 10 = unbearable pain) and the mean Lysholm knee score was 63.7 (0 = worse to 100 = best).

Table 1 Comparison of baseline characteristics of participants and non-participants

Characteristic	**Participants (n=134)**	**Non-participants (n=50)**
Age, years, (mean ± sd)	40.2 ± 12.2	40.4 ± 11.3
Gender male, (n,(%))	74 (55.2)	32 (66.7)
Onset during sports activity, (n,(%))	61 (45.5)	16 (33.5)
Symptom side right, (n, (%))	70 (52.2)	19 (39.6)
Pain severity (0-10), (mean ± sd)	4.7 ± 2.4	4.2 ± 2.5
Lysholm knee function score (0-100), (mean ± sd)	63.7 ± 18.9	66.5 ± 23.3

MRI results

The results from MRI studies are presented in Table 2. The median of time between trauma and MRI was 36 days (range 9-81 days); 70% of all patients had their MRI within 6 weeks after the initial trauma. In 14 patients (10.4%) there were no signs of effusion, ligamentous lesions or meniscal tears on the MRI, and 38 patients (28.4%) showed only effusion without detectable ligamentous lesions or meniscal tears. Thus, 52 patients (38.8%) had no signs of meniscal tears or ligamentous lesions. Meniscal tear is defined as all meniscal tears, excluding degenerative meniscal tears.

MCL lesions detected by MRI were seen in 35 patients (26.1%). Eight patients had a LCL lesion (6.0%). Of all patients, 16 (11.9%) had an isolated MCL lesion and 12 (9.0%) had a combination of MCL lesion with meniscal tear.

Table 2 MR imaging findings in patients with knee injury (n=134) in general practice

Diagnosis as seen on MR imaging	**N (%)**
No lesion or hydrops, n (%)	14 (10.4)
Contusion (hydrops, no ligament or meniscal lesion), n (%)	38 (28.4)
Medial collateral ligament lesion, n (%)	35 (26.1)
Lateral collateral ligament lesion, n (%)	8 (6.0)
Anterior cruciate ligament lesion, n (%)	28 (20.9)
Posterior cruciate ligament, n (%)	6 (4.4)
Meniscal tear, n (%)	47 (35.1)
Isolated Medial collateral ligament lesion, n (%)	16 (11.9)
Isolated Lateral collateral ligament lesion, n (%)	2 (1.5)
Medial collateral ligament lesion and meniscal tear, n (%)	12 (9.0)

MR = magnetic resonance

History taking and physical examination

In 128 patients (95.5%) both the history taking and the physical examination were available. The questionnaires were available for 130 patients (97.0%); four questionnaires were not returned by the patient (Figure 1). Physical examination was performed in 132 patients (98.5%); 2 patients had plaster immobilization at the time of the MRI.

From history taking, 5 determinants showed an association ($p<0.15$) with MCL lesions (Table 3). These 5 determinants, "trauma during sport", "trauma by external force to knee", "rotational trauma", "foot/leg blocked" and "effusion (continuous)" result in a higher probability when found positive.

Ten test results obtained by physical examination, "genu flexum", "increased temperature", "fluctuation/minor effusion test", "medial joint line pain", "pain palpation MCL", "pain at passive flexion", "pain at passive extension", "pain valgus stress 0^{o}", "pain valgus stress 30^{o}" and "laxity valgus stress 30^{o}", showed an association ($p<0.15$) with MCL lesions (Table 3). These 10 variables raise the probability of an MCL lesion when found positive.

Table 4 shows the multivariate association of items with MCL lesions. After multivariate modelling "trauma by external force to leg", "rotational trauma", "pain valgus stress 30^{o}" and "laxity valgus stress 30^{o}" indicated an independent association ($p<0.15$) with the presence of a MCL lesion.

Diagnostic value of history taking and physical examination

The prevalence of MCL lesion (prior probability) in this study population was 0.26. The Se, Sp, PVP, PVN, LR+ and LR- are presented in Table 5.

The PVP of an MCL lesion increased from 0.26 to 0.41 (95% CI 0.18-0.47) for "trauma by external force to leg", to 0.33 (95% CI 0.18-0.47) with a positive "rotational trauma", to 0.44 (95% CI 0.31-0.57) for "pain valgus stress $30^{o''}$ and to 0.37 (95% CI 0.26-0.48) for "laxity valgus stress $30^{o''}$. Combining the determinants from history taking did not increase the PVP significantly. Adding "pain valgus stress $30^{o''}$ or "laxity valgus stress $30^{o''}$ to the combination of determinants from history taking when at least one out of two determinants was positive, increased the PVP to 0.56 (95% CI 0.33-0.79) and to 0.43 (95% CI 0.26-0.61) respectively. The PVP increased to 0.63 (95% CI 0.39-0.86) when combining at least one out of two determinants from history taking was positive, combined with "pain valgus stress 30^{o}" and "laxity valgus stress $30^{o''}$.

The probability of the absence of an MCL lesion increased from 0.74 to 0.85 (95% CI 0.75-0.95) for negative test results for "rotational trauma", to 0.90 (95% CI 0.83-0.97) for "pain valgus stress $30^{o''}$ and to 0.94 (95% CI 0.87-1.00) for "laxity valgus stress $30^{o''}$.

Combining the determinants of history taking did not increase the PVN substantial. Also, adding the determinants from physical examination did not increase the PVN.

Table 3 Number of patients with positive test result and association of items with MCL lesions

Variables [(reference)]	**Patients available N**	**MCL lesion present‡ (n=35)**	**MCL lesion absent‡ (n=99)**	**OR**	**95% CI**
History taking					
Age over 40	134	20	44	1.7	0.8-3.6
Gender (male/female)	134	21/14	53/46	0.8	0.4-0.7
Mechanism of injury					
Trauma during sport†	126	20	41	2.2**	0.9-4.9
> 90° of flexion during trauma	124	8	20	1.2	0.5-3.1
Fall on the knee	124	8	23	1.0	0.4-2.5
Trauma by external force to leg†	127	7	10	2.3*	0.8-6.5
Trauma while landing on leg	125	11	31	1.0	0.4-2.3
Trauma by forceful rising	126	2	10	0.6	0.1-2.7
Trauma during push off	127	7	23	0.8	0.3-2.2
Weight bearing on the knee	113	21	61	1.4	0.5-4.0
Rotational trauma†	93	13	27	2.7**	1.0-7.4
Foot/leg blocked†	107	16	27	2.9***	1.2-7.0
Signs at trauma					
Continuation activity impossible	127	19	46	1.4	0.6-3.2
Immediate pain at trauma	126	24	78	0.5	0.2-1.3
Immediate effusion after trauma	125	13	38	1.0	0.4-2.2
"Popping" sensation during trauma	126	14	30	1.5	0.7-3.5
Present symptoms					
Pain score ≥ 6 (0-10 NRS)	127	15	37	1.2	0.5-2.6
Effusion (continuous)†	128	14	25	2.1**	0.9-4.7
Crepitation (continuous)	129	6	24	0.6	0.2-1.7
Lysholm knee score < 80 [14]	130	26	75	0.9	0.4-2.3
Physical examination					
Genu flexum [15,16]†	132	14	20	2.6***	1.1-5.9
Increased temperature[15]†	132	20	36	2.3***	1.0-5.0
Ballottement test[15,16]	132	22	56	1.2	0.6-2.7
Fluctuation / Minor effusion test[15]†	128	7	6	3.8***	1.2-12.3
Medial joint line pain[15]†	132	27	48	3.4***	1.4-8.3
Pain palpation MCL[15]†	132	28	43	5.0***	2.0-12.6
Pain at passive flexion[15,16]†	134	27	60	2.2**	0.9-5.3
Pain passive extension[15]†	134	24	44	2.7***	1.2-6.2
Pain valgus stress 0° [15,16]†	121	20	22	7.1***	2.8-17.8
Laxity valgus stress 0° [15,16]	121	8	27	0.9	0.4-2.3
Pain valgus stress 30° [15,16]†	128	25	32	7.1***	2.8-18.3
Laxity valgus stress 30° [15,16]†	128	29	49	9.3***	2.6-32.5

MCL = Medial Collateral Ligament; OR = odds ratio; CI = confidence interval; NRS = numeric rating scale.

*p < 0.15; **p < 0.10; ***p < 0.05.

‡ as detected on MRI.

† = clinically important.

The isolated determinants "trauma by external force to leg" and "pain valgus stress 30°" had a clinically important LR+, 2.0 (95% CI 0.8-4.8) and 2.3 (95% CI 1.7-3.3) respectively. Combining determinants from history taking did not increase the LR+. De LR+ increased to 4.8 (95% CI 2.2-10.4) when at least one of the two determinants from history taking positive was combined with "pain valgus stress 30°", to 2.9 (95% CI 1.8-4.8) when combined with "laxity valgus stress 30°" and to 6.4 (95% CI 2.7-15.2) when combined with "pain valgus stress 30°" and "laxity valgus stress 30°".

The determinants "pain valgus stress 30°" and "laxity valgus stress 30°" had a low LR-, 0.3 (95% CI 0.2-0.6) and 0.2 (95% CI 0.1-0.6) respectively. The combinations did not alter the LR- substantially.

Table 4 Multivariate association (and 95% confidence interval) of items with MCL lesions

Variable from history taking or physical examination	**MCL lesion‡**
History taking	OR (95% CI)
Trauma by external force to leg	4.1** (0.8-20.9)
Rotational trauma	5.7*** (1.5-21.8)
Physical examination	
Pain valgus stress 30^0	3.1* (0.8-12.3)
Laxity valgus stress 30^0	4.2** (0.8-20.8)
Explained variance (%)	34.9

MCL = Medial Collateral Ligament; OR = odds ratio; CI = confidence interval.

*p < 0.15, **p < 0.1, ***p < 0.05

‡ As detected on MRI

Discussion

The present study is the first study to investigate the diagnostic value of history taking and physical examination in patients with an MCL lesion in a primary care setting. In this study MCL lesions were seen in 26% of the 134 included patients.

There is limited literature available on the diagnostic value of history taking and physical examination of MCL lesions.[11] The study of Rasenberg et al.[12] reported on MCL lesions, but concerned patients in secondary care. They concluded that there is a very high degree of agreement between the results in grading acute MCL injuries with MRI and an instrumented valgus-varus laxity tester. However, they did not report about the prediction whether there is an MCL lesion or not. Therefore no relevant information is available to which we can compare our results.

The present study shows that the isolated determinants "trauma by external force to leg" from history taking and "pain valgus stress 30°" from physical examination may be considered diagnostic tools for the GP in predicting MCL lesions. Also the absence of the isolated determinants "pain valgus stress 30°" and "laxity valgus stress 30°" from physical examination are potentially relevant diagnostic tools for excluding MCL lesions.

Table 5 Diagnostic values (and 95% CI) of isolated determinants and combinations of determinants with MCL lesions (prevalence = 0.26/N=35).

Variable	**N**	**SE**	**SP**	**PVP**	**PVN**	**LR+**	**LR-**
Isolated determinants							
Trauma by external force to leg	17	0.21 (0.07-0.35)	0.89 (0.83-0.96	0.41 (0.18-0.65)	0.76 (0.68-0.84)	2.0 (0.8-4.8)	0.9 (0.7-1.1)
Rotational trauma	40	0.62 (0.41-0.83)	0.63 (0.51- 0.74)	0.33 (0.18-0.47)	0.85 (0.75-0.95)	1.7 (1.1-2.6)	0.6 (0.3-1.1)
Pain valgus stress 30^0	57	0.78 (0.64-0.92)	0.67 (0.57- 0.76)	0.44 (0.31-0.57)	0.90 (0.83-0.97)	2.3 (1.7-3.3)	0.3 (0.2-0.6)
Laxity valgus stress 30^0	78	0.91 (0.81-1.00)	0.49 (0.39-0.59)	0.37 (0.26-0.48)	0.94 (0.87-1.00)	1.8 (1.4-2.2)	0.2 (0.1-0.6)
Combinations							
History ≥ 1 out 2	49	0.86 (0.71-1.00)	0.57 (0.46-0.68)	0.37 (0.23-0.50)	0.93 (0.86-1.00)	2.0 (1.4-2.7)	0.3 (0.1-0.7)
History ≥ 2 out 2	6	0.05 (0.00-0.14)	0.93 (0.87-0.99)	0.17 (0.00-0.46)	0.77 (0.68-0.86)	0.7 (0.1-5.6)	1.0 (0.9-1.0)
History ≥ 1 out 2 + PVLS30	18	0.56 (0.33-0.79)	0.88 (0.81-0.96)	0.56 (0.33-0.79)	0.88 (0.81-0.96)	4.8 (2.2-10.4)	0.5 (0.3-0.8)
History ≥ 1 out 2 + LVLS30	30	0.72 (0.52-0.93)	0.75 (0.65-0.86)	0.43 (0.26-0.61)	0.91 (0.84-0.99)	2.9 (1.8-4.8)	0.4 (0.2-0.8)
History ≥ 2 out 2 + LVLS30	3	0.06 (0.00-0.16)	0.97 (0.93-1.00)	0.33 (0.00-0.87)	0.80 (0.71-0.80)	1.9 (0.2-20.0)	1.0 (0.9-1.1)
History ≥ 1 out 2 + PVLS30 + LVLS30	16	0.56 (0.33-0.79)	0.91 (0.85-0.98)	0.63 (0.39-0.86)	0.89 (0.81-0.96)	6.4 (2.7-15.2)	0.5 (0.3-0.8)

CI = confidence interval; N = prevalence of the determinant or combination; Se = sensitivity, SP = specificity, PVP = predictive value positive, PVN = predictive value negative, LR+ = positive likelihood ratio, LR- = negative likelihood ratio; PVLS30 = pain valgus stress 30^0; LVLS30 = laxity valgus stress 30^0.
"History ≥ 2 out 2 + PVLS30" and "History ≥ 2 out 2 + PVLS30 + LVLS30" not executed because n=1.

The most important isolated determinant of history taking seems to be "trauma by external force to leg". The PVP and LR+ of this determinant are higher than that for "rotational trauma". However, the patients available (n=93) for evaluating the determinant "rotational trauma" is only moderate, because 37 patients answered "I don't know" for this question. Twelve of these 37 patients had an MCL lesion. Therefore, the diagnostic value of "rotational trauma" could be over- or underestimated in detecting MCL lesions.

The present study shows also that history taking combined with physical examination increased the diagnostic value. The GP can nearly exclude MCL lesions when "laxity valgus stress $30^{o"}$ is negative or when at least one of the two of determinants of history taking is negative, which is important to avoid unnecessary diagnostic interventions and treatment. The GP can predict with a maximum of 63% chance whether there is an MCL lesion, when at least one of the two determinants from history taking is positive combined with a positive "pain valgus stress $30^{o"}$ and positive "laxity valgus stress $30^{o"}$.

Therefore, based on history taking and physical examination, the probability of an MCL lesion could be more than doubled, but it still leaves a large measure of uncertainty. Indelicato et al.[21] suggested that an MRI could confirm the diagnosis of MCL lesion, but is only necessary when the GP considered surgery; in case of great instability of the MCL and in suspicion of an MCL lesion combined with anterior cruciate injury. There is, however, great uncertainty on the effectiveness of treatment in such lesions.

Some limitations of our study have to be mentioned. In the present study only MCL lesions are considered, even though some patients may suffer from a combination of MCL lesion with other lesions, especially meniscal tears. These combinations might influence the outcome of determinants and thereby the diagnostic value. In our study 14 (40%) of the patients had a combined MCL lesion and meniscal tear (excluding degenerative tears).

We allowed a time period of up to 5 weeks between the trauma and the inclusion of the patient. One could argue that patients seen soon, within 2 weeks, would be sicker and have more pain or problems than patients seen after that; this could have influenced the results. However, most patients (119; 89%) were seen by the general practitioner within 2 weeks. Therefore, we think the long inclusion period should not have influenced the results.

All patients were examined by one physical therapist. Previous studies have shown that reproducibility is rather poor, even among experienced clinicians.[6,22,23] Although in our study the examiner was highly experienced and performed the physical examination according to a written standardized protocol, one has to take into account that in daily general practice there is more variation in the performance of physical examination by clinicians. Therefore, the predictive values of the physical examination in this study may be overestimated compared with daily practice.

We had a small study population (n=134) and we used a cut-off point of 0.15 in our univariate analysis for inclusion in the multivariate model. Some determinants nearly reached the cut-off point and might have been included with a larger study population. Therefore, the results we presented should preferably be validated in a larger study population in general practice.

A strong element of our study is the use of the MRI as reference method. Most research of traumatic knee disorders has been done in secondary care with arthroscopy as gold standard.[8-11] The advantage of using MRI as the gold standard is the absence of verification bias in contrast to an arthroscopy. Another advantage is the excellent visualizing of the MCL on MRI in contrast to arthroscopy, because the MCL is an extra-articulair ligament and frequently not seen by arthroscopy.

The Dutch Guideline “traumatic knee disorders”[24] for GPs recommend a “wait and see policy” unless there is locking of the knee or suspicion of a fracture. Only non-randomised clinical trials [21,25-28] investigating the effect of the treatment of MCL lesions are available. Three clinical trials [21,25,26] reported that surgical repair of a complete isolated MCL lesion

has the same results as a conservative treatment. For partial isolated MCL lesions, two clinical trials [27,28] reported that partial MCL lesions successfully can be treated with a conservative treatment. Conservative treatment of an MCL lesion consisted of relative rest, cold application, compression and elevation of the leg in the first 48 to 72 hours [27]. We suggest that if the GP predicts a high chance of MCL lesion, conservative treatment should take place. If the knee complaints have not decreased after several weeks of conservative treatment, an MRI and referral to secondary care should be considered. Because there is a lack of information about the treatment and prognosis of MCL lesions, randomised controlled trials about the treatment of MCL lesions with a long follow-up are recommended, especially for complete MCL lesions.

Conclusions

Based on history taking and physical examination the GP can reasonably diagnose the absence of an MCL lesion. Our study also shows that a GP can predict the existence of an MCL lesion with a maximum of 63% certainty, therefore he can not be completely certain whether there is an MCL lesion. Clinically, this may not be a problem, because the treatment of an MCL lesion initially consists of conservative treatment. If complaints persist further diagnostic testing including MRI scan may be indicated.

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CHAPTER 3

Diagnostic value of history taking and physical examination for assessing effusion of the knee in traumatic knee patients in general practice

Diagnostic value of history taking and physical examination to assess effusion of the knee in traumatic knee patients in general practice.
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Abstract

Objective: To assess the diagnostic value of history taking and physical examination for knee joint effusion in patients with a knee injury presenting in general practice. In addition, to determine the association between effusion seen on MRI and internal derangement of the knee.

Methods: Patients aged 18 to 65 years with a traumatic knee injury who consulted their general practitioner within 5 weeks after trauma filled out a questionnaire, underwent a standardized physical examination and underwent a magnetic resonance imaging (MRI) scan. Multivariate logistic regression analysis was used to determine the diagnostic value of history taking and physical examination ($p<0.15$) as assessed by sensitivity, specificity, predictive values and likelihood ratios. The relationship between effusion and internal derangement of the knee was assessed with a Chi-square test.

Results: Of the 134 participating patients, 42 had knee joint effusion seen on MRI. Multivariate analysis showed an association with knee joint effusion for the symptom "Self-noticed swelling" (history taking) and for the "Ballottement test" (physical examination). The likelihood ratio positive (LR+) was 1.5 for "Self-noticed swelling" and 1.6 for the "Ballottement test". These two combined improved the diagnostic value to an LR+ of 3.6. Effusion showed a positive association with internal derangement of the knee ($p= 0.002$); 31 of the 42 patients with knee joint effusion had internal derangement of the knee.

Conclusion: In patients with traumatic knee injury, knee joint effusion is frequently seen on MRI. The combination of self-noticed swelling and the ballottement test was of diagnostic value. Knee joint effusion was associated with internal derangement of the knee.

Introduction

Knee injury is a frequent reason to consult the general practitioner (GP). The incidence of traumatic knee injuries (excluding fractures) reported in Dutch general practice is about 5.3 per 1000 patients per year.[1] Effusion is frequently seen in traumatic knee patients and a positive correlation between effusion (on MRI) and internal derangement of the knee is reported.[2] Additionally, Kolman et al.[3] reported that symptomatic patients with no significant effusion in the lateral aspect of the suprapatellar pouch on MRI are free of internal derangement in 86% of the cases. In the Netherlands, about 25% of all patients presenting in general practice with traumatic knee injuries is referred to secondary care.[4] Therefore, in traumatic knee patients it would be useful if the GP could detect knee joint effusion by means of history taking and physical examination.

Various questions from history taking (e.g. Is your knee swollen?) and various physical examination tests are available to evaluate the presence and amount of knee joint effusion. Tests from physical examination include palpation of effusion and/or Baker cyst in the fossa poplitea,[5] the peripatellar fluctuation test (minor effusion test)[5] and the floating patella test (ballottement test).[5,6] However, the diagnostic value of history taking and physical examination is often questioned by clinicians.[7,8] Further, in routine practice it is still unclear what the diagnostic value of history taking and physical examination is, when and which test to use, and which test is most effective to evaluate effusion.

The present study aims to determine the diagnostic value of items from history taking and physical examination in detecting effusion of the knee joint as seen on MRI in traumatic knee patients in primary care. The second aim is to investigate the association between effusion seen on MRI and internal derangement of the knee in this primary care population. MRI was selected as the reference test because it is a highly accurate diagnostic tool for detecting effusion of the knee joint.[3,9]

Methods

Design

The present study was performed within the HONEUR knee cohort[10] (a prospective, observational cohort study of patients consulting the GP for all types of new knee complaints). In the present study, patients who had a traumatic knee complaint less than 5 weeks before consultation and were aged 18 to 65 years, but had no MRI contraindications (pregnancy, metal implants or a pacemaker), were asked for informed consent for an additional MRI.

Data collection

An appointment was made for the MRI and patients filled out a self-report questionnaire,[10] which they had to bring along at MRI examination. A standardized physical examination[10] was performed immediately after the MRI by a trained physical

therapist. The physical therapist was blinded for the MRI results, as was the radiologist who scored the MRI for the results of the physical examination and questionnaire. Both the patient and the GP were informed about the outcome of the MRI or physical examination; this was to avoid influencing the behaviour of the patient, or the management by the GP during follow-up.

The baseline questionnaire[10] collected data on age, gender, socio-economic status, history of previous knee injuries and/or operations, present symptoms, mechanism of injury, level of activity in work, household, study and sports, pain severity and the Lysholm knee score.[11] In the present study we used the question: did the patient notice any swelling of the knee? Answer possibilities were 'no', 'sometimes' or 'always'; we dichotomised these answers in 'no' versus 'sometimes and always'.

Physical examination[10] of both knees consisted of inspection (alignment and joint effusion[5]), palpation (temperature, collateral ligaments and joint line tenderness[5]), assessment of effusion [palpation of effusion or Baker cyst in the fossa poplitea, the peripatellar fluctuation test (minor effusion test) and the floating patella test (ballottement test)[5,6]], passive range of motion in flexion and extension,[5,6] knee stability tests (such as the valgus/varus stress test and the anterior drawer test[12]), and meniscal tests (such as the McMurray test[13]). In the present study we focused on the following tests: palpation of effusion or Baker cyst in the fossa poplitea, the peripatellar fluctuation test (minor effusion test), and the floating patella test (ballottement test).[5,6] We regarded the ballottement test as positive when a click could be heard, or when one could feel the patella floating.

MRI was scheduled 3 to 6 weeks after the initial trauma and was performed with a 1.0 Tesla (General Electric) device. Two radiologists classified the MRI scans independently from one another. In case of disagreement, the findings were discussed until consensus was reached. Detailed information about the MRI procedure is reported elsewhere.[14]

Regarding effusion, patient outcome was defined as absent, small (fluid in 1 or 2 compartments), moderate (fluid in 3 compartments) or severe (fluid in 3 compartments with bulging of the capsule and pericapsular soft tissue) knee joint effusion (accumulation of intra-articular fluid in suprapatellar, medial or lateral compartment) as seen on MRI.[14] In this study we dichotomised effusion into 'none to small' versus 'moderate to severe' effusion. We designated moderate to severe effusion as being clinically important effusion.

The study protocol was approved by the Medical Ethics committees of the Erasmus Medical Center Rotterdam and of the Medical Center Rijnmond Zuid.

Statistical analysis

Descriptive statistics were used to present the results of the MRI. Univariate logistic regression analysis (SPSS, version 11.0) was used to determine the association between

knee joint effusion and separate symptoms from history taking and signs from physical examination, expressed as odds ratios (OR). The symptoms and signs indicating a univariate association ($p<0.15$) with knee joint effusion were analysed with multivariate logistic regression analysis (Backward Wald method, entry 0.10, removal 0.20). Separate analyses were performed for history taking and physical examination. Finally, we analysed the remaining symptoms and signs ($p<0.15$) together (using the Enter method) to compose a diagnostic model for knee joint effusion.

We determined the diagnostic value of the isolated symptoms from history taking and signs from physical examination which had a significant independent relationship with knee joint effusion ($p<0.15$) by calculating the sensitivity (Se), specificity (Sp), predictive value-positive (PVP) and predictive value-negative (PVN).[15] We also determined the likelihood ratio (LR) for positive (LR+) and negative (LR-) examination.[15] In general, an LR+ of 1 to 2 or an LR- between 0.5 and 1 changes the probability of the presence or absence of knee joint effusion by only a small degree.[16] An LR+ of 2 to 10 or an LR- between 0.1 and 0.5 may be considered clinically important.[16] An LR+ greater than 10 or an LR- less than 0.1 may have substantial impact on the probability of the diagnosis. Finally, we combined symptoms and signs from the composed diagnostic model for knee joint effusion ($p<0.15$) and determined the diagnostic value of these combinations.

The relationship between effusion and internal derangement of the knee (cruciate ligament lesion and/or meniscal lesion with the exception of degenerative lesions) was assessed with a Chi-square test with a significance level of 0.05.

Results

Study population

Of the 184 eligible patients, 134 (73%) were included in the present study. No significant differences were found between the baseline characteristics of the participants and non-participants (data not shown). Table 1 presents the characteristics of the participating patients.

Of the 134 participating patients, 61 (45.5%) reported that the knee injury was caused by sport activities. Mean age of the participants was 40.2 (SD 12.2) years and 55.2% was male. Baseline mean pain severity, as measured on an 11-point numerical rating scale (0 = no pain to 10 = unbearable pain) was 4.7, and the mean Lysholm knee score (0 = worse to 100 = best) was 63.7.

Table 1 Characteristics of the participants (n=134) and diagnosis as seen on MRI

Characteristic	
Age in years, mean (± sd)	40.2 ± 12.2
Gender male, n (%)	74 (55.2)
Onset during sports activity, n (%)	61 (45.5)
Symptom side right, n (%)	70 (52.2)
Pain severity (0-10), mean (± sd)	4.7 ± 2.4
Lysholm knee function score (0-100), mean (± sd)	63.7 ± 18.9
Diagnosis as seen on MRI	
No lesion or effusion‡, n (%)	14 (10.4)
Contusion (effusion‡, with no ligament or meniscal lesion), n (%)	38 (28.4)
Clinically important effusion* , n (%)	42 (31.3)
Medial collateral ligament lesion, n (%)	35 (26.1)
Lateral collateral ligament lesion, n (%)	8 (6.0)
Anterior cruciate ligament lesion, n (%)	28 (20.9)
Posterior cruciate ligament, n (%)	6 (4.4)
Meniscal tear, n (%)	47 (35.1)

‡Effusion: small, moderate and severe effusion
*Clinically important effusion: moderate and severe effusion

MRI results

Table 1 also gives the MRI results. The average period between trauma and MRI was 38 (range 9-81) days; 70% of all patients had their MRI within 6 weeks after the initial trauma. In 14 patients (10.4%) there were no signs of effusion, ligamentous lesions or meniscal tears on the MRI, and 38 patients (28.4%) showed only effusion (small, moderate and severe) without detectable ligamentous lesions or meniscal tears (meniscal tear is defined as all meniscal tears, excluding degenerative meniscal tears).

From all these 134 traumatic knee patients, 50% had small effusion, 25% had moderate effusion and 7.4% had severe effusion. Clinically important effusion (moderate and severe effusion) detected by MRI was seen in 42 patients (31.3%). On MRI, cruciate and/or meniscal lesions were seen in 64 of all patients (47.7%). In 31 of the 42 patients (73.8%) with clinically important effusion a cruciate ligament lesion or meniscal tear was seen on MRI; a positive association [OR 5.0 (95%CI 2.2 to 11.1)] of clinically important effusion with internal derangement of the knee could be shown (p=0.002).

History taking and physical examination

Of the 134 patients, for 128 patients (95.5%) both the history taking and the physical examination were available. Completed questionnaires were available for 130 patients (97.0%); 4 questionnaires were not returned. Physical examination was performed in 132 patients (98.5%); 2 patients had plaster immobilization at the time of the MRI.

Table 2 shows the association between items from history taking and physical examination with knee joint effusion.

Table 2 Number of patients with positive test result and association of items with knee joint effusion

Variables [(reference)]	**Patients available n**	**Effusion moderate/ severe ‡ (n=42)**	**Effusion absent/ small ‡ (n=91)**	**OR**	**95% CI**
History taking					
Self-noticed swelling	128	32	40	4.8***	2.0-11.6
Physical examination					
Effusion fossa poplitea[5]	129	31	55	2.1**	0.9-5.0
Bakers cyst fossa poplitea[5]	129	5	7	1.7	0.5-5.6
Fluctuation/Minor effusion test[5]	127	6	7	2.0	0.6-6.4
Ballottement test[5,6]	131	34	44	5.1***	2.0-12.6

‡ as detected on MRI
*p < 0.15, **p < 0.10, ***p < 0.05

From history taking one symptom showed an association (p<0.15) with effusion (Table 2); this symptom ("Self-noticed swelling") resulted in a higher probability when found positive, OR 4.8 (95% CI 2.0-11.6). Three test results obtained by physical examination ("Increased temperature", "Effusion fossa poplitea" and positive "Ballottement test") showed an association (p<0.15) with effusion with an OR of 2.0 (95% CI 0.9-4.2), 2.1 (95% CI 0.9-5.0) and 5.1 (95% CI 2.0-12.6), respectively. These three signs raise the probability of effusion when found to be positive.

Table 3 shows the multivariate association of items from history taking and physical examination with effusion. After multivariate modelling "Self-noticed swelling" from history taking and the "Ballottement test" from physical examination showed an independent association (p<0.15) with the presence of effusion with an OR of 5.3 (95% CI 2.1-13.6) and 5.7 (95% CI 2.2-15.2), respectively.

Table 3 Multivariate association (and 95% confidence interval) of items with knee joint effusion

Variable from history taking or physical examination	**Effusion moderate/severe‡**
History taking	OR (95% CI)
Self-noticed swelling	5.3*** (2.1-13.6)
Physical examination	
Ballottement test	5.7*** (2.2-15.2)
Explained variance (%)	27.9

‡ As detected on MRI
*p < 0.15, **p < 0.1, ***p < 0.05

Diagnostic value of history taking and physical examination

In this study population the prevalence of effusion (prior probability) was 0.31 (42/134). Table 4 presents the sensitivity (Se), specificity (Sp), predictive value-positive (PVP), predictive value-negative (PVN), the likelihood ratio positive (LR+), and the likelihood ratio negative (LR-).

Table 4 Diagnostic values (and 95% confidence interval) of isolated symptoms and signs, and combinations of symptoms and signs, with knee joint effusion (prevalence = 0.31/n=42).

Variable	n†	SEΦ	SPΦ	PVPΦ	PVNΦ	LR+Φ	LR-Φ
Isolated symptoms and signs							
Self-noticed swelling	72	0.80 (0.68-0.92)	0.45 (0.35-0.39)	0.40 (0.29-0.51)	0.83 (0.73-0.94)	1.5 (1.1-1.9)	0.4 (0.2-0.9)
Ballottement test	78	0.83 (0.71-0.94)	0.49 (0.39-0.59)	0.43 (0.32-0.53)	0.86 (0.77-0.96)	1.6 (1.3-2.1)	0.3 (0.2-0.7)
Combination							
Self-noticed swelling + Ballottement test	42	0.67 (0.52-0.81)	0.82 (0.73-0.90)	0.62 (0.47-0.77)	0.85 (0.77-0.92)	3.6 (2.2-5.9)	0.4 (0.3-0.6)

† N = prevalence of the determinant or combination

Φ Se = sensitivity, SP = specificity, PVP = predictive value positive, PVN = predictive value negative, LR+ = positive likelihood ratio, LR- = negative likelihood ratio

The PVP of effusion increased from 0.31 to 0.40 (95% CI 0.29-0.51) for “Self-noticed swelling” and to 0.43 (95% CI 0.32-0.53) for the “Ballottement test”. The PVP increased to 0.62 (95% CI 0.47-0.77) when “Self-noticed swelling” from history taking and the “Ballottement test” from physical examination were both present.

The probability of the absence of effusion increased from 0.69 to 0.83 (95% CI 0.73-0.94) if “Self-noticed swelling” was absent and to 0.86 (95% CI 0.77-0.96) if the “Ballottement test” was negative. Absence of “Self-noticed swelling” together with a negative “Ballottement test” did not further increase the PVN.

The isolated symptom “Self-noticed swelling” and the “Ballottement test” showed an LR+ of 1.5 (95% CI 1.1-1.9) and 1.6 (95% CI 1.3-2.1), respectively; altering the probability of effusion by only a small degree. The LR+ increased to a clinically important value of 3.6 (95% CI 2.2-5.9) when the symptom “Self-noticed swelling” from history taking and the “Ballottement test” from physical examination were both present.

The symptom “Self-noticed swelling” and the “Ballottement test” had a clinically important LR-of 0.4 (95% CI 0.2-0.9) and 0.3 (95% CI 0.2-0.7), respectively. Absence of “Self-noticed swelling” together with a negative “Ballottement test” did not further decrease the LR-.

Discussion

The present study is the first to investigate the diagnostic value of history taking and physical examination for knee effusion seen on MRI, among patients in a primary care setting. The study population consisted of a relevant selection of traumatic knee patients, ranging from those with no abnormalities on MRI to patients with a severe effusion combined with meniscal tear and/or ligamentous lesion of the knee. Clinically important effusion was seen in 31.3% of these 134 patients.

In the present study the isolated symptom “Self-noticed swelling” from history taking and the “Ballottement test” from physical examination showed diagnostic value in detecting knee joint effusion. Therefore, both this particular symptom and test are diagnostic tools for the GP in predicting knee joint effusion. Moreover, the absence of this symptom and sign are valuable diagnostic tools to exclude knee joint effusion because they show a high PVN and a low LR-. Combining the symptom from history taking and the sign from physical examination resulted in a more clinically important PVP and LR+. In this case GPs can predict with a 62% chance whether there is knee joint effusion, but still cannot be certain about the actual presence of effusion. Further, GPs can reasonably exclude (with an 83-86% chance) knee joint effusion when “Self-noticed swelling” and/or the “Ballottement test” is negative, which could help to avoid unnecessary diagnostic interventions. However, Boks et al.[14] showed that in case of absence of effusion some patients still have internal derangement of the knee.

To our knowledge, the only other study addressing the detection of knee joint effusion focused on the accuracy of sonographic examination. Wang et al.[17] reported a sensitivity, specificity, PVP and PVN of sonographic examination (compared with MRI) for detecting knee effusion of 79.1%, 50%, 86.3% and 37.5%, respectively; they concluded that sonographic examination can accurately detect effusion of the knee. Compared with Wang et al., our study showed equal sensitivity and specificity for “Self-noticed swelling” and the “Ballottement test”. Combining “Self-noticed swelling” and the “Ballottement test” in our study showed a lower sensitivity, but a higher specificity. Further, our study showed lower PVPs, but much higher PVNs for “Self-noticed swelling”, the “Ballottement test”, and the combination of both.

In the present study during history taking we asked the patient whether they had noticed a swelling of the knee; the answer to this question could be ‘no’, ‘sometimes’, or ‘always’. For the statistical analysis we dichotomised the answers into ‘no’ versus ‘sometimes and always’. Alternatively, dichotomising the answer into ‘no and sometimes’ versus ‘always’ did not improve the results.

Further, from physical examination only the “Ballottement test” showed an association with knee joint effusion. Miller et al.[18] found a significant association between Baker cyst and effusion, whereas we did not. An explanation for this difference could be that we had

only 12 patients with a Baker cyst and (in contrast to Miller et al.) we palpated for a Baker cyst instead of using MRI, whereby a small Baker cyst could be missed.

The literature[5,6] assumes that one can evaluate the presence of effusion with the minor effusion test and the ballottement test. However, our study shows that, of these two tests, only the ballottement test has an association with clinically important effusion. Although one might argue that the minor effusion test may be better in detecting minor effusion, we found no association between the minor effusion test and small or minor effusion.

Discussion remains about interpretation of the ballottement test. Is the test positive when you hear a click[5,6] or is it positive when you feel a floating patella?[5] In the present study we considered both a click and a floating patella to be a positive test result. In most of our patients a positive ballottement test concerned a floating patella (n=74) and only a few concerned a click (n=4). Interpreting only floating patella as a positive test result yielded the same OR of 5.1 for effusion seen on MRI as interpreting both a click and floating patella as positive test result. Interpreting only a click as a positive test result was not significant, probably due to the small number of available patients.

For the analyses we dichotomised effusion seen on MRI into 'none to small' and 'moderate to severe' effusion, because Boks et al.[14] reported that a small effusion was very common in asymptomatic knees and might not be clinically meaningful. Kolman et al. [3] also suggested that a small effusion (10 mm or less in the lateral suprapatellar pouch seen on MRI) was not clinically meaningful, but rather a physiological sign.

The period between trauma and MRI was 38 (range 9-81) days. In this period, natural healing of lesions (also effusion) might have occurred, and some effusion might have changed from moderate or severe to small. Because history taking was assessed earlier than physical examination and MRI, the relationship between history taking and effusion on MRI could be underestimated.

We had a small study population (n=134) and used a cut-off point of 0.15 in the univariate analysis for inclusion in the multivariate model. However, some symptoms and signs almost reached the cut-off point and might have been included had we tested a larger study population. Therefore, the results presented here should be validated in a larger study population in general practice.

The Dutch Clinical Guideline 'Traumatic knee disorders'[19] for GPs reported that in case of effusion within a few hours after the trauma, in the presence of a positive ballottement test or locking of the knee there is suspicion of internal derangement of the knee; they recommend a "wait and see policy" unless there is locking of the knee or suspicion of a fracture. Some data are available concerning the clinical value of effusion. Duncan et al.[2] describe a positive correlation between effusion and internal derangement of the knee. In addition, Kolman et al.[3] reported that symptomatic patients with no significant effusion in the lateral aspect of the suprapatellar pouch on MRI are free of internal derangement in

86% of the cases. Our study confirmed also a positive association between clinically important effusion and internal derangement of the knee. Additionally, and more important for GPs, is the question whether there is also an association between history taking/physical examination (focused on effusion) and internal derangement of the knee. We found a small relationship between positive "Self-noticed swelling" together with a positive "Ballottement test" and internal derangement of the knee (univariate logistic regression, OR 1.9, p=0.094), predicting a 59% chance of internal derangement of the knee (data not shown). The presence of only the symptom "Self-noticed swelling" showed almost the same relationship with internal derangement of the knee, but the presence of only a positive "Ballottement test" did not show this relationship (data not shown). Based on the present results we recommend the following: if GPs suspect effusion of the knee, because the patient has noticed swelling of the knee and the ballottement test is positive, they should consider the possibility of internal derangement of the knee. A "wait and see policy" is recommended unless there is locking of the knee or suspicion of a fracture. However, because of the association between effusion and internal derangement of the knee, GPs might use the predicted chance of effusion as a selection criterion for MRI and/or referral to secondary care.

Conclusions

Our study indicates that GPs can reasonably exclude knee joint effusion in patients with a knee trauma based on the absence of "Self-noticed swelling" and/or a negative "Ballottement test". This could argue against further diagnostic interventions, but the GP has to bear in mind that some patients with knee joint effusion could be missed. The data also show that GPs can predict knee joint effusion with a maximum of 62% certainty, based on the presence of "Self-noticed swelling" together with a positive "Ballottement test". In addition, our study results support that knee joint effusion in primary care patients is associated with internal derangement of the knee.

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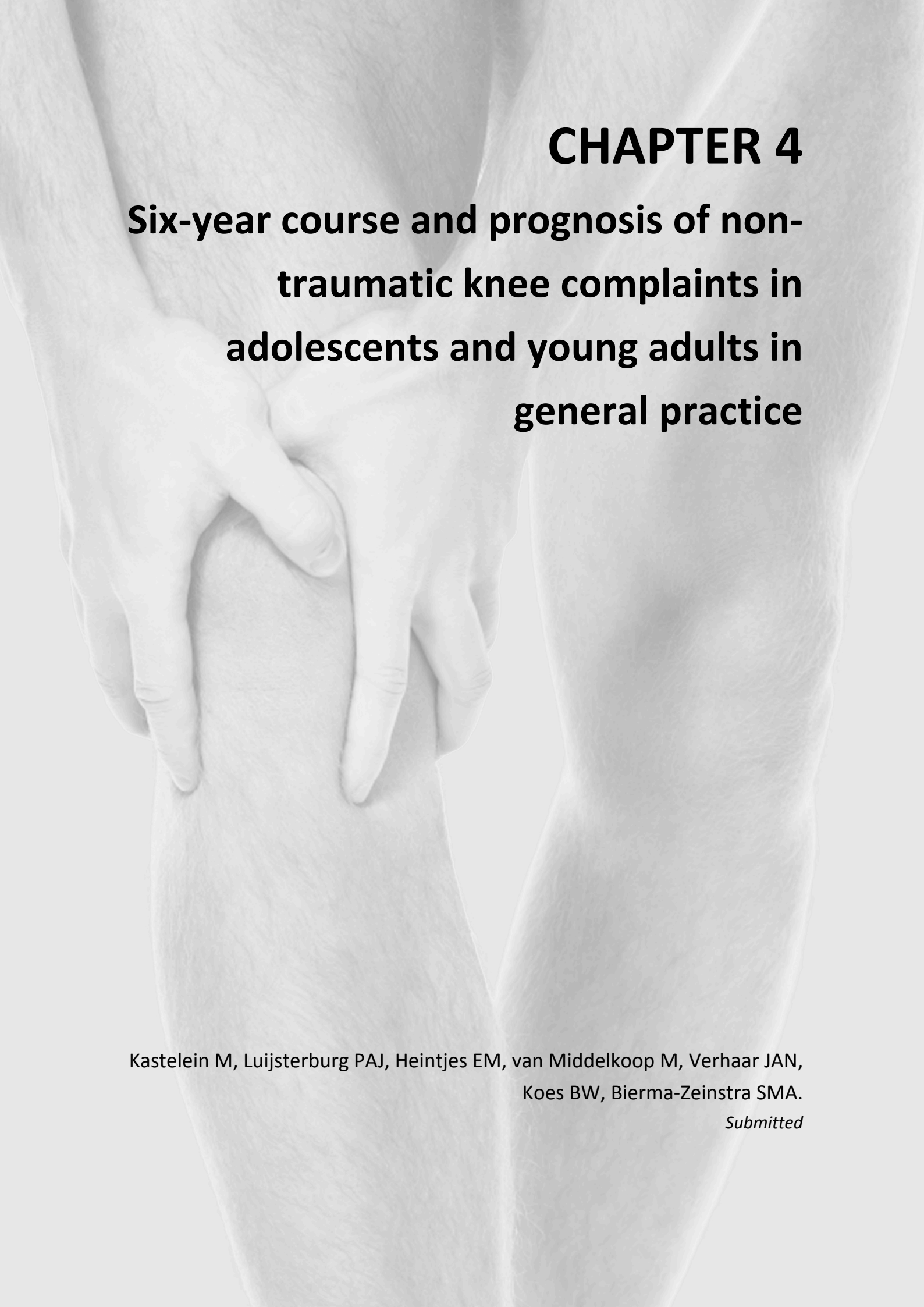

CHAPTER 4

Six-year course and prognosis of non-traumatic knee complaints in adolescents and young adults in general practice

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Submitted

Abstract

Objective: To assess the 1 and 6-year course of non-traumatic knee complaints in adolescents and young adults presenting in general practice, and to identify prognostic factors for persistent knee complaints.

Methods: Adolescents and young adults (12-35 years; n=191) with non-traumatic knee complaints were included by their general practitioner and were followed for 6 years. Between baseline and 6-year follow-up patients filled out questionnaires on demographics, knee symptoms and perceived recovery. A standardized physical examination was carried out at baseline and at 1-year follow-up. Descriptive statistics were used to describe the course of the knee complaints. Multivariable logistic regression analysis was used to identify prognostic factors for persistent knee complaints at 1 and 6-year follow-up and area under the receiver operating curve was calculated (AUC).

Results: Persistent knee complaints were reported by 47% of the patients at 1-year follow-up and by 27% of the available patients at 6-year follow-up. Patients with patellofemoral pain syndrome had the worse prognosis, with 40% reporting persistent knee complaints at 6-year follow-up. There was a positive relationship, OR 4.8, 95% CI 1.8-12.8, between having persistent knee complaints at 1-year follow-up and at 6-year follow-up. Prognostic factors assessed at baseline associated with persistent knee complaints at 1-year follow-up were body mass index (BMI) >25, low/middle education level, poor general health, bilateral complaints, self-reported swollen knee, locking of the knee, painful patellar ligament, and absence of floating patella, AUC 0.75. At 6-year follow-up low/middle education level, self-reported swollen knee, painful patellar edges and absence of floating patella were associated with persistent knee complaints, AUC 0.76.

Conclusion: The prognosis of non-traumatic knee complaints in adolescents and young adults in general practice is not as good as previously assumed. Various prognostic factors collected at baseline were associated with persistent knee complaints at follow-up. Further research focusing on patellofemoral pain syndrome is recommended.

Introduction

General practitioners (GPs) are frequently consulted by patients with non-traumatic knee complaints. Non-traumatic knee complaints in adolescents and young adults account for 20% of all non-traumatic knee complaints in general practice and include patellofemoral pain syndrome, jumper's knee (knee extensor tendinitis), Osgood-Schlatter disease, bursitis, iliotibial tract friction syndrome and popliteal cysts.[1] The incidence of these types of complaints in adolescents and young adults reported in general practice is about 19 per 1000 patients per year.[1] The prognosis of non-traumatic knee complaints in general practice is assumed to be good, but to our knowledge no studies have examined the short and long-term follow-up and prognosis of these complaints in adolescents and young adults in general practice.[2] However, such information is important for GPs with regard to treatment and referral, and to provide more valid information for these patients.

Therefore, this prospective cohort study was performed in general practice to assess the 1 and 6-year course of non-traumatic knee complaints in adolescents and young adults, and to identify prognostic factors for persistent knee complaints at 1 and 6-year follow-up.

Methods

Design

The present study took place within the research network HONEUR (40 GPs) established by the department of General Practice of Erasmus MC University Medical Centre. It is part of a prospective, observational cohort study (n=1068) in which consecutive patients visiting their GP with a new episode of knee complaints were enrolled and initially followed for 1 year.[3] Due to the high percentage of persistent knee complaints at 1-year follow up, the follow-up period was extended to 6 years.

At baseline, new knee complaints were defined as episodes of complaints presented to the GP for the first time. Recurrent symptoms for which the GP was not consulted within the past 3 months were also considered to be new complaints. Traumatic knee complaints were defined as knee complaints caused by a sudden impact or wrong movement within 1 year before consulting the GP. All other knee complaints were considered to be non-traumatic knee complaints.

Patients were eligible for the present study if they were aged 12 through 35 years and had consulted their GP for non-traumatic knee complaints. Exclusion criteria were knee symptoms that required urgent medical attention (e.g. fractures, infection), patients with malignancies, neurologic disorders or musculoskeletal diseases (e.g. Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), as well as patients incapable of understanding the ramifications of study participation. The study protocol was approved by the Medical Ethics committee of the Erasmus MC University Medical Centre.

Data collection

Patients filled out a self-report questionnaire at baseline, at 3, 6 and 9 months follow-up, and at 1 and 6-year follow-up. The baseline and follow-up questionnaire collected data on age, gender, socioeconomic status, previous knee history of previous injuries or operations, present symptoms, level of daily activities and sports, hindrance and sick leave from daily activities, health-related quality of life, and treatments received. Additionally, the 1 and 6-year follow-up questionnaire collected data on experienced recovery or worsening of the knee complaints (i.e. outcome). In case of non-response at 6-year follow-up, we asked the patient by telephone to their experienced recovery of the knee complaints at 6-year follow-up.

Functional disability and pain were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [4,5] (assessed at baseline to 1-year follow-up), the Knee Injury Osteoarthritis Outcome Score (KOOS) [6] (assessed at 6-year follow-up), the Medical Outcomes Study Short Form 36 Health Survey (SF-36) [7,8], the Knee Society Score (KSS) function questions [9], the Lysholm Knee Scoring Scale [5,10], the Tampa Scale for Kinesophobia [11] (only assessed at baseline) and the COOP/WONCA charts [12,13] (only assessed at baseline to 1-year follow-up). The outcome measurement, experienced recovery of knee complaints, was measured on a 7-point Likert scale. For all scores, except the Lysholm and SF-36, lower scores represent better function/outcome.

A standardized physical examination was carried out by a trained physiotherapist at baseline and at 1-year follow-up. Physical examination of the knee consisted of inspection (alignment and joint effusion), palpation (temperature, collateral ligaments, and joint line tenderness), assessment of effusion, passive range of motion in flexion and extension, meniscal tests and knee stability tests. [14,15]

GPs were asked to note the working diagnosis according to the International Classification of Primary Care (ICPC) in the patient's computerized medical file at first consultation.[16]

Statistical analysis

Descriptive statistics were used to describe patient characteristics, complaint characteristics, experienced recovery and working diagnosis of the GP.

Univariable logistic regression analysis was used to determine which baseline variables from history taking and physical examination were associated with persistent knee complaints, expressed as odds ratios (OR). The baseline variables chosen for the univariable analysis were based on literature [17] and clinical relevance. The variables were divided in three domains: patient characteristics, complaint characteristics and physical examination findings. To enable easy interpretation of prognostic factors in a clinical setting we chose to dichotomize most variables. Imputation of missing data was carried out by multiple imputation, creating a total of 5 imputed databases [18-20]. The variables showing an univariable association with persistent knee complaints in at least 3 out of 5

imputed databases ($p \leq 0.20$), were analyzed in a multivariable logistic regression model (backward LR method, entry 0.10, removal 0.15). If a variable was selected in at least 3 out of 5 imputed databases in the multivariable analysis it was included in the final model (Enter method) and the area under the receiver operating curve (AUC) was calculated. First, separate models for patient characteristics, complaint characteristics and physical examination findings were built. Subsequently, we combined the remaining variables of each domain to build a model of patient and complaint characteristics, and a model of patient and complaint characteristics together with physical examination findings, to evaluate the addictive predictive value of the different domains. All models were adjusted for gender and age. Separate analyses were performed for the outcome measurement perceived recovery at 1 and 6-year follow-up.

The outcome measurement self-reported perceived recovery was dichotomized into clinical recovery of knee complaints ("completely recovered" and "much improved") versus persistent knee complaints ("slightly improved", "no change", "slightly worsened", "much worsened" and "worse than ever").

The analyses were performed using SPSS version 17.02 (SPSS Inc., Chicago, Ill).

Results

Study population

A total of 191 patients were included; Table 1 presents their baseline characteristics. Mean age of the patients was 24.1 (SD 7.7) years, and 52.4% was male. ICPC codes from the GPs' computerized medical files yielded 100 patients (52.4%) with unspecified knee complaints (L15), 74 patients (38.7%) with patellofemoral pain syndrome (L97.1, currently L99.7), and 8 patients (4.2%) with Osgood-Schlatter disease (L94.2). The GPs diagnosed 9 patients (4.7%) with knee distortions or acute traumatic knee injuries (L78 or L96). Since these latter patients indicated that overuse (rather than trauma) caused the injuries, and no signs of recent trauma were evident during physical examination, they were included in the non-traumatic subpopulation of the cohort, and further considered as unspecified knee complaints. In total, 122 patients (66.3%) reported that the duration of their knee complaints was less than 3 months at time of consultation, 83 patients (45.1%) had bilateral knee complaints, and 97 patients (53.0%) reported to have recurrent knee complaints. At baseline, the mean knee pain severity, measured on a 0-10 point numerical rating scale (NRS) was 4.0 (SD 2.2), the mean Lysholm knee score was 70.9 (SD 18.9) and the mean WOMAC index was 20.3 (SD 17.1).

At 1-year follow-up, 165 patients (86.4%) were still available for the study. At 6-year follow-up, 83 patients (43.5%) completed the questionnaire and 23 patients (12.0%) reported their experienced recovery of their knee complaints by telephone, resulting in 106 patients (55.5%) still available for the study. The patients available at 1 and 6-year

follow-up showed no significant differences compared with the total study population at baseline regarding age, gender, working diagnosis, knee complaints, pain score (NRS), Lysholm score and WOMAC index (Table 1). The patients available at 6-year follow-up also showed no significant difference compared with those available at 1-year follow-up regarding their perceived recovery at 1-year follow-up (OR 1.04, 95% CI 0.83-1.30). Reasons for no longer participating were: lack of time and/or lack of interest (n=37; 43.5%), being inaccessible because of changed address and/or telephone number (n=38; 44.7%) and for 10 patients (11.8%) no reason was available.

Table 1 Baseline characteristics of the total group of patients and the patients available at 1 and 6-year follow-up.

Baseline characteristic	**Total group (n=191)**	**Available at 1-year follow-up (n=165)**	**Available at 6-year follow-up (n=106)**
General			
Age in years, mean ± SD	24.1 ± 7.7	24.2 ± 7.7	24.2 ± 7.6
Male, n (%)	100 (52.4)	84 (50.9)	56 (52.8)
Working diagnosis general practitioner			
Unspecified (L15), n (%)	100 (52.4)	86 (52.1)	54 (50.9)
Acute distortion (L78), n (%)	4 (2.1)	2 (1.2)	1 (0.9)
Osgood Schlatter (L94.2), n (%)	8 (4.2)	8 (4.8)	5 (4.7)
Acute meniscus/ligament rupture (L96), n (%)	5 (2.6)	4 (2.4)	1 (0.9)
Patellofemoral syndrome (L97.1), n (%)	74 (38.7)	65 (39.4)	45 (42.5)
Knee complaints			
Duration at consultation < 3 months, n (%)	122 (66.3)	104 (64.6)	62 (60.8)
Bilateral, n (%)	83 (45.1)	71 (44.1)	49 (48.0)
Recurrent, n (%)	98 (53.0)	86 (53.8)	51 (50.0)
Measures of severity			
Knee pain NRS (0-10), mean ± SD	4.0 ± 2.2	4.0 ± 2.2	3.9 ± 2.2
Lysholm knee function score (0-100), mean ± SD	70.9 ± 19.8	71.9 ± 18.1	71.8 ± 19.8
WOMAC index (0-100), mean ± SD	20.3 ± 17.1	19.7 ± 16.3	19.0 ± 17.0

Course and prognosis

Figure 1 presents the 6-year course of the total group regarding mean knee pain severity (measured on a NRS), mean Lysholm knee score and mean WOMAC index. The mean pain score, mean Lysholm knee score and mean WOMAC index showed the largest improvement in the first 3 months following consultation with the GP. Improvement in pain level in the first 3 months proved to discriminate between patients with and without persistent knee complaints at 6-year follow-up.

Table 2 shows the number of patients with persistent knee complaints at 1 and 6-year follow-up for the total group and also specified according to the working diagnoses; Table 3 presents the characteristics of these patients.

Figure 1 Course of knee complaints (mean scores) of the total group.

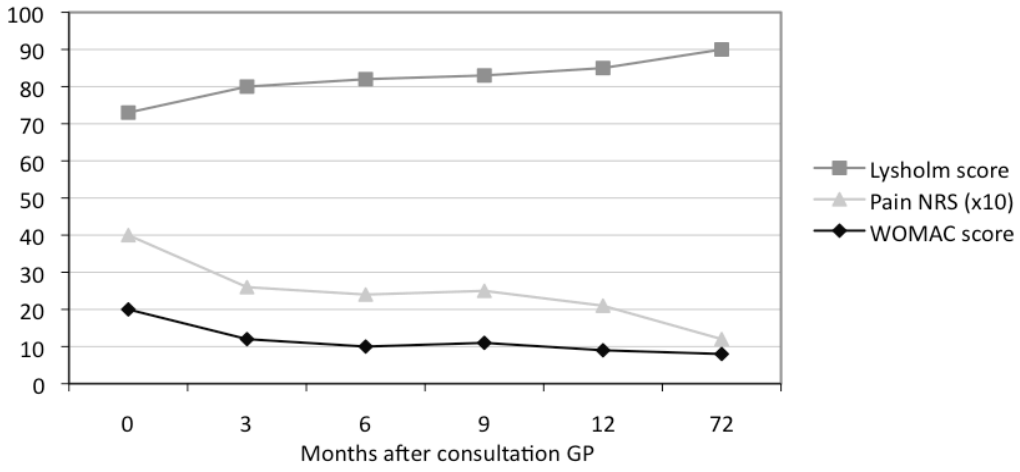

Table 2 Number of patients with persistent knee complaints at 1 and 6-year follow-up according to diagnosis.

Diagnosis	**1 year**	**6 years**
Total group (n=165 and 106), n (%)	78 (47.3)	29 (27.4)
Specified according to working diagnosis of the general practitioner		
Unspecified (L15) (n=91 and 56), n (%)	37 (40.7)	10 (17.9)
Osgood Schlatter (L94.2) (n=8 and 5), n (%)	4 (50.0)	1 (20.0)
Patellofemoral syndrome (L97.1) (n=65 and 45), n (%)	37 (56.9)	18 (40.0)

Table 3 Characteristics of the patients with persistent knee complaints at 1 and 6-year follow-up.

Characteristic	**1 year (n=68)**	**6 years (n=26)**
Knee complaints		
Bilateral, n (%)	42 (61.8)	17 (65.4)
Kind of knee complaints compared with baseline		
Other complaints, n (%)	-	4 (13.8)
Same complaints, n (%)	-	18 (62.1)
Same complaints and other complaints, n (%)	-	4 (13.8)
Measures of severity		
Pain complaints (KSS) (0-7), mean ± SD	4.0 ± 1.5	4.0 ± 1.6
Knee pain (0-10), mean ± SD	3.5 ± 2.2	2.7 ± 1.7
Lysholm knee function score (0-100), mean ± SD	74.1 ± 16.3	79.3 ± 13.8
WOMAC index (0-100), mean ± SD	15.3 ± 16.0	18.3 ± 14.3
WOMAC pain (0-100), mean ± SD	17.5 ± 16.9	24.6 ± 18.8
WOMAC stiffness (0-100), mean ± SD	18.0 ± 21.1	31.2 ± 24.6
WOMAC physical function (0-100), mean ± SD	14.4 ± 16.5	15.4 ± 14.2

Of the 165 patients available at 1-year follow-up, 78 patients (47.2%) reported persistent knee complaints. In relation to the working diagnosis, 37 of 91 patients (40.7%) with unspecified knee complaints, 4 of 8 patients (50.0%) with Osgood-Schlatter disease and 37 of 65 patients (56.9%) with patellofemoral pain syndrome reported persistent knee

complaints. At 1-year follow-up, 42 patients (61.8%) with persistent knee complaints reported bilateral complaints. Their mean knee pain severity at that time, measured with a NRS, was 3.5 (SD 2.2), their mean Lysholm knee score was 74.1 (SD 16.3) and their mean WOMAC index was 15.3 (SD 16.0), with an almost equal distribution on the different domains of the WOMAC index (pain, stiffness and physical function).

At 6-year follow-up, of the 106 patients (55.5%) available, 29 patients (27.4%) reported persistent knee complaints. With regard to the working diagnosis, 10 of 56 patients (17.9%) with unspecified knee complaints, 1 of 5 patients (20.0%) with Osgood-Schlatter disease, and 18 of 45 patients (40.0%) with patellofemoral pain syndrome reported persistent knee complaints. There was a positive relationship between having persistent knee complaints at 1-year follow-up and having persistent knee complaints at 6-year follow-up (OR 4.78, 95% CI 1.79-12.75). At 6-year follow-up, 17 patients (65.4%) with persistent knee complaints reported that their knee complaints were bilateral. In addition, compared with baseline the kind of knee complaints had changed to another kind of complaint in the same knee in 4 patients (13.8%), 18 patients (62.1%) had exactly the same knee complaint, and 4 patients (13.8) had the same complaint combined with other kinds of knee complaints. Their mean knee pain severity, measured with a NRS, was 2.7 (SD 1.7), the mean Lysholm knee score was 79.3 (SD 13.8) and the mean WOMAC index was 18.3 (SD 14.3); there were some higher scores on the pain and stiffness domains and some lower score on the physical function domain compared with the mean WOMAC index.

Prognostic factors

Table 4 presents the univariable associations between baseline characteristics and persistent knee symptoms at 1 and 6-year follow-up.

At 1-year follow-up, the patient characteristics BMI >25, low/middle education level, non-skeletal co morbidity and poor general health at baseline were associated with persistent knee complaints. Of the symptom characteristics lasting >3 months, bilateral complaints, self-reported warm knee, self-reported swollen knee, locking of the knee, instability of the knee, history of knee operation and nuisance in work/study/household were associated with persistent knee complaints. From the physical examination prominent tibial tuberosity, painful tibial tuberosity, painful patellar ligament, painful patellar edges, absence of floating patella and painful active flexion were associated with persistent knee complaints.

At 6-year follow-up low/middle education level was associated with persistent knee complaints. Of the symptom characteristics, self-reported swollen knee and locking of the knee were associated with persistent knee complaints. From physical examination prominent painful patellar edges and absence of floating patella were associated with persistent knee complaints.

Table 4 Univariable association between baseline characteristics and persistent knee symptoms at 1 and 6-year follow-up.

Variable	**Univariate 1 year (n=165)**			**Univariate 6 year (n=106)**		
	Pooled OR	Pooled 95% CI	Pooled Sig	Pooled OR	Pooled 95% CI	Pooled Sig
Patient characteristics						
Age	1.01	0.97-1.05	0.71	1.02	0.97-1.08	0.44
Gender	0.73	0.39-1.34	0.31	1.29	0.55-3.02	0.57
Body mass index > 25	1.80	0.93-3.47	0.08*	1.10	0.45-2.69	0.83
Low/middle education level	2.37	1.26-4.47	0.01*	1.92	0.79-4.71	0.15*
Co morbidity skeletal system	0.84	0.42-1.70	0.63	1.59	0.61-4.15	0.34
Non-skeletal co morbidity	1.73	0.75-3.98	0.20*	0.91	0.31-2.70	0.87
Kinesiophobia (Tampa>37)	0.98	0.52-1.85	0.98	1.52	0.62-3.74	0.36
Poor mental health (COOP-WONCA)	0.95	0.41-2.20	0.90	1.75	0.57-5.34	0.33
Poor general health (COOP-WONCA)	2.29	0.86-6.06	0.10*	1.97	0.63-6.14	0.24
Sport	0.75	0.36-1.55	0.43	0.82	0.29-2.36	0.71
Symptom characteristics						
Duration > 3 months	1.61	0.85-3.08	0.15*	1.32	0.55-3.16	0.54
Recurrent complaints	0.95	0.51-1.78	0.88	1.12	0.46-2.74	0.80
Bilateral complaints	2.03	1.07-3.82	0.03*	1.51	0.62-3.69	0.37
Pain (11-point scale)	0.94	0.82-1.08	0.38	1.03	0.84-1.26	0.77
Self-report warm knee	1.60	0.81-3.16	0.18*	0.93	0.36-2.40	0.88
Self-report swollen knee	1.85	0.93-3.65	0.08*	2.32	0.91-5.91	0.08*
Self-report crepitus knee	0.83	0.36-1.91	0.66	1.12	0.36-3.52	0.85
Locking of the knee (Lysholm)	2.22	0.93-5.26	0.07*	2.20	0.77-6.28	0.14*
Instability of the knee (Lysholm)	1.55	0.81-2.96	0.19*	1.11	0.44-2.82	0.83
History of traumatic knee complaints	1.38	0.62-3.10	0.43	0.91	0.30-2.82	0.87
History of non-traumatic knee complaints	1.17	0.61-2.27	0.63	1.29	0.52-3.23	0.58
History of knee operation	3.23	0.81-12.7	0.09*	1.13	0.22-5.84	0.88
Use of medication for knee	0.81	0.33-1.99	0.64	0.68	0.20-2.35	0.54
Nuisance in work/study/household	1.62	0.86-3.07	0.14*	1.26	0.53-3.03	0.60
Limitation during daily function (WOMAC > 20)	1.07	0.58-2.00	0.83	1.17	0.49-2.77	0.73
Pain during daily function (WOMAC > 20)	1.27	0.67-2.39	0.46	1.14	0.47-2.77	0.78
Stiffness knee (WOMAC > 20)	1.10	0.59-2.03	0.76	1.63	0.68-3.86	0.27
Physical examination						
Valgus	1.45	0.72-2.95	0.30	0.87	0.32-2.38	0.79
Varus	1.30	0.64-2.63	0.47	1.08	0.40-2.92	0.88
Prominent tibial tuberosity	2.17	0.54-8.70	0.27*	1.23	0.21-7.18	0.82
Pain tibial tuberosity	1.96	0.61-6.30	0.26*	1.23	0.29-5.27	0.78
Pain patellar ligament	2.21	1.01-4.87	0.05*	1.57	0.55-4.42	0.40
Pain patellar edges	1.96	1.03-3.73	0.04*	3.07	1.18-7.98	0.02*
Floating patella	0.50	0.24-1.02	0.06*	0.16	0.04-0.74	0.02*
Pain active flexion	1.92	0.83-4.44	0.13*	1.20	0.40-3.60	0.74
Pain passive flexion	1.41	0.69-2.87	0.35	1.35	0.52-3.52	0.54
Pain active extension	1.25	0.55-2.85	0.60	0.76	0.20-2.91	0.69
Pain passive extension	1.11	0.57-2.19	0.76	1.09	0.41-2.96	0.86

* selected in ≥ 3 out 5 imputed databases ($p \leq 0.20$)

Table 5 presents the multivariable associations between baseline characteristics and persistent knee complaints at 1-year follow-up. The patient characteristics BMI >25, low/middle education level and poor general health showed an independent association with persistent knee complaints at 1-year follow-up, with an AUC of 0.67. From the symptom characteristics bilateral complaints, self-reported swollen knee and locking of the knee were independently associated with persistent knee complaints, with an AUC of 0.65. From the physical examination a painful patellar ligament and absence of floating patella were independently associated with persistent knee complaints, with an AUC of 0.60. Adding the symptom characteristics to the patient characteristics the AUC increased with 0.06 to a value of 0.73. Poor general health did not remain in the model (p>0.15). Adding items from physical examination increased the AUC with 0.02 to a value of 0.75. Poor general health was dropped from the model (p>0.15).

Table 5 Multivariable associations between baseline characteristics and persistent knee complaints at 1-year follow-up.

Model	**Multivariable 1 year (n=165)**			
	Pooled OR	**Pooled 95% CI**	**Pooled p-value**	**AUC**
Patient characteristics				0.67
Body mass index > 25	1.79	0.87-3.68	0.12	
Low/middle education level	2.49	1.25-4.96	0.01	
Poor general health (COOP-WONCA)	2.58	0.91-7.32	0.08	
Symptom characteristics				0.65
Bilateral complaints	2.23	1.13-4.39	0.02	
Self-report swollen knee	1.96	0.96-4.00	0.06	
Locking of the knee (Lysholm)	2.21	0.89-5.45	0.09	
Physical examination				0.60
Painful patellar ligament	2.20	0.99-4.89	0.05	
Floating patella	0.50	0.24-1.06	0.07	
Patient characteristics and symptom characteristics				0.73
Body mass index > 25	2.12	0.97-4.65	0.06	
Low/middle education level	2.58	1.26-5.26	0.01	
Bilateral complaints	3.00	1.40-6.45	0.01	
Self report swollen knee	1.75	0.80-3.84	0.15	
Locking of the knee (Lysholm)	3.18	1.19-8.44	0.02	
Patient characteristics, symptom characteristics and physical examination				0.75
Body mass index > 25	2.27	1.01-5.08	0.05	
Low/middle education level	2.71	1.30-5.64	0.01	
Bilateral complaints	2.65	1.22-5.76	0.01	
Self-report swollen knee	1.83	0.83-4.04	0.14	
Locking of the knee (Lysholm)	2.73	1.01-7.42	0.05	
Painful patellar ligament	2.17	0.85-5.51	0.10	
Floating patella	0.52	0.22-1.21	0.13	

Table 6 presents the multivariable associations between baseline characteristics and persistent knee complaints at 6-year follow-up. Low/middle education level showed an independent association with persistent knee complaints at 6-year follow-up, with an AUC of 0.61. Of the symptom characteristics only self-reported swollen knee was independently associated with persistent knee complaints, with an AUC of 0.60. From physical examination a painful patellar edges and absence of floating patella were independently associated with persistent knee complaints, with an AUC of 0.70. Adding the symptom characteristic to the patient characteristics increased the AUC with 0.09 to a value of 0.70. Both variables remained in the model ($p<0.15$). Adding items from physical examination increased the AUC with 0.06 to a value of 0.76. Low/middle education level did not remain in the model ($p>0.15$).

Table 6 Multivariable associations between baseline characteristics and persistent knee complaints at 6-year follow-up.

Model	**Multivariable 6 year (n=106)**			
	Pooled OR	**Pooled 95% CI**	**Pooled p-value**	**AUC**
Patient characteristics				0.61
Low/middle education level	1.94	0.78-4.80	0.15	
Symptom characteristics				0.60
Self-report swollen knee	2.32	0.91-5.91	0.08	
Physical examination				0.70
Pain patellar edges	2.56	0.96-6.84	0.06	
Floating patella	0.20	0.04-0.92	0.04	
Patient characteristics and symptom characteristics				0.65
Low/middle education level	1.99	0.78-5.10	0.15	
Self -report swollen knee	2.45	0.93-6.47	0.07	
Patient characteristics, symptom characteristics and physical examination				0.76
Self-report swollen knee	2.82	1.01-7.87	0.05	
Pain patellar edges	2.66	0.92-7.73	0.07	
Floating patella	0.15	0.03-0.73	0.02	

Discussion

The present study investigated the 1 and 6-year course and prognostic factors of non-traumatic knee complaints in adolescents and young adults in general practice.

At 1-year follow-up a surprisingly high percentage of patients (i.e. 47%) reported persistent knee complaints, with an even higher percentage of persistent knee complaint for patients with Osgood-Schlatter (50%) and patellofemoral pain syndrome (57%) compared to patients with unspecified knee complaints (41%). At 6-year follow-up, 27% of the patients still reported persistent knee complaints, with a much higher percentage of persistent knee complaints for patients with patellofemoral pain syndrome (40%) than

for patients with Osgood-Schlatter (20%) and unspecified knee complaints (18%). Having persistent knee complaints at 1-year follow-up showed a positive association with having persistent knee complaints at 6-year follow-up. Because of the relatively high percentage of persistent knee complaints after this long-term follow-up, the assumed 'good' prognosis for non-traumatic knee complaints in adolescents and young adults in general practice, as mentioned in the Dutch Guideline Non-traumatic knee complaints in adolescents and young adults in general practice needs to be reconsidered.[2] The prognosis mentioned in this Dutch Guideline was based on consensus, due to the lack of research in this field. In the present study, the finding that patients with patellofemoral pain syndrome had the worst prognosis is in accordance with the (few) reports available from secondary care.[21-26]

Prognostic factors independently associated with persistent knee complaints at 1-year follow-up were the patient characteristics BMI >25, low/middle education level and poor general health, the symptom characteristics bilateral complaints, self-reported swollen knee and locking of the knee, and from physical examination a painful patellar ligament and absence of floating patella. At 6-year follow-up, low/middle education, self-reported swollen knee, and painful patellar edges and absence of floating patella were independently associated. Based on the different prognosis pattern of patients with patellofemoral pain syndrome, and the possibility that they may have their own prognostic factors, it seems preferable to present the prognostic factors for patellofemoral pain syndrome and other knee complaints separately. However, due to our relatively small study population, there was insufficient statistical power to do this. Repeating the analyses adjusted for patellofemoral pain syndrome did not influence the prognostic factors that were associated (data not shown).

No other studies have examined prognostic factors in adolescents and young adults with non-traumatic knee complaints in general practice. However, most of the prognostic factors revealed in the present study (especially the patient and symptom characteristics) are also reported in other studies on prognostic factors in adults with knee pain [27-30], in patients with other musculoskeletal disorders [17,31] or in patients with patellofemoral pain syndrome.[32,33] Some prognostic factors arising from physical examination are particularly interesting because they seem to be the most relevant (the highest AUC) at 6-year follow-up. A painful patellar ligament could be a sign of jumper's knee. Its presence as a prognostic factor at 1-year follow-up only, could indicate that jumper's knee has a bad short-term prognosis but a better long-term prognosis. The presence of painful patellar edges may indicate patellofemoral pain syndrome. This factor was included in the model at 6-year follow-up only; at 1-year follow-up it was dropped from the multivariable model because of the overlap with painful patellar ligament.

The negative association of floating patella with persistent knee complaints at 1 and 6-year follow-up, with a stronger effect at 6-year follow-up, was surprising. It is also

noteworthy that self-reported swelling and floating patella had an opposite association; in the case of self-reported swelling at baseline there was a higher chance for persistent knee complaints at 1 and 6-year follow-up, whereas with a floating patella at baseline there was a higher chance for no persistent knee complaints at 1 and 6-year follow-up. Closer analysis of patients with self-reported swelling and/or a floating patella showed that those with self-reported swelling were not always the same patients as those with a floating patella, and vice versa, with an overlap of only 40% (data not shown). This phenomenon was also observed in our earlier study (on a traumatic subgroup of the cohort) showing that both these factors are useful for evaluating the presence of effusion of the knee (compared with MRI).[34] In the present study it seems that these two factors have another prognostic value in this group of adolescents and young adults. Any explanation for this phenomenon would be pure speculation.

One limitation of the present study is that a relatively large percentage was lost to follow-up, especially at 6-year follow-up (44%). This is probably due to the lack of regular contact with patients between 1 and 6-year follow-up. For example, some people changed address and some lost interest in the study. However, the patients available at 1 and 6-year follow-up showed no difference in their baseline characteristics (Table 1).

We decided to perform univariable regression analysis with a relatively large p-value of 0.20 to determine which factors to test in multivariable analysis; this was due to the difficulty in choosing possible prognostic factors in view of the lack of research in this field. Consequently, we tested a relatively large number of prognostic factors in the univariable analysis.

Another limitation was the relatively small sample size (n=191 at baseline, n=165 at 1 year, and n=106 at 6-year follow-up) and the arbitrary p-value of 0.15 used in the multivariable analysis. Therefore, the present results should be validated in a larger population general practice population.

For adolescents and young adults with non-traumatic knee complaints, GPs should consider those with patellofemoral pain syndrome as a separate group, because their prognosis is worse than other types of knee complaints. More studies are needed to confirm the present results and to investigate prognostic factors for the different knee disorders separately. In particular, we need to elucidate the mechanisms behind patellofemoral pain syndrome.[35-38] Exploring why these patients have a worse prognosis compared to patients with a floating patella could be a starting point for investigating different treatments to improve prognosis. Finally, it would be worthwhile to explore what exactly is measured with the ballottement test and with the self-reported swelling question, and to establish why there is a difference between these two measurements.

Conclusions

The prognosis of non-traumatic knee complaints in adolescents and young adults in general practice is not as good as previously assumed. In this study, at 1-year follow-up 47% of the patients and at 6-year follow-up 27% of the patients still report persistent knee complaints. Having persistent knee complaints at 1 year is an important prognostic factor for having persistent knee complaints at 6-year follow-up (OR 4.8). Various baseline prognostic factors seem to be associated with persistent knee complaints at 1 and 6-year follow-up. The prognosis of the subgroup with patellofemoraal pain syndrome is much worse than for other non-traumatic knee complaints, with 40% having persistent knee complaints at 6-year follow-up. Therefore it seems useful to differentiate between the separate diagnoses.

Consequently, adolescents and young adults with non-traumatic knee complaints may require more realistic information about their (less favorable) prognostic course. More research is needed, especially on patellofemoral pain syndrome, to confirm these results and investigate how to improve the prognosis in these patients.

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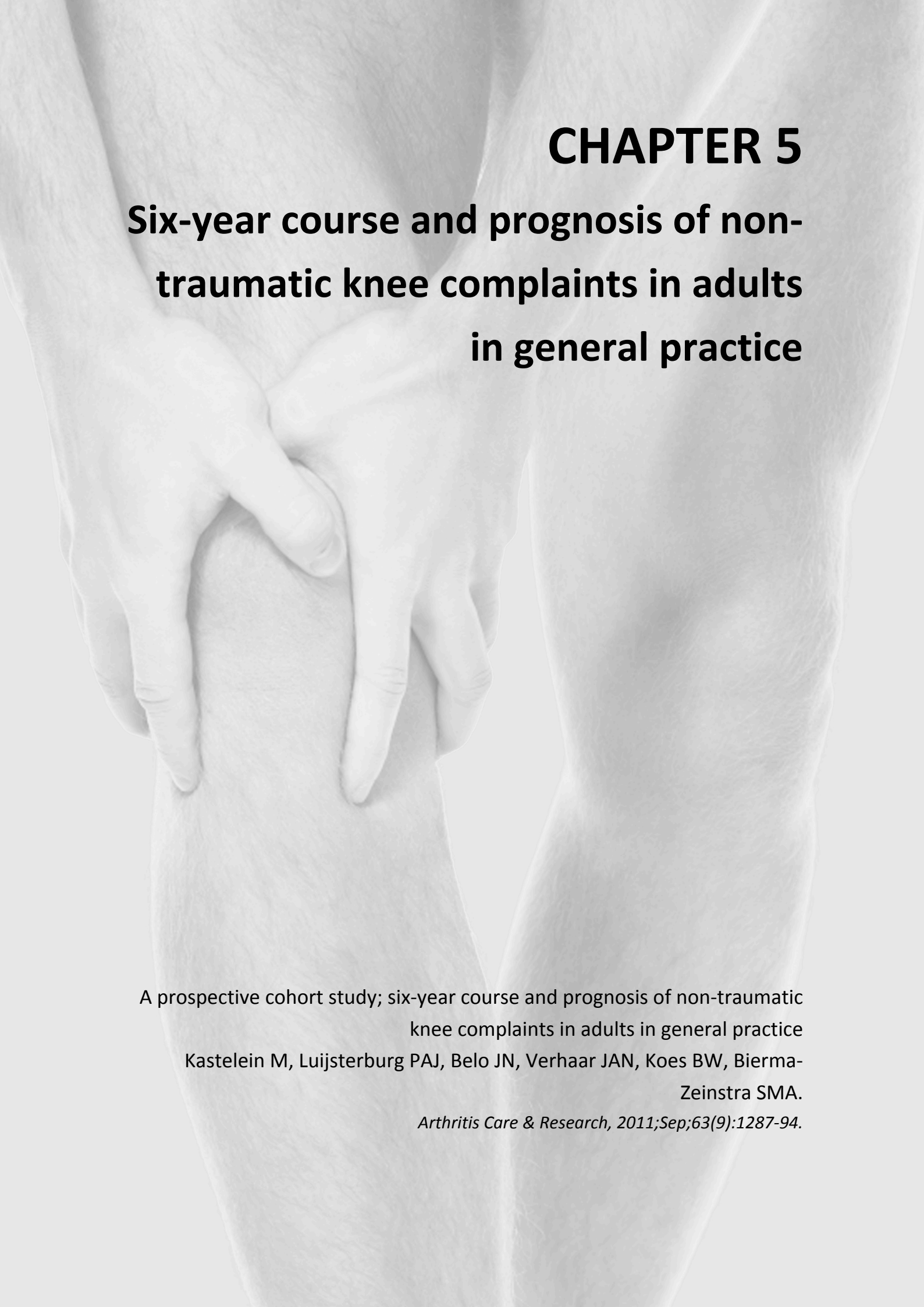

CHAPTER 5

Six-year course and prognosis of non-traumatic knee complaints in adults in general practice

A prospective cohort study; six-year course and prognosis of non-traumatic knee complaints in adults in general practice

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Abstract

Objective: To examine the 6-year course of non-traumatic knee complaints in adults in general practice, to identify prognostic factors for unfavorable outcome and to develop a clinical prediction rule.

Methods: Adults (>35 years) with incident non-traumatic knee complaints (n=549) were followed for 6 years. Multivariable logistic regression analysis was used to identify prognostic factors associated with an unfavorable outcome, the area under the receiver operating curve (AUC) was calculated to determine discriminative ability and a clinical prediction rule was developed. Unfavorable outcome is defined as persistent knee complaints at 6-year follow-up, or having undergone knee replacement surgery during follow-up.

Results: At 6-year follow-up, 42.1% of the patients had an unfavorable outcome. Having persistent knee complaints (OR 5.31, 95% CI 3.27-8.61) and fulfilling the clinical ACR criteria for osteoarthritis (OA) (OR 2.65, 95% CI 1.48-4.73) at 1-year follow-up were significantly associated with unfavorable outcome, while fulfilling the clinical ACR criteria for OA at baseline was not. Baseline factors independently associated with an unfavorable outcome were low/middle education level, co-morbidity of the skeletal system, duration of knee complaints >3 months, bilateral knee complaints, self-reported warm knee, history of non-traumatic knee complaints, valgus alignment, pain at passive knee flexion/extension, and bony enlargement of the knee joint (AUC 0.80).

Conclusion: Non-traumatic knee complaints in adults in general practice appear to become a chronic disorder in nearly half of the patients. The developed clinical prediction rule with 10 baseline prognostic factors can be used to select high-risk patients for an unfavorable outcome at long term.

Introduction

Patients with non-traumatic knee complaints are common in general practice. In adults, the incidence of such complaints reported in Dutch general practice is about 23 per 1000 patients per year, including bursitis, tendinitis, osteoarthritis (OA) and unspecified knee complaints.[1]

In spite of this high incidence, few data are available on the natural course and factors influencing the prognosis of these complaints in general practice. Although there are some reports on the 1-3 year course and prognostic factors of non-traumatic knee complaints in adults aged ≥ 50 years in general practice,[2-5] to our knowledge no studies have examined the longer-term follow-up in general practice. However, data on the long-term natural course and factors influencing prognosis are important for general practitioners (GPs) to establish which patients are at risk to develop chronic knee complaints. Moreover, GPs can use this prognostic information to better manage and inform these patients. For example, in patients with musculoskeletal pain in general practice only 33% had received prognostic information from their GP, whereas 82% thought that prognostic information was important.[6]

Therefore, this study evaluates the course of non-traumatic knee complaints in adults in general practice to identify prognostic factors for an unfavorable outcome at 6-year follow-up and to develop a clinical prediction rule.

Methods

Design

The present study was conducted within the HONEUR network (including 40 GPs) established by the Dept. of General Practice of Erasmus Medical Center Rotterdam.[7] It is part of a prospective, observational cohort study (n=1068) in which consecutive patients visiting their GP with a new episode of knee complaints were initially followed for 1 year.[7] Because of the high percentage of patients with persistent knee complaints at 1-year follow-up, the follow-up was extended to 6 years. At baseline, new knee complaints were defined as episodes of complaints presented to the GP for the first time. Recurrent symptoms for which the GP was not consulted within the past 3 months were also considered as new complaints. Traumatic knee complaints were defined as those caused by a sudden impact or wrong movement within 1 year before consulting their GP; all other knee complaints were considered as non-traumatic knee complaints.

Patients were eligible for the present study if they were aged >35 years and had consulted their GP for non-traumatic knee complaints. The cut-off of 35 years was chosen because around this age the predominance of specific diagnoses shifts from patellofemoral pain syndrome to OA of the knee.[1] Exclusion criteria at baseline were knee symptoms that required urgent medical attention (fractures, infection), patients with malignancies, neurologic disorders or musculoskeletal diseases (e.g. Parkinson's disease,

rheumatoid arthritis, amyotrophic lateral sclerosis), as well as patients with insufficient understanding of the Dutch language and/or incapable of understanding the ramifications of participation.
The study protocol was approved by the local Medical Ethics committee.

Data collection

Patients filled out a self-report questionnaire at baseline and at 3, 6, 9 months, 1 year and 6-year follow-up. The questionnaires collected data on the following domains that were all are assessed at baseline and follow-up unless otherwise stated:

- Demographics: age, gender, composition of household, education level and co morbidity (only assessed at baseline).
- Knee complaints; history of previous knee injuries or operations, duration and recurrence of knee complaints, knee pain with an 11-point numeric rating scale (NRS), knee pain and function with as well the Knee Society Score function questions (KSS)[8] as the Lysholm Knee Scoring Scale [9-11] and knee pain, stiffness and function with as well the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [12,13] as the Knee Injury Osteoarthritis Outcome Score (KOOS) [14] (KOOS was only assessed at 6-year follow-up).
- Knee loading: daily activities and physical exercise, data on impact of the knee complaint as hindrance and sick leave from daily activities.
- Health-related quality of life with the Medical Outcomes Study Short-Form 36 Health Survey (SF-36).[15,16]
- Coping with the Tampa Scale for Kinesiophobia.[17,18]
- Treatment: advise given by the GP, knee medication, visits to health care professionals and operations.

For all scores, except the Lysholm and SF-36, lower scores represent better function/outcome. In addition, the questionnaire at 1 and 6-year follow-up collected also data on experienced recovery, measured on a 7-point Likert scale, ranging from completely recovered to worse than ever. Persistent knee complaints were defined as knee complaints that were “slightly improved”, “not changed”, “slightly worsened”, “much worsened” or “worse than ever”. Clinically important recovery was defined as knee complaints that were “completely recovered” or “much improved”.
A standardized physical examination was carried out by a trained physiotherapist at baseline and at 1-year follow-up and consisted of inspection (alignment and joint effusion), palpation (temperature, collateral ligaments, and joint line tenderness), assessment of effusion, passive range of motion in flexion and extension, meniscal tests and knee stability tests.[19,20]
We extracted data from the questionnaires and physical examination to assess the clinical American College of Rheumatology (ACR) criteria for osteoarthritis (OA) of the knee at

baseline and 1-year follow-up.[21] According to these criteria, OA of the knee is defined as knee pain + at least 3 out of 6 the following items: age>50 years, stiffness <30 minutes, crepitus, bony tenderness, bony enlargement and no palpable warmth.

Statistical analysis

Descriptive statistics were used to describe patient characteristics, diagnosis, complaint characteristics and outcome. Unfavorable outcome was defined as having persistent knee complaints at 6-year follow-up, or having undergone knee replacement surgery during this period. Favorable outcome was defined as experiencing clinical recovery of knee complaints at 6-year follow-up and not having undergone knee replacement surgery in this period. Univariate logistic regression analysis was performed to determine which baseline variables from history taking and physical examination are associated with an unfavorable outcome of the index knee, expressed as odds ratios (OR). In case of bilateral symptoms at baseline, the index knee was determined as the knee with the most severe symptoms at baseline; in case of equal severity of symptoms of both knees at baseline we took the right knee for the analysis. The baseline variables used for the univariate analysis are based on literature [22] and clinical relevance. The variables were divided into three domains: patient characteristics, complaint characteristics and physical examination findings. To enable easy interpretation of prognostic factors in a clinical setting we chose to dichotomize most variables. Imputation of missing data was carried out by multiple imputation, creating a total of 5 imputed databases, which is a common number of databases to ending up [23-25] Univariate analysis was performed separately on all 5 imputed databases. The variables showing a univariate association with an unfavorable outcome in at least 3 of 5 imputed databases ($p \leq 0.20$), were analyzed in a multivariable (backward) logistic regression model (entry 0.05, removal 0.10). The p-value of 0.20 in the univariate analysis was chosen because when using a stricter p-value you could eliminate prognostic factors in the univariate analysis that are multivariable significant due to confounding.[26] Also the multivariate analysis was performed separately on all 5 imputed databases. If a variable was selected in at least 3 of 5 imputed databases in the multivariate analysis, it was included in the final model (enter method) and the area under the receiver operating curve (AUC) was calculated to determine the discriminative ability of the logistic regression model.

First, separate models for patient characteristics, complaint characteristics and physical examination findings were built. Subsequently, the remaining variables of each domain were combined to build a model of patient and complaint characteristics, and a model of patient- and complaint characteristics together with physical examination findings to evaluate the additional value of the different domains. All models were adjusted for gender and age.

To make the model of patient- and complaint characteristics together with physical examination suitable for use in clinical practice, we transformed this logistic regression equation into a clinical prediction rule through a score chart. The coefficients in the logistic regression equation were multiplied by 10 and rounded to the nearest integer to obtain the score per variable. The sum of all scores reflects the probability of an unfavorable outcome at 6-year of follow-up.
Analyses were performed with SPSS version 17.02 (SPSS Inc., Chicago, Ill, USA).

Results

Study population

Table 1 shows the baseline characteristics of the 549 patients included in the study. Their mean age was 53.8 (SD 11.4) years and 50.5% was male. According to the clinical ACR criteria for OA[21] assessed at baseline, 344 patients (62.7%) suffered from OA of the knee. At baseline, 155 patients (28.7%) had knee complaints for ≤ 3 months, 172 patients (31.9%) had bilateral knee complaints and 231 patients (42.9%) reported recurrent knee complaints. At baseline, the mean knee pain severity, measured with a numerical rating scale (NRS), was 4.3 (SD 2.1), the mean Lysholm knee score was 67.5 (SD 18.7), and the mean WOMAC index was 28.5 (SD 19.7).

Table 1 Baseline characteristics of the total study group and of those available at 6-year follow-up.

Baseline characteristic	**Total group (n=549)**	**Available at 6- year follow-up (n=340)**
General		
Age in years, mean ± SD	53.8 ± 11.4	53.2 ± 10.7
Male, n (%)	277 (50.5)	179 (52.8)
Diagnosis based on clinical ACR criteria		
Osteoarthritis	344 (62.7)	202 (59.4)
Knee complaints		
Duration at consultation < 3 months, n (%)	386 (71.3)	243 (72.1)
Bilateral, n (%)	172 (31.9)	101 (30.1)
Recurrent, n (%)	231 (42.9)	148 (44.2)
Measures of severity		
Knee pain (0-10), mean ± SD	4.3 ± 2.1	4.4 ± 2.1
Lysholm knee function score (0-100), mean ± SD	67.5 ± 18.7	68.0 ± 17.8
WOMAC index (0-100), mean ± SD	28.5 ± 19.7	28.4 ± 20.1

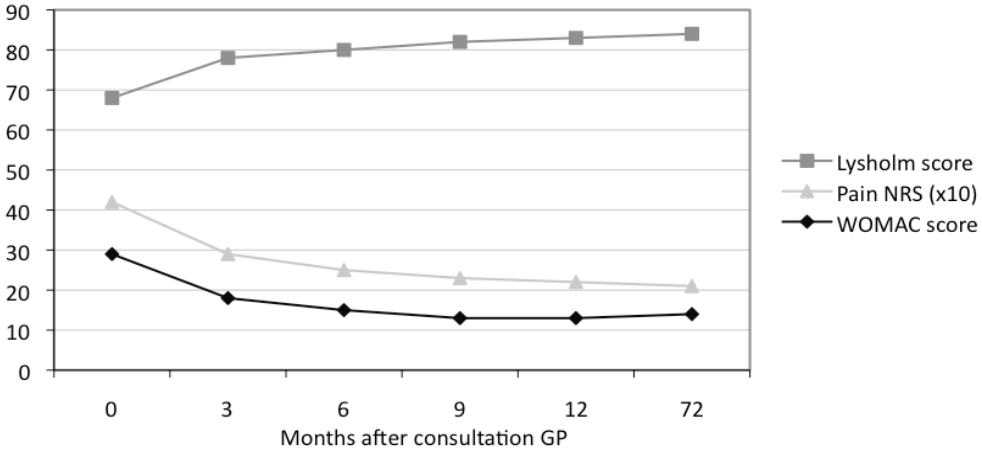
At 6-year follow-up, 340 patients (61.9%) were available for analysis, their baseline characteristics are showed in table 1. The 209 patients (38.1%) lost to follow-up showed no significant differences compared with those available at 6-year follow-up regarding baseline age, gender, diagnosis based on the clinical ACR criteria, knee complaints, pain score (NRS), Lysholm score and WOMAC index. Patients lost to follow-up also showed no

significant differences compared with those available at 6-year follow-up regarding self-reported outcome at 1-year follow-up (OR 1.10, 95% CI 0.76-1.58). Reasons for no longer participating at 6-year follow-up were lack of time and/or lack of interest (n=121, 57.6%), being inaccessible due to change of address and/or telephone number (n=41, 19.5%) and/or personal circumstances (n=11, 5.2%); in addition, 23 patients (11.0%) had died during the follow-up period and for 13 patients (6.2%) no reason was available.

Course and prognosis

Figure 1 shows the 6-year course of the total group for mean knee pain severity (NRS), mean Lysholm knee score and mean WOMAC index: all three showed the greatest improvement in the first 3 months after the initial GP consultation. Improvement in these three scores at 3 months allows to discriminate significantly between patients with a favorable and an unfavorable outcome at 6-year follow-up; mean difference in improvement for pain (NRS) between these two groups was 1.24 (SE 0.31, p<0.001), for Lysholm knee score 6.92 (SE 2.01, p<0.001) and for WOMAC index 6.91 (SE 2.30, p=0.003).

Figure 1 Course of knee complaints of the total group (mean scores).



At 6-year follow-up, 131 patients (38.6%) reported persistent knee complaints. At 6-year follow-up, 66 of these patients with persistent knee complaints (54.5%) had bilateral knee complaints. Moreover, compared with baseline, in 15 patients (12.8%) the complaints had changed to other complaints in the same knee, 80 patients (68.4%) had the same knee complaints, and 22 patients (18.8%) had the same complaints but combined with other knee complaints. At 6-year follow-up, mean knee pain severity of these patients was 4.2 (SD 2.1), mean Lysholm knee score was 67.9 (SD 16.9) and mean WOMAC index was 31.2 (SD 21.1), with some higher scores on the stiffness domain and similar scores on the pain and physical function domain compared with the mean WOMAC index. These scores indicate moderate disease.

Table 2 Univariable association between baseline characteristics and unfavorable outcome (n=143) at 6-year follow-up.

Variable	**Unfavorable outcome**		
	Pooled OR	**Pooled 95% CI**	**Pooled p-value**
Patient characteristics			
Age	1.03	1.01-1.06	0.00*
Female gender	1.73	1.12-2.67	0.01*
Body mass index > 27	1.51	0.98-2.34	0.06*
Low/middle education level	2.38	1.47-3.85	0.00*
Co-morbidity skeletal system	2.09	1.34-3.27	0.00*
Non-skeletal co-morbidity	0.76	0.46-1.29	0.32
Kinesiophobia (Tampa > 37)	1.10	0.71-1.71	0.66
Poor mental health (SF-36 < 50)	2.81	1.16-6.83	0.02*
Poor general health (SF-36 < 50)	1.82	0.92-3.60	0.08*
Paid employment (>8 hours/week)	0.49	0.31-0.76	0.00*
Sport	0.73	0.46-1.15	0.17*
Symptom characteristics			
Duration > 3 months	2.45	1.51-3.98	0.00*
Recurrent complaints	1.89	1.21-2.95	0.01*
Bilateral complaints	2.80	1.73-4.51	0.00*
Pain (11-point scale)	1.09	0.98-1.21	0.13*
Self-report warm knee	2.36	1.51-3.68	0.00*
Self report swollen knee	1.88	1.20-2.93	0.01*
Self report crepitus knee	2.04	1.28-3.25	0.00*
Locking of the knee (Lysholm)	0.89	0.51-1.79	0.89
Instability of the knee (Lysholm)	1.94	1.23-3.04	0.00*
History of traumatic knee complaints	1.09	0.60-1.98	0.77
History of non-traumatic knee complaints	3.39	2.03-5.65	0.00*
Nuisance in work/study/household	1.39	0.88-2.18	0.16*
Limitation during daily function (WOMAC > 20)	1.64	1.05-2.55	0.03*
Pain during daily function (WOMAC > 20)	1.53	0.95-2.47	0.08*
Stiffness of knee (WOMAC > 20)	1.25	0.79-1.97	0.35
Physical examination			
Valgus	2.25	1.38-3.67	0.00*
Varus	0.54	0.31-0.94	0.03*
Pain active flexion	1.50	0.93-2.41	0.09*
Pain passive flexion	2.44	1.51-3.94	0.00*
Pain active extension	1.63	0.91-2.94	0.10*
Pain passive extension	2.27	1.40-3.71	0.00*
Crepitus active flexion	1.47	0.94-2.31	0.09*
Crepitus passive flexion	1.00	0.97-1.02	0.84
Crepitus active extension	1.32	0.83-2.10	0.25
Crepitus passive extension	1.65	0.99-2.73	0.15*
Floating patella	1.40	0.86-2.29	0.18*
Bony enlargement of the joint	3.05	1.38-6.72	0.01*
Pain internal rotation hip	2.03	1.11-3.69	0.02*
Baker's cyst	2.02	0.75-5.46	0.17*
Pain bursa prepatellaris	1.33	0.65-2.75	0.43
Pain iliotibial tract	1.71	0.91-3.20	0.10*

* selected in ≥3 out of 5 imputed databases ($p \leq 0.20$)

During the 6-year follow-up, 17 patients (5.0%) underwent knee replacement surgery. The mean time of knee replacement surgery after inclusion in this study was 3.6 years (SD 1.8). Of these patients, 11 of 16 patients (68.8%) reported recovery and 5 of 16 patients (31.3%) reported persistent knee complaints, and for 1 patient no recovery score was available at 6-year follow-up. Combining the patients who reported persistent knee complaints with those who underwent knee replacement surgery resulted in 143 of 340 patients (42.1%) having an unfavorable outcome at 6-year follow-up.

Regarding diagnosis, fulfilling the clinical ACR criteria for OA at baseline was not significantly associated with an unfavorable outcome at 6-year follow-up (OR 1.18, 95% CI 0.76-1.84). In contrast, fulfilling the clinical ACR criteria for OA at 1-year follow-up was significantly associated with an unfavorable outcome at 6-year follow-up (OR 2.65, 95% CI 1.48-4.73). Having persistent knee complaints at 1-year follow-up was also significantly associated with an unfavorable outcome at 6-year follow-up (OR 5.31, 95% CI 3.27-8.61).

Prognostic factors

Table 2 presents the pooled univariable associations between baseline characteristics and an unfavorable outcome at 6-year follow-up.

The patient characteristics age, female gender, body mass index (BMI) >27, low/middle education level, co-morbidity of the skeletal system, poor mental health, poor general health and absence of paid employment were univariably associated with an unfavorable outcome. Of the symptom characteristics duration >3 months, recurrent complaints, bilateral complaints, pain, self-reported warm knee/swollen knee/crepitus of the knee, instability of the knee, history of non-traumatic knee complaints, nuisance in work/household/study, limitation during daily function, and pain during daily function were univariably associated with an unfavorable outcome. From physical examination valgus alignment, absence of varus alignment, pain at active or passive flexion, pain at active or passive extension, crepitus at active flexion, crepitus at passive extension, floating patella, bony enlargement of the joint, pain with internal rotation of the hip, Baker's cyst and pain of the iliotibial tract were univariably associated with an unfavorable outcome.

Table 3 presents the pooled multivariate associations between baseline characteristics and an unfavorable outcome.

The patient characteristics age, low/middle education level, co-morbidity of the skeletal system and poor mental health showed an independent association with an unfavorable outcome at 6-year follow-up (AUC of 0.68). From the symptom characteristics, complaint duration > 3 months, bilateral complaints, self-reported warm knee, history of non-traumatic knee complaints and limitation during daily function were independently associated with an unfavorable outcome (AUC of 0.73). From physical examination valgus

alignment, pain at passive flexion/ extension and bony enlargement of the joint were independently associated with an unfavorable outcome (AUC of 0.67). Adding the symptom characteristics to the patient characteristics, the AUC increased by 0.08 to 0.76. Age, poor mental health and limitation during daily function no longer remained in the model (p >0.10). Adding items from physical examination increased the AUC by 0.04 to 0.80. All 10 variables remained in the model (p ≤0.10).

Table 3 Multivariable associations between baseline characteristics and unfavorable outcome at 6-year follow-up (n=143).

Model	**Pooled OR**	**Pooled 95% CI**	**Pooled p-value**	**AUC**
Patient characteristics				0.68
Age	1.03	1.00-1.05	0.02	
Low/middle education level	1.94	1.18-3.19	0.01	
Co-morbidity skeletal system	1.79	1.12-2.87	0.02	
Poor mental health (SF-36 < 50)	2.95	1.16-7.48	0.02	
Symptom characteristics				0.73
Duration > 3 months	2.20	1.27-3.78	0.01	
Bilateral complaints	1.89	1.11-3.19	0.02	
Self-report warm knee	2.07	1.27-3.36	0.00	
History of non-traumatic knee complaints	2.59	1.52-4.41	0.00	
Limitation during daily function (WOMAC > 20)	1.52	0.93-2.49	0.09	
Physical examination				0.67
Valgus	2.07	1.24-3.48	0.01	
Pain passive flexion	1.94	1.17-3.21	0.00	
Pain passive extension	1.72	1.01-2.92	0.05	
Bony enlargement of the joint	2.64	1.17-5.96	0.02	
Patient and symptom characteristics				0.76
Low/middle education level	2.27	1.33-3.86	0.00	
Co-morbidity skeletal system	1.54	0.94-2.55	0.09	
Duration > 3 months	2.11	1.21-3.67	0.01	
Bilateral complaints	1.83	1.06-3.16	0.03	
Self-report warm knee	2.06	1.25-3.38	0.01	
History of non-traumatic knee complaints	2.40	1.38-4.16	0.00	
Patient characteristics, symptom characteristics and physical examination				0.80
Low/middle education level	2.25	1.28-3.93	0.01	
Co-morbidity skeletal system	1.67	0.98-2.84	0.06	
Duration > 3 months	2.62	1.42-4.83	0.00	
Bilateral complaints	2.21	1.22-4.01	0.01	
Self-report warm knee	1.95	1.15-3.33	0.01	
History of non-traumatic knee complaints	2.08	1.16-3.73	0.01	
Valgus	1.96	1.07-3.57	0.03	
Pain passive flexion	2.08	1.16-3.71	0.01	
Pain passive extension	1.82	0.97-3.44	0.06	
Bony enlargement of the joint	2.22	0.86-5.73	0.10	

Clinical prediction rule

The score chart that we derived from the logistic regression model of patient- and symptom characteristics together with findings from physical examination is presented in table 4. Table 5 provides the score chart legend to convert the total score into the predicted probability of an unfavorable outcome.

Table 4 Score chart

Item	**Score**
Low/middle education level	8
Co-morbidity skeletal system	5
Duration > 3 months	10
Bilateral complaints	8
Self-report warm knee	7
History of non-traumatic knee complaints	7
Valgus	7
Pain passive flexion	7
Pain passive extension	6
Bony enlargement of the joint	8
	Total score

Table 5 Score chart legend

Total score	**Probability***
<16	0-20%
16-25	20-40%
26-33	40-60%
34-43	60-80%
44-73	80-100%

* Probability that an unfavorable outcome is present at 6 year after consultation

Discussion

The present study investigated the 6-year course and prognostic factors of incident non-traumatic knee complaints in adults in general practice.

At 6-year follow-up 38.6% of all patients reported persistent knee complaints. When combining this group with those who underwent knee replacement surgery during the 6-year period (also defined up as being an adverse outcome), then 42.1% of all patients had an unfavorable outcome at 6-year follow-up. Having persistent knee complaints at 1-year follow-up was strongly associated with an unfavorable outcome at 6-year follow-up (OR 5.31, 95% CI 3.27-8.61).

Until now, only studies with a short-term follow-up (1-3 years) are available [2-5] and these studies also showed a high percentage of patients with an unfavorable outcome. It seems logical that many patients in the present study had an unfavorable outcome at 6-year follow-up, because many already suffered from or had developed OA of the knee. However, fulfilling the clinical ACR criteria at baseline was not significantly associated with persistent knee complaints at 1-year follow-up,[27] and was not significantly associated with an unfavorable outcome at 6-year follow-up. This result might be due to the intermittent progressive character of OA and/or the clinical ACR criteria may not be appropriate for use in general practice. However, fulfilling the clinical ACR criteria at 1-year follow-up was significantly associated with an unfavorable outcome at 6-year follow-up (OR 2.65, 95% CI 1.48-4.73). Apparently, assessing the clinical ACR criteria only at

baseline is not sufficient for prognostic purposes in adults with non-traumatic knee complaints in general practice. Follow-up assessments of the clinical ACR criteria are required for prognostic purposes in general practice and/or other baseline prognostic may be used.

Baseline prognostic factors independently associated with an unfavorable outcome at 6-year follow-up were low/middle education level, co-morbidity of the skeletal system, duration >3 months, bilateral complaints, self-reported warm knee, history of non-traumatic knee complaints, valgus alignment, pain at passive flexion extension and bony enlargement of the joint. These prognostic factors are similar to those reported in comparable studies with a shorter-term outcome (1-3 year).[2-5] Moreover, most prognostic factors found in the present study indicate a degree of severity or duration of knee complaints and are therefore valid prognostic factors. Our results are also in line with a systematic review on prognostic factors of musculoskeletal pain in primary care,[22] although some of our factors needs further explanation. In the present study only valgus alignment (and not varus alignment) was significantly associated with an unfavorable outcome at 6-year follow-up. This is in contrast to a recent systematic review which found an independent relation between both valgus and varus alignment and OA of the knee.[28] However, they used radiographic and MRI methods which may have contributed with the difference of our results. Besides, although many of our patients probably had OA of the knee, our results are not directly comparable with studies investigating OA because our population included all types of non-traumatic knee complaints. In addition, our results are also not directly comparable with studies performed in secondary care because these latter patients generally have more severe complaints than patients in general practice. Two similar (short-term) studies, performed in primary care, did not investigate the relation with malalignment [3,4] and two other similar (short-term) studies found no relation with valgus or varus alignment.[2,5] Therefore, our results are also not in concordance with these results. In the present study, BMI (often considered a prognostic factor for musculoskeletal disorders [29]) was not independently associated with an unfavorable outcome.

We decided to use a combined outcome measurement (i.e. including knee replacement surgery as unfavorable outcome, besides self reported persistent knee complaints) because it is not desirable that patients undergoing such surgery during follow-up could (otherwise) have had a favorable outcome, because they noticed clinical recovery at the 6-year follow-up questionnaire. Even though they report clinical recovery after surgery, knee replacement surgery indicates severe symptomatic OA and, in this context, is an unfavorable outcome. When repeating the analysis with persistent knee complaints alone as outcome measurement (i.e. without taking knee replacement surgery into account) the associated prognostic factors and AUCs were practically the same (data not shown), indicating that knee replacement surgery has not influenced our results.

It was also possible to choose another outcome measurement, such as the total WOMAC score, however we did not because we had a preference for an outcome that it is more easy to use and interpret in clinical practice than the total WOMAC score. However, unfavorable outcome was strongly significantly related with an increased total WOMAC score at 6-year follow-up (continuous: OR 1.16, p<0.001, cut-off point at 39: OR 80.5, p<0.001). Therefore, using unfavorable outcome would not have importantly influenced the results.

One limitation of the present study is that a relatively large percentage of patients (38.1%) was lost to follow-up. This was mainly due to lack of contact, change of address, loss of interest, severe illness and/or death between 1 and 6-year follow-up. However, patients lost to follow-up did not appear to be a selected group of patients.

Another limitation is the relatively heterogeneous study group. Investigating the course and prognostic factors of different diagnoses is preferable, but this requires a larger population and a confirmed diagnosis at baseline.

Besides, we developed a clinical prediction rule that we have not externally validated. Therefore our results could be overestimated and the clinical prediction rule should be validated in another similar study population.

The present results should be validated in studies with a long-term follow-up in primary care, and the natural course and prognostic factors of the different knee complaints should (preferably) be investigated separately. This will enable GPs to better inform patients about prognosis and identify patients at risk of developing an unfavorable outcome who might need referral or special treatment. Such studies may also help to identify appropriate starting points to establish the effect of treatments on prognosis, when prognostic factors are found that are modifiable. However, because the prognostic factors found in the present study are not modifiable, our results could only be used to select high-risk patients and can be used to further investigate whether early treatment (for example exercise therapy, which is an effective treatment for OA [30]) is also effective in these high-risk patients.

Conclusions

At 6-year follow-up, non-traumatic knee complaints in adults in general practice still affect 42% of the patients. Many patients with persistent knee complaints at 1-year follow-up also had an unfavorable outcome at 6-year follow-up. Even though fulfilling the clinical ACR criteria at baseline was not significantly associated with an unfavorable outcome, OA of the knee may well be involved. Follow-up assessment of the ACR criteria seems warranted for prognostic purposes in general practice; however, their value is limited compared with self-reported perceived recovery at 1-year follow-up.

In the present study, the prognostic factors identified with an unfavorable outcome and the resulting prediction rule may help the GP to better inform and evaluate the prognosis

of patients with non-traumatic knee complaints. Moreover, these results can be used in the whole medical community, that are in charge of patients with non-traumatic knee complaints, for early diagnosis and treatment in high risk groups of patients with non-traumatic knee complaints.

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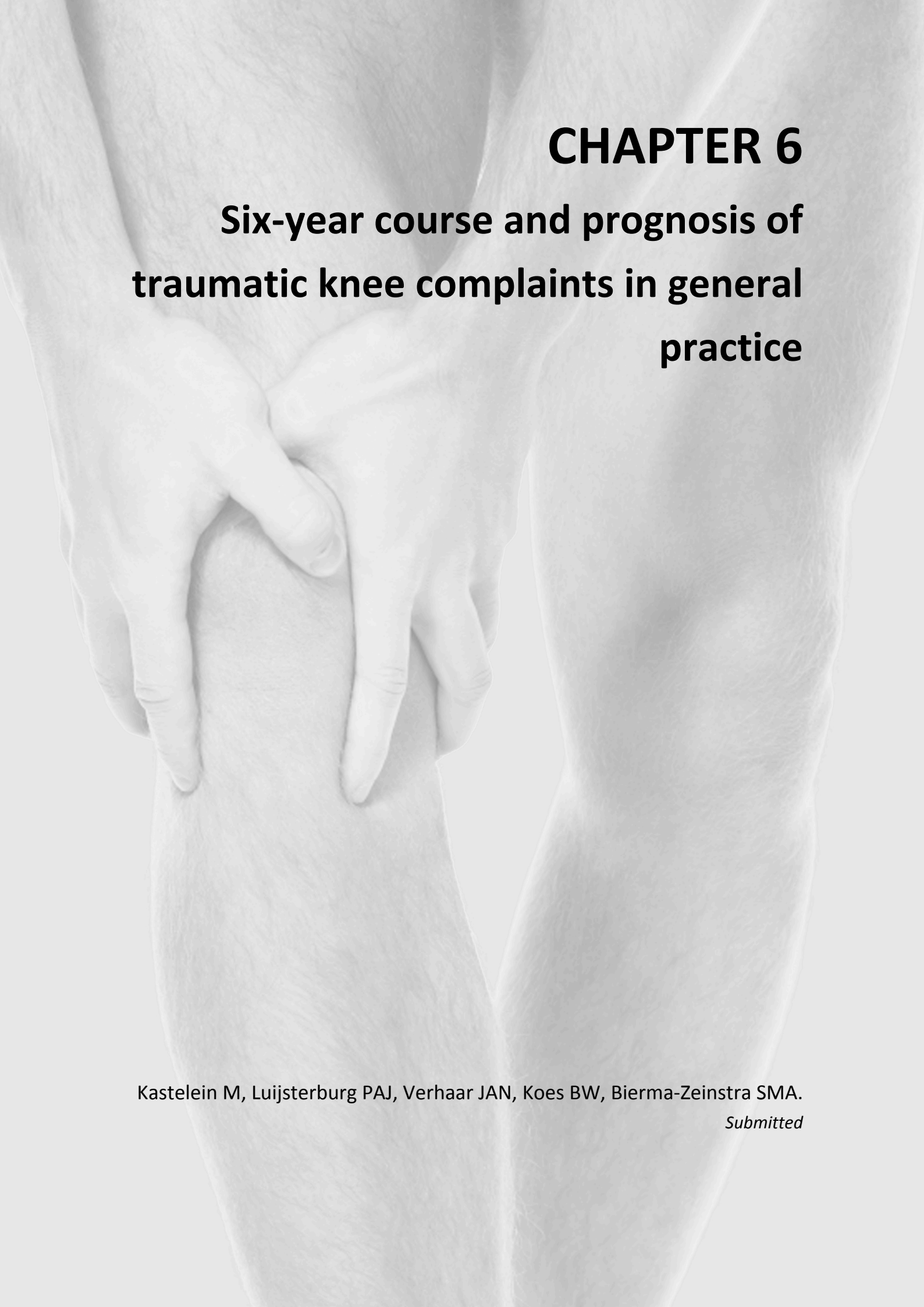

CHAPTER 6

Six-year course and prognosis of traumatic knee complaints in general practice

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Submitted

Abstract

Objective: To describe the 1 and 6-year course of traumatic knee complaints in adolescents and adults presenting in general practice, and to identify prognostic factors for persistent knee complaints.

Methods: Adolescents (≥ 12 years) and adults with traumatic knee complaints (n=328) were included by their general practitioner and followed for 6 years. Patients filled out self-report questionnaires and underwent a standardized physical examination. Descriptive statistics were used to describe the course of the knee complaints. Multivariate logistic regression analysis was used to identify prognostic factors for persistent knee complaints at 1 and 6-year follow-up, and the area under the receiver operating curve (AUC) was calculated.

Results: Persistent knee complaints were reported by 27% of the patients at 1 year and by 33% at 6 years. There was a strong relationship (OR 11.0, 95% CI 5.0-24.2) between having persistent knee complaints at 1 year and at 6-year follow-up. Patients reporting recovery during follow-up had a mean recovery period of 7.4 months. Prognostic factors associated with persistent knee complaints at 1 year were age, poor general health, history of non-traumatic knee complaints, absence of floating patella and laxity on the anterior drawer test (AUC 0.72). At 6-year follow-up, age, body mass index > 27, non-skeletal co-morbidity, self-reported crepitus of the knee, history of non-traumatic knee complaints, and laxity on the anterior drawer test were associated with persistent knee complaints (AUC 0.82).

Conclusion: Traumatic knee complaints in general practice seem to become a chronic disorder in 1 of 3 patients. Having knee complaints at 1-year follow-up is an important predictor for persistent knee complaints at 6-year follow-up. Several prognostic factors assessed at baseline are associated with persistent knee complaints at 1 and 6-year follow-up.

Introduction

The incidence of traumatic knee complaints reported in Dutch general practice is about 5.3 per 1000 patients per year, including contusion, distortion, collateral ligament lesions, cruciate ligament lesions and meniscal tears.[1] Most of these traumatic knee complaints arise from sports participation or leisure activities.[2]

According to the Dutch clinical guideline 'Traumatic knee complaints in general practice' most patients with a knee injury presenting in general practice suffer from a contusion or distortion. Therefore, it is assumed that most patients with traumatic knee complaints in general practice are complaint free in a few weeks and can resume their daily activities.[2] However, no studies in primary care are available to support this assumed natural course, and no studies have evaluated factors possibly influencing the prognosis of patients with traumatic knee complaints in general practice.

The few data available on the natural course of traumatic knee complaints originate from secondary care.[3] However, patients from secondary care are not comparable with those from general practice, because the former are a selected group of patients, i.e. mostly young athletes with a moderate or severe knee injury, or patients with persistent complaints or limitations after knee injury. In general practice, all types of knee injuries are seen (mild to severe) and in a wide variety of patients, ranging from the young athlete to the elderly person with osteoarthritis (OA).

Nevertheless, information on the natural course of traumatic knee complaints and factors that influence prognosis are important for general practitioners (GPs) in their management and referral of patients. Information about the expected natural course is also important for their patients.[4]

Therefore, we performed a prospective cohort study in general practice to assess the course of traumatic knee complaints, and to identify prognostic factors for persistent knee complaints at 1 and 6-year follow-up.

Methods

Design

The present study took place within the research network HONEUR (with 40 GPs) established by the Department of General Practice of Erasmus Medical Center Rotterdam. It is part of a prospective, observational cohort study (n=1068) in which consecutive patients visiting their GP with a new episode of knee complaints were enrolled and initially followed for 1 year.[5]

Because of high percentages of persistent knee complaints at 1-year follow-up, the follow-up was extended to 6 years. At baseline, a new episode of knee complaints was defined as an episode of complaints presented to the GP for the first time. Recurrent symptoms for which the GP was not consulted within the past 3 months were also considered as new episodes. Patients were eligible for the present study if they were

aged ≥ 12 years and had consulted their GP for traumatic knee complaints. Traumatic knee complaints were defined as knee complaints caused by a sudden impact or wrong movement within 1 year before consulting their GP. All other knee complaints were considered as non-traumatic knee complaints. Exclusion criteria were knee symptoms that required urgent medical attention (fractures, infection), patients with malignancies, neurologic disorders or musculoskeletal diseases (e.g. Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), and patients unable to understanding the ramifications of study participation.

The study protocol was approved by the Medical Ethics committee of the Erasmus Medical Center Rotterdam.

Data collection

Patients filled out a self-report questionnaire at baseline, at 3, 6 and 9 months follow-up, and at 1 and 6-year follow-up. A standardized physical examination was carried out by a trained physiotherapist at baseline and at 1-year follow-up.

At baseline and follow-ups, the questionnaire collected data on age, gender, socioeconomic status, previous knee history of previous injuries or operations, present symptoms, level of daily activities and sports, hindrance and sick leave from daily activities, health-related quality of life, and treatments received. In addition, the questionnaire at 1 and 6-year follow-up collected data on experienced recovery or worsening of the knee complaints (outcome). In case of non-response at 6-year follow-up, we asked the patient by telephone to their experienced recovery of the knee complaints at 6-year follow-up.

Functional disability and pain were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [6] (assessed at baseline to 1 year follow-up), the Knee Injury Osteoartritis Outcome Score (KOOS) [7] (assessed at 6-year follow-up), the Medical Outcomes Study Short Form 36 Health Survey (SF-36) [8,9], the Knee Society Score function questions (KSS) [10], the Lysholm Knee Scoring Scale [11] (all assessed at baseline to 6 year follow-up), the Tampa Scale for Kinesiophobia [12] (assessed at baseline) and the COOP/WONCA charts [13,14] (assessed at baseline to 1 year follow-up). The outcome measurement 'experienced recovery of knee complaints' was measured on a 7-point Likert scale.

Physical examination of the knee consisted of inspection (alignment and joint effusion), palpation (temperature, collateral ligaments, and joint line tenderness), assessment of effusion, passive range of motion in flexion and extension, meniscal tests and knee stability tests. [15,16]

Statistical analysis

Descriptive statistics are used to describe patient/complaint characteristics and experienced recovery, and to analyze whether there was selective loss to follow-up.

Univariate logistic regression analysis was used to determine which baseline variables from history taking and physical examination were associated with persistent knee complaints, expressed as odds ratios (OR). The baseline variables used for the univariate analysis were based on literature [17] and clinical relevance. The variables were divided into three domains: patient characteristics, complaint characteristics and physical examination findings. To enable easy interpretation of prognostic factors in a clinical setting we chose to dichotomize most of the variables. Imputation of missing data was carried out by multiple imputation, creating a total of 5 imputed databases [18-20]. Only baseline variables used for logistic regression were imputated. The variables showing an univariate association with persistent knee complaints in at least 3 out of 5 imputed databases ($p \leq 0.20$), were analyzed in a multivariate logistic regression model (Backward logistic regression method: entry 0.05, removal 0.10). If a variable was selected in at least 3 out of 5 imputed databases in the multivariate analysis, it was included in the final model (Enter method) and the area under the receiver operating curve (AUC) was calculated. First, separate models for patient characteristics, complaint characteristics and physical examination findings were built. Subsequently, we combined the remaining variables of each domain to build a model of patient and complaint characteristics, and a model of patient and complaint characteristics together with physical examination findings, to evaluate the addictive value of the different domains. All models were adjusted for gender and age. Separate analyses were performed for the outcome perceived recovery at 1 and 6-year follow-up. Perceived recovery was dichotomized into clinical recovery of knee complaints ('completely recovered' and 'much improved') versus persistent knee complaints ('slightly improved', 'no change", 'slightly worsened', 'much worsened' and 'worse than ever'). Because of the heterogeneity of the total group, we repeated the analysis for the subgroup of patients without a history of non-traumatic knee complaints, and for the subgroup of patients aged 12-35 years.

The analyses were performed using SPSS version 17.02 (SPSS Inc., Chicago, Ill., USA).

Results

Study population

Table 1 presents the baseline characteristics of the 328 patients who participated in this study. Their mean age was 41.9 (SD 15.7) years and 56.4% was male. A total of 86 patients (30.8%) reported a history of traumatic knee complaints and 124 patients (40.8%) reported a history of non-traumatic knee complaints of the same knee. A total of 252 patients (76.8%) reported that the duration of their current traumatic knee complaint was ≤ 3 weeks at the time of consultation, 58 (17.7%) reported a duration of 3 weeks to 3

months, and 18 patients (5.5%) reported a duration of 3 months to 1 year. The traumatic knee complaints were caused by sport activity in 137 patients (41.8%), by leisure activity in 102 (31.1%), by work-related activity in 46 (14.0%) and by traffic-related activity in 43 patients (13.1%). At baseline, the mean knee pain severity, measured with a numerical rating scale (NRS), was 4.5 (SD 2.3), the mean Lysholm knee score was 65.1 (SD 21.0) and the mean WOMAC index was 33.4 (SD 23.5).

Table 1 Baseline characteristics of the total group of patients and patients available at 1and 6-year follow-up.

Baseline characteristic	**Total group (n=328)**	**Available at 1 year follow-up (n=296)**	**Available at 6 year follow-up (n=183)**
General			
Age, mean ± SD in years	41.9 ± 15.7	42.3 ± 15.9	42.2 ± 15.2
Male, n (%)	185 (56.4)	165 (55.7)	102 (55.7)
Knee complaints			
History of traumatic knee complaints	86 (30.8)	80 (31.5)	48 (31.2)
History of non-traumatic knee complaints	124 (40.8)	111 (40.2)	63 (37.5)
Duration at consultation			
< 3 weeks, n (%)	252 (76.8)	226 (76.4)	134 (73.2)
3 weeks – 3 months, n (%)	58 (17.7)	53 (17.9)	40 (21.9)
3 months – 1 year, n (%)	18 (5.5)	17 (5.7)	9 (4.9)
Cause			
Sport activity, n (%)	137 (41.8)	125 (42.2)	75 (41.0)
Leisure activity, n (%)	102 (31.1)	90 (30.4)	53 (29.0)
Work related, n (%)	46 (14.0)	42 (14.2)	27 (14.8)
Traffic related, n (%)	43 (13.1)	39 (13.2)	27 (14.8)
Measures of severity			
Knee pain NRS (0-10), mean ± SD	4.5 ± 2.3	4.4 ± 2.3	4.4 ± 2.4
Lysholm knee function score (0-100), mean ± SD	65.1 ± 21.0	66.2 ± 19.7	64.1 ± 22.2
WOMAC index (0-100), mean ± SD	33.4 ± 23.5	32.7 ± 22.9	32.8 ± 22.7

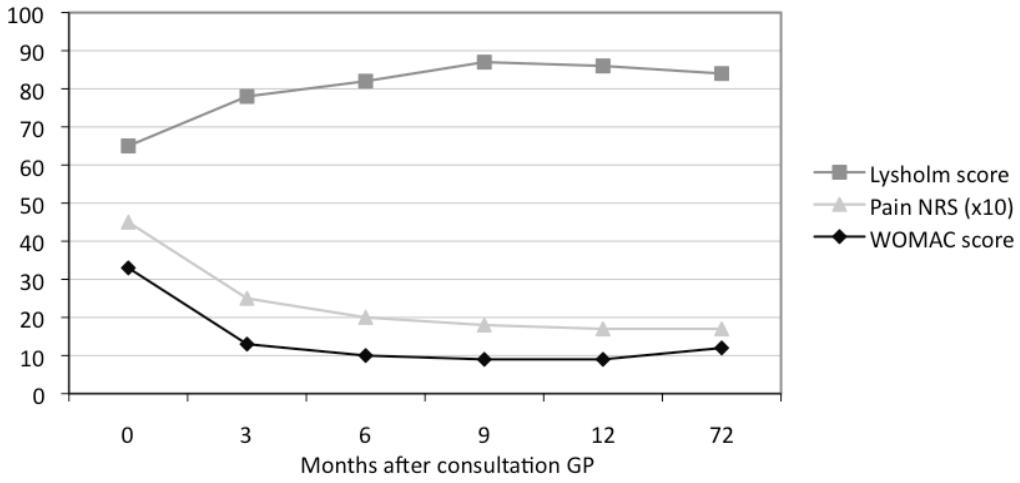
At 1-year follow-up 296 patients (90.2%) were still available for the study. At 6-year follow-up, 160 patients (48.8%) completed the questionnaire and 23 patients (7.0%) reported their experienced recovery of their knee complaints by telephone, resulting in 183 patients (55.8%) still available for the study. The patients available at 1 and 6-year follow-up showed no clinically relevant differences compared with the total study population at baseline regarding baseline age, gender, knee complaints, pain score (NRS), Lysholm score and WOMAC index (Table 1). Also, patients available at 6-year follow-up showed no significant difference compared with those available at 1-year follow-up regarding their perceived recovery at 1-year follow-up (OR 0.88, 95% CI 0.53-1.48). Reasons for no longer participating were lack of time and/or lack of interest (n=69, 47.6%), being inaccessible because of changing address and/or telephone number (n=56,

38.6%), or personal circumstances (n=2, 1.4%); in addition, 5 patients (3.4%) died during the follow-up period and for 13 patients (9.0%) no reason was available.

Course and prognosis

Figure 1 presents the course of the total group regarding mean knee pain severity (NRS), mean Lysholm knee score and the mean WOMAC index over the 6 years of follow-up. The mean pain score, and both the mean Lysholm knee score and mean WOMAC index showed the largest improvement in the first 3 months after consultation. The improvement of pain and WOMAC score in the first 3 months allows to make a significant discrimination ($p<0.05$) between patients with persistent knee complaints and those who were recovered at 6-year follow-up. Of those with persistent knee complaints at 6-year follow-up, mean pain severity, mean Lysholm knee score and mean WOMAC index had deteriorated at 1-year follow-up.

Figure 1 Course of knee complaints (mean scores) of the total group.



Of the 296 patients available at 1-year follow-up, 81 (27.4%) reported persistent knee complaints. At 1-year follow-up, the mean knee pain severity of these patients with persistent knee complaints (NRS) was 3.4 (SD 2.3), their mean Lysholm knee score was 73.5 (SD 16.2) and their mean WOMAC index was 18.7 (SD 16.4). Compared with the mean WOMAC index, some scores were higher on the stiffness domain, and very similar scores were found on the pain and physical function domain (Table 2). Patients who reported to be recovered at 1-year follow-up had a mean recovery period of 6.3 (SD 10.5) months.

Of the 183 patients available at 6-year follow-up, 60 (32.8%) reported persistent knee complaints. There was a positive relationship between having persistent knee complaints at 1-year follow-up and having persistent knee complaints at 6-year follow-up (OR 11.0, 95% CI 5.0-24.2). Compared with baseline, the kind of knee complaints had changed to

another type of complaint of the same knee in 4 patients (8.0%), 37 patients (74.0%) had exactly the same knee complaints, and 9 patients (18.0%) had the same complaints combined with another type of knee complaint. In this group mean knee pain severity (NRS) was 3.6 (SD 2.2), mean Lysholm knee score was 68.8 (SD 16.0) and the mean WOMAC index was 26.6 (SD 20.2). Compared with the mean WOMAC index, there were some higher scores on the stiffness domain, and some scores were almost equal on the pain and physical function domain (Table 2). Patients who reported to be recovered at 6-year follow-up had a mean recovery period of 7.4 (SD 13.1) months.

Table 2 Characteristics of patients with persistent knee complaints at 1 and 6-year follow-up.

Characteristic	**1 year (n=71)***	**6 year (n=56)***
Kind of knee complaints compared with baseline		
Other complaints, n (%)	-	4 (8.0)
Same complaints, n (%)	-	37 (74.0)
Same complaints and other complaints, n (%)	-	9 (18.0)
Measures of severity		
Pain complaints (KSS) (0-7), mean ± SD	3.8 ± 1.7	4.5 ± 1.5
Knee pain (0-10), mean ± SD	3.4 ± 2.3	3.6 ± 2.2
Lysholm knee function score (0-100), mean ± SD	73.5 ± 16.2	68.8 ± 16.0
WOMAC index (0-100), mean ± SD	18.7 ± 16.4	26.6 ± 20.2
WOMAC pain (0-100), mean ± SD	17.7 ± 16.1	28.9 ± 20.1
WOMAC stiffness (0-100), mean ± SD	24.5 ± 23.7	37.5 ± 26.7
WOMAC physical function (0-100), mean ± SD	18.3 ± 17.2	24.2 ± 20.7

* Number of patients with persistent knee complaints differ, because not all patients available at these follow-up times filled out the 1 and 6-year questionnaire.

Of the subgroup of 185 patients without a history of non-traumatic knee complaints available at 1-year follow-up, 39 (21.1%) reported persistent knee complaints at 1-year follow-up. At 6- year follow-up, 29 of the 120 available patients at 6-year follow-up without a history of non-traumatic knee complaints (24.2%) reported persistent knee complaints. Patients without a history of non-traumatic knee complaints who were recovered at 6-year follow-up had a mean recovery period of 7.6 (SD13.6) months.

Of the subgroup of 108 patients aged 12-35 years available at 1-year follow-up, 17 (15.7%) reported persistent knee complaints at 1-year follow-up. Of the 188 patients aged ≤ 36 years available at 1-year follow-up, 64 (34.0%) reported persistent knee complaints at 1-year follow-up. At 6-year follow-up, 13 of the 62 available patients aged 12-35 years (21.0%) and 47 of the 121 available patients aged ≥ 36 years (38.8%) reported persistent knee complaints. The mean recovery period of patients who were recovered at 6-year follow-up was 7.8 (SD13.0) months for patients aged 12-35 years and 7.1 (SD13.3) months for patients aged ≥ 36 years.

Table 3 Univariable association between baseline characteristics and persistent knee symptoms at 1- and 6-year follow-up.

Characteristic	**Univariable 1 year (n=296)**			**Univariable 6 year (n=183)**		
	Pooled OR	**Pooled 95% CI**	**Pooled Sig**	**Pooled OR**	**Pooled 95% CI**	**Pooled Sig**
Patient characteristics						
Age	1.03	1.01-1.05	0.00*	1.04	1.01-1.06	0.00*
Female gender	1.24	0.74-2.07	0.41	0.70	0.37-1.31	0.26
Body Mass Index > 27	1.89	1.12-3.19	0.02*	3.30	1.72-6.32	0.00*
Low/middle education level	1.70	0.99-2.93	0.06*	1.65	0.87-3.13	0.13*
Co morbidity skeletal system	1.32	0.79-2.23	0.29	1.98	1.05-3.73	0.04*
Non-skeletal co morbidity	1.49	0.82-2.70	0.19*	2.14	0.98-4.69	0.06*
Kinesiofobie (Tampa>37)	1.41	0.84-2.36	0.20*	1.53	0.80-2.90	0.20
Poor mental health (SF-36 <50)	1.69	0.54-5.27	0.36	1.31	0.22-7.92	0.77
Poor general health (SF-36 <50)	2.64	0.93-7.52	0.07*	2.37	0.68-8.34	0.18*
Paid employment (>8 hours/wk)	0.57	0.33-0.99	0.04*	1.13	0.55-2.34	0.73
Sport participation	0.77	0.44-1.34	0.33	0.58	0.29-1.15	0.12*
Mechanism and symptom characteristics						
Trauma during sport	0.69	0.40-1.18	0.18*	0.63	0.31-1.27	0.20*
Fall on the knee	1.19	0.65-2.16	0.57	1.24	0.59-2.60	0.57
Weight bearing on knee	1.06	0.56-2.02	0.86	1.22	0.61-2.46	0.57
Rotational trauma	0.74	0.35-1.53	0.40	0.92	0.41-2.09	0.84
Foot/leg blocked	1.09	0.63-1.87	0.77	0.77	0.38-1.57	0.47
Immediate pain at trauma	0.75	0.43-1.31	0.31	0.78	0.40-1.52	0.47
Immediate effusion after trauma	0.73	0.43-1.26	0.26	0.85	0.44-1.64	0.62
Popping sensation at trauma	1.47	0.85-2.54	0.17*	1.78	0.87-3.63	0.11*
Continuation activity impossible	1.15	0.68-1.95	0.59	1.01	0.54-1.91	0.97
Pain (11point scale)	1.03	0.92-1.15	0.65	1.01	0.88-1.15	0.90
Self report warm knee	1.27	0.76-2.12	0.36	0.95	0.51-1.80	0.88
Self report swollen knee	1.58	0.93-2.69	0.09*	1.26	0.65-2.45	0.49
Self report crepitus knee	1.35	0.80-2.29	0.26	3.28	1.65-6.49	0.00*
Locking of the knee (Lysholm)	0.95	0.49-1.85	0.89	1.02	0.45-2.32	0.97
Instability of the knee (Lysholm)	1.10	0.64-1.90	0.73	1.33	0.69-2.57	0.40
History of traumatic knee complaints	1.48	0.82-2.68	0.19*	1.56	0.75-3.22	0.23*
History of non-traumatic knee complaints	1.94	1.14-3.28	0.01*	2.96	1.53-5.73	0.00*
Nuisance in work/study/household	1.41	0.79-2.51	0.24	1.22	0.61-2.43	0.58
Limitation and pain during daily function	0.88	0.50-1.54	0.65	1.41	0.69-2.88	0.34
Physical examination						
Floating patella	0.52	0.30-0.91	0.02*	0.67	0.34-1.32	0.24
Pain at active flexion	0.97	0.57-1.64	0.91	1.40	0.73-2.71	0.32
Pain at passive flexion	0.97	0.57-1.67	0.92	1.45	0.70-2.98	0.32
Pain at active extension	1.02	0.49-2.14	0.96	1.25	0.60-2.61	0.55
Pain at passive extension	1.02	0.55-1.90	0.96	0.74	0.38-1.46	0.38
Laxity valgus stress test 30°	0.86	0.50-1.48	0.59	0.88	0.46-1.68	0.69
Laxity varus stress test 30°	0.87	0.49-1.55	0.63	1.63	0.86-3.09	0.13*
Laxity anterior drawer test	1.70	1.00-2.86	0.05*	1.67	0.84-3.30	0.14*
Effusion fossa poplitea	1.61	0.91-2.84	0.10*	1.26	0.64-2.47	0.50
Mc Murray meniscal test	1.04	0.52-2.10	0.91	1.18	0.52-2.71	0.69
Appley grinding test	1.04	0.55-1.94	0.91	0.70	0.36-1.36	0.29
Aply traction test	1.03	0.45-2.35	0.94	1.32	0.42-4.10	0.61

* Selected in ≥ 3 out 5 imputed databases ($p \leq 0.20$)

Prognostic factors

Table 3 presents the univariate associations between baseline characteristics and persistent knee symptoms at 1 and 6-year follow-up.

At 1-year follow-up the patient characteristics age, BMI > 27, low/middle education level, non-skeletal co-morbidity, kinesiophobia, poor general health and paid employment < 8 h/week were associated with persistent knee complaints. Of the symptom characteristics trauma during sport, popping sensation at trauma, self-reported swollen knee, history of traumatic knee complaints and history of non-traumatic knee complaints were associated. From physical examination, absence of floating patella, laxity on the anterior drawer test and effusion of the fossa poplitea were associated.

Table 4 Multivariable associations between baseline characteristics and persistent knee complaints at 1-year follow-up.

Model	**Multivariable**			
	Pooled OR	**Pooled 95% CI**	**Pooled p-value**	**AUC**
Patient characteristics				0.65
Age	1.03	1.01-1.05	0.00	
Poor general health (SF-36 <50)	3.10	1.18-8.16	0.02	
Symptom characteristics				0.58
History of non-traumatic knee complaints	1.94	1.14-3.28	0.01	
Physical examination				0.64
Floating patella	0.48	0.27-0.84	0.01	
Laxity anterior drawer test	1.68	0.98-2.88	0.06	
Effusion fossa poplitea	1.68	0.94-3.03	0.08	
Patient characteristics and symptom characteristics				0.68
Age	1.03	1.01-1.05	0.00	
Poor general health (SF-36 <50)	3.00	1.08-8.31	0.04	
History of non-traumatic knee complaints	1.92	1.11-3.30	0.02	
Patient characteristics, symptom characteristics and physical examination				0.72
Age	1.04	1.02-1.06	0.00	
Poor general health (SF-36 <50)	4.11	1.37-12.35	0.01	
History of non-traumatic knee complaints	1.86	1.06-3.25	0.03	
Floating patella	0.46	0.25-0.85	0.01	
Laxity anterior drawer test	2.31	1.29-4.15	0.01	

At 6-year follow-up the patient characteristic age, BMI > 27, low/middle education level, co-morbidity of the skeletal system, non-skeletal co morbidity, poor general health and sport participation were associated with persistent knee complaints. Of the symptom characteristics trauma during sport, popping sensation at trauma, self-reported crepitus of the knee, history of traumatic knee complaints and history of non-traumatic knee

complaints were associated. From physical examination, laxity on the varus stress test, and 30° laxity on the anterior drawer test were associated.

Table 4 presents the multivariate associations between baseline characteristics and persistent knee complaints at 1-year follow-up. The patient characteristics age and poor general health showed an independent association with persistent knee complaints at 1-year follow-up, with an AUC of 0.65. From the symptom characteristics only history of non-traumatic knee complaints remained in the model, with an AUC of 0.58. From physical examination absence of floating patella, laxity on the anterior drawer test and effusion of the fossa poplitea were independently associated, with an AUC of 0.64. Adding the symptom characteristics to the patient characteristics the AUC increased by 0.03 to 0.68. All three variables remained in the model ($p<0.10$). Adding items from physical examination increased the AUC by 0.04 to 0.72. Effusion of the fossa poplitea was eliminated from the model ($p>0.10$).

Table 5 Multivariable associations between baseline characteristics and persistent knee complaints at 6-year follow-up.

Model	**Multivariable**			
	Pooled OR	**Pooled 95% CI**	**Pooled p-value**	**AUC**
Patient characteristics				0.73
Age	1.03	1.01-1.05	0.02	
Body Mass Index > 27	2.86	1.44-5.68	0.00	
Non-skeletal co morbidity	2.40	1.04-5.57	0.04	
Symptom characteristics				0.70
Self report crepitus knee	2.22	1.38-3.59	0.00	
History of non-traumatic knee complaints	2.28	1.15-4.53	0.02	
Physical examination				0.57
Laxity anterior drawer test	1.67	0.84-3.30	0.14	
Patient characteristics and symptom characteristics				0.79
Age	1.04	1.02-1.07	0.00	
Body Mass Index > 27	2.18	1.03-4.64	0.04	
Non-skeletal co morbidity	2.55	0.98-6.64	0.06	
Self report crepitus knee	2.54	1.51-4.29	0.00	
History of non-traumatic knee complaints	2.22	1.03-4.78	0.04	
Patient characteristics, symptom characteristics and physical examination				0.82
Age	1.05	1.02-1.08	0.01	
Body Mass Index > 27	2.23	1.04-4.80	0.04	
Non-skeletal co morbidity	2.53	0.95-6.75	0.06	
Self report crepitus knee	2.60	1.53-4.41	0.00	
History of non-traumatic knee complaints	2.27	1.04-4.94	0.04	
Laxity anterior drawer test	2.59	1.12-5.99	0.03	

Table 5 presents the multivariate associations between baseline characteristics and persistent knee complaints at 6-year follow-up. The patient characteristic age, BMI > 27 and non-skeletal co-morbidity showed an independent association with persistent knee complaints at 6-year follow-up, with an AUC of 0.73. From the symptom characteristics self-reported crepitus of the knee and history of non-traumatic knee complaints were independently associated, with an AUC of 0.70. From physical examination only laxity on the anterior drawer test remained in the model, with an AUC of 0.57. Adding the symptom characteristic to the patient characteristics increased the AUC by 0.06 to 0.79. All five variables remained in the model ($p<0.10$). Adding items from physical examination increased the AUC by 0.03 to 0.82. All six variables remained in the model ($p<0.10$).

Repeating the univariate and multivariate analysis for assessing prognostic factors for persistent knee complaints at 1 and 6-year follow-up for the subgroup without a history of non-traumatic knee complaints and the subgroup aged 12-35 years, yielded results similar to those for the total group (data not shown). However, due to lack of power, some variables that were significant in the total group were dropped from the model in these subgroups.

Discussion

The present study investigated the 1 and 6-year course and prognostic factors of traumatic knee complaints in adolescents and adults in general practice.

The percentage of patients with persistent knee complaints at 1 and 6-year follow-up was similar, i.e. 27% and 33%, respectively. Patients without a history of non-traumatic knee complaints and/or aged 12-35 years reported less frequent persistent knee complaints compared with patients with a history of non-traumatic knee complaints and/or aged ≥ 36 years, at both 1 and 6-year follow-up.

Of patients reporting persistent knee complaints at 1-year follow-up, 71% also reported these complaints at 6-year follow-up. Of patients who reported to be recovered at 1-year follow-up, 18% reported persistent knee complaints at 6-year follow-up (18%); the reasons for this could be due to recurrent trauma, other co-existing knee pathology (e.g. OA), and/or developing OA of the knee. It is known that traumatic knee complaints are associated with the development of OA of the knee within 10-20 years after knee injury.[21] However, our follow-up period of 6 years might be too short to detect OA of the knee due to knee trauma. Nevertheless, many patients in the present study reported a history of non-traumatic knee complaints and/or were aged ≥ 36 years. Therefore, their knee injury may have accelerated the development or progression of OA, because some traumatic knee lesions are associated with progression of knee OA.[22,23] In a subgroup of our traumatic patients, at 1-year follow-up progression and new onset of signs of OA of the injured knee is visible on MRI.[24] We plan to investigate the relationship between

traumatic knee complaints and the development/progression of OA of the knee in this subgroup of patients at 6-year follow-up.

The patients who reported recovery at 6-year follow-up, had a mean recovery period of 7.4 months. This recovery period was similar for patients without a history of non-traumatic knee complaints and patients aged 12-35 years, compared to patients with a history of non-traumatic knee complaints and patients aged ≥ 36 years. Comparing our results with the assumed prognosis mentioned in the Dutch guideline 'Traumatic knee complaints in general practice' [2] (i.e. that most patients with a traumatic knee complaints in general practice will be complaint free in a few weeks and can resume daily activities) allows to conclude that this consensus-based prognosis is somewhat overestimated for patients with a traumatic knee complaint in general practice.

Prognostic factors independently associated with persistent knee complaints at 1 year follow-up were age, poor general health, history of non-traumatic knee complaints, absence of floating patella and laxity on the anterior drawer test. At 6-year follow-up, age, BMI > 27, non-skeletal co-morbidity, self-reported crepitus of the knee, history of non-traumatic knee complaints and laxity on the anterior drawer test were independently associated with persistent knee complaints. The general patient characteristics associated with persistent knee complaints at 1 and 6-year follow-up were as expected, and are also associated with persistent knee complaints in patients with non-traumatic knee complaints [25-28] and/or in patients with other musculoskeletal disorders.[17]

Other prognostic factors need more explanation. Presence of history of non-traumatic knee complaints as a prognostic factor for persistent knee complaints at 1 and 6-year follow-up, and self-reported crepitus of the knee as a prognostic factor for persistent knee complaints at 6-year follow-up, indicate that patients with co-existing knee complaints (most likely OA) had a higher risk of persistent knee complaints. Absence of floating patella was associated with persistent knee complaints at 1-year follow-up only; perhaps intra-articular effusion contributes to a better resilience of the knee injury. Laxity on the anterior drawer test was associated with persistent knee complaints at 1 and 6-year follow-up. This could indicate that patients with anterior cruciate lesions lesion have a worse prognosis compared to other patients. However, this is in contrast to Wagemakers et al. who reported on a subgroup of patients with traumatic knee complaints within this cohort (n=134).[29] Besides filling out questionnaires and undergoing a physical examination, these patients underwent an additional MRI of their knee at baseline; the results showed no significant relationship between the type of lesion seen on baseline MRI and perceived recovery at 1-year follow-up. Perhaps the study population was too small to detect a different prognosis between anterior cruciate lesions and other lesions, or the type of anterior cruciate lesion and/or remaining function of the anterior cruciate after lesion might be important for recovery. Boks et al. summarized the little information available on the natural course of traumatic knee

complaints from secondary care and concluded that in most patients with cruciate lesions, improvement was reported within 3 months to 1 year but that doubt remains about functional recovery.[3]

One limitation of the present study is the relatively large loss to follow-up (44.2%) at 6-year follow-up. This was probably due to the lack of contact between the investigators and patients between the 1 and 6-year follow-up (some changed address, and some lost interest in the study). However, the patients available at 1 and 6-year follow-up did not appear to be a selected group of patients.

Another limitation was that we had a heterogeneous study population with all kinds of traumatic knee complaints. However, all patients included in this study suffered from a knee injury with a clearly-defined trauma mechanism. Investigating the course and prognostic factors by separate diagnoses might be preferable, but this requires a larger study population and a standardized diagnosis at baseline. However, in daily practice the GP generally does not have a clear diagnosis in patients with a traumatic knee complaint.

Also, many patients reported previous knee complaints and/or co-existing knee complaints (e.g. OA), which influenced the results of our study. However, this study represents the population of patients with traumatic knee complaints seen in general practice. Moreover, because the prognostic factor 'history of non-traumatic knee complaints' is included in the multivariate analysis, all other prognostic factors are independently associated with previous knee complaints and/or co-existing knee complaints. In addition, repeating the analysis in patients without a history of non-traumatic knee complaints yielded almost identical results.

The present results should be validated in similar studies with a long-term follow-up in primary care; preferably, the natural course and prognostic factors of these traumatic knee complaints should be investigated for separate diagnoses. Such studies will enable GPs to inform their patients in a more valid way, and perhaps help identify patients at high risk of developing persistent knee complaints and those which need referral to secondary care or who require specific treatment.

Conclusions

At 1 and 6-year follow-up, traumatic knee complaints in adolescents and adults in general practice still affect nearly one third of the patients. Patients who recover during follow-up had a mean recovery period of 7.4 months. Having persistent knee complaints at 1-year follow-up is an important predictor for having persistent knee complaints at 6-year follow-up. In addition, various prognostic factors assessed at baseline are associated with persistent knee complaints at 1 and 6-year follow-up. Patients without a history of non-traumatic knee complaints and/or aged 12-35 years seem to have a better prognosis. However, about 40% of patients with a traumatic knee complaint seen in general practice suffer from a history of non-traumatic knee complaints and approximately 60% are aged ≥

36 years. More research is needed to confirm these results, to investigate the role and/or development of OA, and to investigate how to improve the prognosis in these patients.

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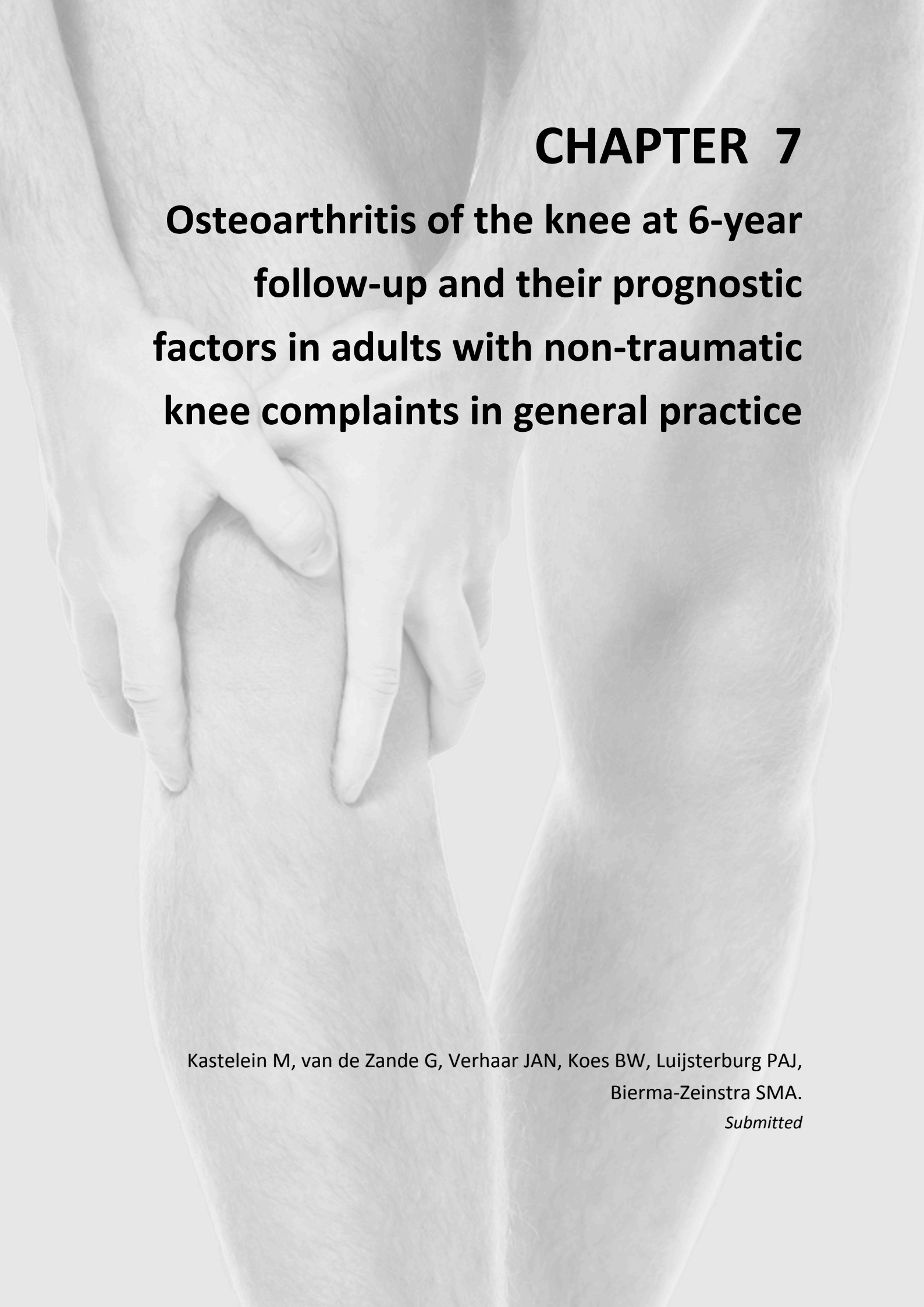

CHAPTER 7

Osteoarthritis of the knee at 6-year follow-up and their prognostic factors in adults with non-traumatic knee complaints in general practice

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Submitted

Abstract

Objective: To investigate how to identify which patients with knee complaints in general practice will develop knee osteoarthritis (OA) at 6-year follow-up.

Methods: Adults (aged >35 years) with incident non-traumatic knee complaints (n=549) were followed for 6 years for the presence of knee OA, according to the clinical American College of Rheumatology (ACR) criteria. In addition, at 6-year follow-up the presence of knee OA was identified based on a radiograph and the clinical & radiographic ACR criteria. Multivariable logistic regression analysis was used to identify baseline prognostic factors associated with the presence of knee OA at 6-year follow-up and the area under the receiver-operating curve (AUC) was calculated.

Results: According to the clinical ACR criteria, at baseline and at 1 and 6-year follow-up, 63%, 44% and 39% of the patients suffered from knee OA, respectively. In total, 45% of the patients switched from ACR positive/negative at the different follow-up points. Also, at 6-year follow-up, 39% and 31% of the patients suffered from knee OA based on the radiographs and the clinical & radiographic ACR criteria, respectively. Of the clinical ACR criteria, only age was independent significantly related with clinical and radiographic knee OA at 6-year follow-up. In addition, a body mass index of >27, self-reported swollen knee, history of non-traumatic knee complaints and self-reported instability of the knee were also independent significantly related with clinical and radiographic knee OA (AUC of 0.81). Results from physical examination had no additional value.

Conclusions: Of patients with non-traumatic knee complaints seen in general practice, 31%-39% suffer from knee OA at 6-year follow-up. The clinical ACR criteria for knee OA are not appropriate for predicting which patients with knee complaints in general practice will develop knee OA at follow-up. For this, five baseline patient and symptom characteristics seemed more appropriate.

Introduction

General practitioners (GPs) are frequently consulted by patients with non-traumatic knee complaints. The incidence of these complaints reported in Dutch general practice is about 23 per 1000 patients per year.[1] Osteoarthritis (OA) of the knee is a common disorder among these patients with knee complaints, especially in older persons.[2]

Predicting which patients with knee complaints in general practice will develop knee OA at follow-up may be important for diagnosis and management of the GP. Also, this may promote the development and testing of interventions for OA in an early stage, with the aim to diminish the burden of knee OA.

However, diagnosis of knee OA in general practice is difficult due to lack of a gold standard; moreover, most of the methods used to diagnose knee OA are not appropriate for diagnosis in an early stage. For example, because radiographic changes are insensitive (particularly with early-stage disease) and correlate poorly with symptoms,[3] a radiograph of the knee is not recommended in general practice for diagnosis of knee OA.[4] Therefore, diagnosis is mainly based on history taking and physical examination, even though clinical criteria for this are lacking.[4]

In 2010 the EULAR OA Task Force published a consensus guideline on the clinical diagnosis of knee OA.[5] However, the three symptoms and three clinical signs described in this guideline reflect symptoms and signs of advanced knee OA and are therefore not applicable in early diagnosis of knee OA. Earlier, the American College of Rheumatology (ACR) developed three criteria sets for classifying knee OA, i.e. the 'clinical & laboratory ACR criteria', the 'clinical & radiographic ACR criteria' and the 'clinical ACR criteria'.[6] However, because these criteria were developed for research and mainly distinguish OA from rheumatoid arthritis,[7,8] their usefulness in daily general practice is also doubtful.

The present study investigates how to identify which patients with knee complaints in general practice will develop knee OA at follow-up, so that this information can be used in the future to improve their prognosis. Also examined is the presence of knee OA and its relation with an unfavorable outcome at 6-year follow-up and with other baseline prognostic factors.

Methods

Design

The present study was conducted within the HONEUR network (which includes 40 GPs) established by the department of General Practice at Erasmus Medical Center Rotterdam.[9] It is part of a prospective, observational cohort study (n=1068) in which consecutive patients visiting their GP with a new episode of knee complaints were initially followed for 1 year.[9] Because of the high percentage of patients with persistent knee complaints at 1-year follow-up, the follow-up was extended to 6 years. At baseline, new knee complaints were defined as episodes of complaints presented to the GP for the first

time. Recurrent symptoms for which the GP was not consulted within the past 3 months were also considered as new complaints. Traumatic knee complaints were defined as those caused by a sudden impact or wrong movement within 1 year before consulting the GP. All other knee complaints were considered as non-traumatic knee complaints.

Patients were eligible for the present study if they were aged >35 years and had consulted their GP for non-traumatic knee complaints. Exclusion criteria at baseline were knee symptoms that required urgent medical attention (e.g. fractures, infection), patients with malignancies, neurologic disorders or musculoskeletal diseases (e.g. Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), as well as patients with insufficient understanding of the Dutch language and/or incapable of understanding the ramifications of participation.

The study protocol was approved by the local Medical Ethics committee.

Data collection

Patients filled out a questionnaire at baseline, and at 3, 6 and 9 months and 1 year and 6-year follow-up. Data on the following domains were collected and all assessed at baseline and at follow-up (unless otherwise stated):

- Demographics: age, gender, composition of household, education level and comorbidity (all assessed at baseline only).
- Knee complaints: history of previous knee injuries or operations, duration and recurrence of knee complaints, and knee pain on an 11-point numeric rating scale (NRS); knee pain and function assessed with the Knee Society Score (KSS) scale [10] and the Lysholm Knee Scoring Scale; [11-13] knee pain, stiffness and function assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [14,15] and the Knee Injury Osteoarthritis Outcome Score (KOOS) [16] (the KOOS was only assessed at 6-year follow-up).
- Knee loading: daily activities and physical exercise, data on impact of the knee complaint as hindrance, and sick leave from daily activities.
- Health-related quality of life assessed with the Medical Outcomes Study Short-Form 36 Health Survey (SF-36).[17,18]
- Coping assessed with the Tampa Scale for Kinesiophobia.[19,20]
- Treatment: advice given by the GP, knee medication, visits to healthcare professionals, and operations.

For all scores (except the Lysholm scale and the SF-36), lower scores represent better function/outcome.

In addition, at 1 and 6-year follow-up the questionnaire also collected data on patients' experienced recovery measured on a 7-point Likert scale, ranging from completely recovered to worse than ever. Persistent knee complaints were defined as knee complaints that were "slightly improved", "not changed", "slightly worsened", "much worsened" or "worse than ever". Clinically important recovery was defined as knee

complaints that were “completely recovered” or “much improved”. Additionally, unfavorable outcome was defined as having persistent knee complaints at 6-year follow-up, or having undergone knee replacement surgery during this period. Favorable outcome was defined as experiencing clinical recovery of knee complaints at 6-year follow-up and not having undergone knee replacement surgery in this period.

A standardized 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 effusion, crepitations, passive range of motion in flexion/extension, meniscal tests, and knee stability tests.[21,22] At 6-year follow-up a limited physical examination was performed and focused on whether there was bony swelling of the joint and tenderness of the joint space.

At 6-year follow-up an additional anterior posterior (AP) radiograph of the index knee was made. However, patients who had undergone a radiographic examination of their knee in the past 2 years did not have to undergo this examination to avoid additional radiographic exposure; in this case, after permission from the patient, the researchers asked the hospital for these radiographic results.

To define knee OA we used three different definitions, i.e. ‘clinical OA’, ‘radiographic OA’ and ‘clinical & radiographic OA’.

Using data extracted from the questionnaires and physical examination we assessed clinical OA according to the clinical ACR criteria at baseline, and at 1 and at 6-year follow-up.[6] According to these criteria, knee OA is defined as having knee pain plus at least 3 of the following 6 items: age >50 years, stiffness <30 min, crepitus, bony tenderness, bony enlargement, or no palpable warmth.

To assess radiographic OA at 6-year follow-up, we scored the radiograph according to the classical Kellgren and Lawrence (K&L) grading (0-4) system.[23]

- Grade 0: No OA
- Grade 1: Doubtful: doubtful narrowing of joint space and possible osteophytic lipping
- Grade 2: Mild: definite osteophytes and possible narrowing of joint space
- Grade 3: Moderate: multiple osteophytes, definite narrowing of joint space, some sclerosis plus possible deformity of bone ends
- Grade 4: Severe: large osteophyte, marked narrowing of joint space, severe sclerosis plus definite deformity of bone ends.

Two trained readers independently evaluated the radiographs of the knee, unaware of the clinical status of the patients. Whenever the K&L grade differed, the two readers met to evaluate the radiograph together and a consensus score was determined. Radiographic OA of the knee was defined as present when the K&L grade was ≥ 2.

Using data extracted from the questionnaire and radiograph we assessed clinical & radiographic OA according to the ACR criteria at 6-year follow-up.[6] According to these criteria, knee OA is defined as having knee pain plus osteophytes plus at least 1 of the following 3 items: age>50 years, stiffness <30 min, or crepitus.
Clinical OA, radiographic OA and clinical & radiographic OA were always defined as present in all patients having undergone knee replacement surgery during the follow-up period.

Statistical analysis

Descriptive statistics were used to describe patient characteristics, complaint characteristics, severity of complaints, presence of unfavorable outcome and the presence of knee OA according to the three definitions. Odds ratios (OR) were calculated for the association between the three definitions of knee OA at 6-year follow-up and an unfavorable outcome at 6-year follow-up.
Univariate logistic regression analysis was performed to determine which baseline variables from history taking and physical examination are associated with knee OA of the index knee, expressed as OR. In case of bilateral symptoms at baseline, the index knee was determined as the knee with the most severe symptoms at baseline; in case of equal severity of symptoms of both knees at baseline the right knee was used for the analysis. The baseline variables used for the univariate analysis are based on literature [24] and clinical relevance. The variables were divided into three domains: patient characteristics, complaint characteristics and physical examination findings. To enable ease of interpretation of prognostic factors in a clinical setting, we chose to dichotomize most variables. Imputation of missing data was carried out by multiple imputation, creating a total of 5 imputed databases, which is a common number of databases to end up with [25-27] Univariate analysis was performed separately on all 5 imputed databases. The variables showing a univariate association with an unfavorable outcome on at least 3 of the 5 imputed databases ($p \leq 0.10$), were analyzed in a multivariable (backward) logistic regression model (entry 0.05, removal 0.10). Also, multivariate analysis was performed separately on all 5 imputed databases. If a variable was selected in at least 3 of the 5 imputed databases in multivariate analysis, it was included in the final model (enter method) and the area under the receiver operating curve (AUC) was calculated to determine the discriminative ability of the logistic regression model.
First, separate models for patient characteristics, complaint characteristics and physical examination findings were constructed. Subsequently, the remaining variables of each domain were combined to construct a model of patient and complaint characteristics, and a model of patient and complaint characteristics together with physical examination findings, to evaluate the additional value of the different domains. All models were adjusted for gender and age.

This logistic regression analysis was performed separately for all three definitions of knee OA. Analyses were performed with SPSS version 17.02 (SPSS Inc., Chicago, Ill, USA).

Results

Table 1 presents the baseline characteristics of the 549 study patients; their mean age was 53.8 (SD 11.4) years and 50.5% was male. According to the clinical ACR criteria for knee OA[6] assessed at baseline, 346 patients (63.0%) suffered from OA of the knee. At baseline, 386 patients (70.3%) had knee complaints for ≤ 3 months, 172 patients (31.3%) had bilateral knee complaints, and 231 patients (42.1%) reported recurrent knee complaints. At baseline, the mean knee pain severity (measured on an 11-point NRS) was 4.3 (SD 2.1) and the mean WOMAC score was 28.5 (SD 19.7).

Table 1 Baseline characteristics of the total study group and of those available for analysis at 1 and 6-year follow-up.

Baseline characteristics	Total group (n=549)	Available at 1- year follow-up (n=473)	Available at 6- year follow-up (n=285)	Agreed to radiographic examination (n=147)
General				
Age in years, mean ± SD	53.8 ± 11.4	53.7 ± 11.2	53.2 ± 10.7	54.2 ± 10.0
Male, n (%)	277 (50.5)	239 (50.5)	153 (53.7)	79 (53.7)
Knee OA				
Based on clinical ACR criteria[20], n (%)	346 (63.0)	295 (62.4)	170 (59.6)	94 (64.0)
Knee complaints				
Duration at consultation < 3 months, n (%)	386 (70.3)	338 (71.5)	203 (71.2)	101 (68.7)
Bilateral, n (%)	172 (31.3)	140 (29.6)	79 (27.7)	47 (32.0)
Recurrent, n (%)	231 (42.1)	200 (42.3)	127 (44.6)	76 (51.7)
Severity of complaints				
Knee pain (0-10), mean ± SD	4.3 ± 2.1	4.3 ± 2.1	4.3 ± 2.1	4.4 ± 2.2
WOMAC index (0-100), mean ± SD	28.5 ± 19.7	28.0 ± 19.4	28.9 ± 20.4	28.8 ± 19.4

At 1-year follow-up 473 patients (86.2%) were available for analysis. At 6-year follow-up 285 of the patients (51.9%) were still available for analysis; of these, 147 (51.6%) also had an additional radiograph of their knee. Table 1 presents the characteristics of all these patients available at 1 and/or 6-year follow-up. The patients lost to follow-up showed no clinically relevant differences compared with those available at 1 and/or 6-year follow-up regarding baseline age, gender, diagnosis based on the clinical ACR criteria, knee complaints, severity of knee pain, and WOMAC index. Patients lost to follow-up also showed no significant differences compared with those available at 6-year follow-up regarding self-reported outcome at 1-year follow-up (OR 1.10, 95% CI 0.76-1.58). Reasons for no longer participating at follow-up were lack of time and/or lack of interest (n=121, 45.8%), being inaccessible due to change of address and/or telephone number (n=41,

15.5%) and/or personal circumstances (n=11, 4.2%); in addition, 23 patients (8.7%) had died during the follow-up period, and for 14 patients (5.3%) no reason was available. At follow-up, 54 patients (20.5%) did not give permission for any additional examinations (physical examination and radiograph) of their knee. Also, at 6-year follow-up 138 of the available patients (48.4%) did not give permission for a radiograph of their knee; for these latter patients, a recent radiograph of their knee was also not available.

Course according the clinical ACR criteria

At baseline 346 patients (63.0%) suffered from OA of the knee according to the clinical ACR criteria. At 1-year follow-up 207 patients (43.8%), and at 6-year follow-up 110 patients (38.6%), suffered from OA of the knee according to these criteria. Table 2 presents details on the number of ACR items positive and the diagnosis of knee OA based on these criteria at baseline, and at 1 and 6-year follow-up.

Table 2 Clinical ACR criteria at baseline, and at 1 and 6-year follow-up.

		Baseline (n=549)	At 1-year follow-up (n=473)	At 6-year follow-up (n=285)
Number of ACR items positive, n (%)				
0		21 (3.8)	149 (31.5)	126 (44.2)
1	**No OA**	56 (10.2)	33 (7.0)	11 (3.9)
2		126 (23.0)	83 (17.6)	39 (13.7)
3		168 (30.6)	100 (21.1)	38 (13.3)
4		124 (22.6)	76 (16.1)	38 (13.3)
5	**OA**	45 (8.2)	30 (6.3)	16 (5.6)
6		9 (1.6)	2 (0.4)	3 (1.1)
Knee replacement		0 (0.0)	0 (0.0)	14 (4.9)
Diagnosis osteoarthritis of the knee				
Based on clinical ACR criteria*, n (%)		346 (63.0)	207 (43.8)	110 (38.6)

***Clinical ACR Criteria**:

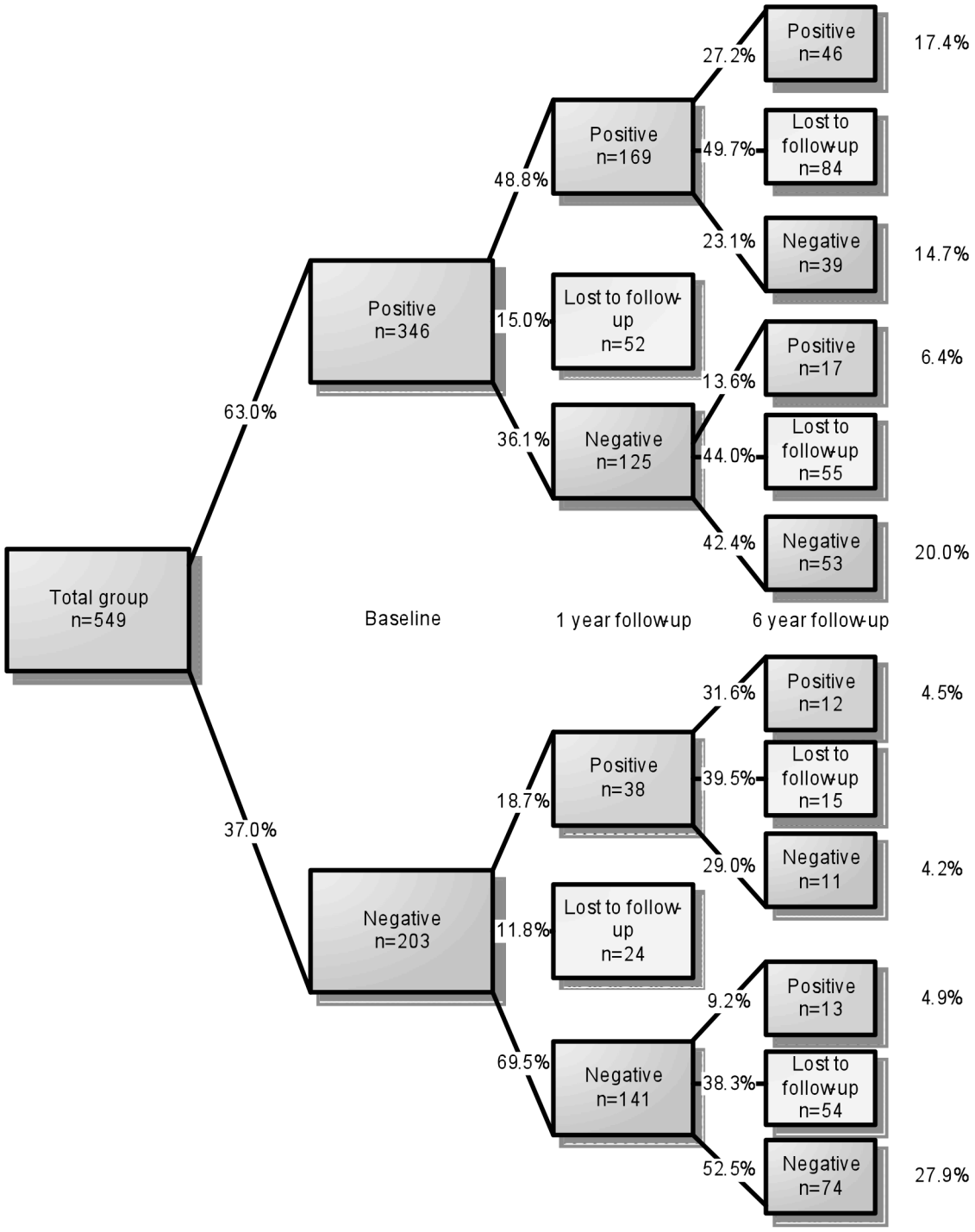
Knee pain plus at least 3 of the following:

1. Age >50 years
2. Stiffness <30 min
3. Crepitus
4. Bony tenderness
5. Bony enlargement
6. No palpable warmt

Figure 1 is a flowchart of the course of the patients according to the clinical ACR criteria at baseline, and at 1 and 6-year follow-up. In total, 46 patients (17.4%) were ACR positive according to these criteria at all follow-up moments; 12 patients (4.5%) were ACR negative at baseline but ACR positive at 1 and 6-year follow-up; and 13 patients (4.9%) were ACR negative at baseline and at 1-year follow-up but ACR positive at 6-year follow-

up. In total, 74 patients (27.9%) were ACR negative at all follow-up moments. The remaining 120 patients (45.3%) switched between ACR positive and ACR negative at the different follow-up times.

Figure 1 Flowchart showing the number of patients with clinical OA of the knee based on clinical ACR criteria at baseline, and at 1 and 6 years follow-up



Osteoarthritis of the knee

At 6-year follow-up, 110 of 285 patients (38.6%) suffered from OA of the knee according to the clinical ACR criteria, 57 of 147 patients (38.8%) according to the K&L score on the radiograph, and 45 of 147 patients (30.6%) according to the clinical & radiographic ACR criteria (Table 3). Of the 67 patients with clinical OA and with an available radiograph, 37 (55.2%) also had radiographic OA and 39 patients (58.2%) also had clinical & radiographic OA. Of the 80 patients without clinical OA, 60 patients (75.0%) also had no radiographic OA, and 74 patients (92.5%) also had no clinical & radiographic OA (data not shown).
In addition, clinical OA (OR 10.03; 95% CI 5.37-18.08), radiographic OA (OR 2.24; 95% CI 1.11-4.54) and clinical & radiographic OA (OR 7.57; 95% CI 2.94-19.50) were significantly related with an unfavorable outcome at 6-year follow-up (Table 3).

Table 3 Frequencies (Freq) of clinical and radiographic knee OA, and clinical & radiographic knee OA, at 6-year follow-up and their relation with unfavorable outcome at 6-year follow-up.

	Frequency	**Unfavorable outcome, n=135/n=84***		
	(%)	**-**	**+**	**OR (95% CI)**
Knee OA				
Clinical OA, n=285/n=147±	38.6	22	86	10.03 (5.57-18.08)
Radiographic OA, n=147	38.8	17	39	2.24 (1.11-4.54)
Clinical & radiographic OA, n=147	30.6	6	38	7.57 (2.94-19.50)

Clinical OA: based on clinical ACR criteria:
Knee pain plus at least 3 of the following:

1. Age >50 years
2. Stiffness <30 min
3. Crepitus
4. Bony tenderness
5. Bony enlargement
6. No palpable warmth.

Radiographic OA: based on Kellgren and Lawrence score ≥ 2:

Grade 0 No OA

Grade 1 Doubtful: doubtful narrowing of joint space and possible osteophytic lipping

Grade 2 Mild: definite osteophytes and possible narrowing of joint space

Grade 3 Moderate: multiple osteophytes, definite narrowing of joint space, some sclerosis + possible deformity of bone ends

Grade 4 Severe: large osteophytes, marked narrowing of joint space, severe sclerosis + definite deformity of bone ends

Clinical & radiographic OA: based on clinical and radiographic ACR criteria:
Knee pain + osteophytes plus at least 1 of the following:

1. Age >50 years
2. Stiffness <30 min
3. Crepitus

* n=135 in patients with clinical OA and n=84 in patients with radiographic & clinical and radiographic OA.
± n=285 for frequency and unfavorable outcome and n=147 for unfavorable outcome with radiographic OA.

Table 4 Multivariable associations between baseline characteristics and clinical and radiographic OA, and clinical & radiographic OA, at 6-year follow-up.

Model		Clinical OA Pooled OR (95% CI)	Radiographic OA Pooled OR (95% CI)	Clinical & radiographic OA Pooled OR (95% CI)
Patient characteristics				
Age		1.04 (1.01-1.07)	1.08 (1.04-1.13)	1.08 (1.04-1.13)
Female gender		2.48 (1.45-4.23)		
Body Mass Index >27			3.32 (1.53-7.21)	3.53 (1.56-7.98)
Low/middle education level		1.58 (0.89-2.81)		
Co morbidity skeletal system		1.79 (1.00-3.18)		
	AUC	***0.72***	***0.74***	***0.74***
Patient characteristics and symptom characteristics				
Age		1.03 (1.00-1.06)	1.09 (1.04-1.15)	1.08 (1.03-1.13)
Female gender		2.30 (1.30-4.07)		
Body Mass Index >27			3.41 (1.45-8.01)	3.86 (1.59-9.35)
Co morbidity skeletal system		1.76 (0.97-3.19)		
Duration >3 months		2.08 (1.06-4.08)		
Self-reported warm knee		2.10 (1.18-3.74)		
Self-reported swollen knee			2.69 (1.16-6.26)	2.48 (1.01-6.08)
History of traumatic knee symptoms			5.32 (2.06-13.7)	
History of non-traumatic knee symptoms		2.27 (1.19-4.32)		3.39 (1.19-9.63)
Instability of the knee (Lysholm)				2.22 (0.92-5.39)
	AUC	***0.77***	***0.81***	***0.81***
Patient characteristics, symptom characteristics and physical examination				
Age			1.09 (1.04-1.15)	1.07 (1.02-1.12)
Female gender		1.93 (1.07-3.49)		
Body Mass Index >27			3.53 (1.40-8.88)	4.09 (1.70-9.87)
Low/middle education level		1.58 (0.85-2.94)		
Co morbidity skeletal system		1.80 (0.98-3.33)		
Duration >3 months		2.25 (1.11-4.57)		
Self-reported warm knee		1.92 (1.04-3.52)		
Self-reported swollen knee			2.96 (1.19-7.33)	
History of traumatic knee symptoms			5.35 (1.97-14.5)	
History of non-traumatic knee symptoms		2.36 (1.22-4.57)		5.38 (1.88-15.38)
Tenderness of the joint space			2.23 (0.80-6.18)	
Pain passive flexion			2.78 (1.10-7.02)	3.33 (1.37-8.13)
Pain passive extension		1.72 (0.86-3.44)		
Crepitus active flexion		1.69 (0.92-3.11)		
Crepitus active extension			2.28 (0.91-5.71)	
Floating patella		1.92 (0.96-3.84)		
	AUC	***0.79***	***0.85***	***0.82***

Prognostic factors

Table 4 presents the pooled multivariable associations between baseline characteristics and OA of the knee at 6-year follow-up, according to the clinical ACR criteria, the K&L score on the radiograph, and the clinical & radiographic ACR criteria.

Clinical OA

The patient characteristics age, female gender, low/middle education level and co-morbidity of the skeletal system showed an independent association with clinical OA at 6-year follow-up (AUC of 0.72). From the symptom characteristics, complaint duration > 3 months, self-reported warm knee, history of non-traumatic knee complaints and instability of the knee were independently associated with clinical OA (AUC of 0.72). Adding the symptom characteristics to the patient characteristics, the AUC increased by 0.05 to 0.77. Low/middle education level and instability of the knee no longer remained in the model (p >0.10). From physical examination, valgus alignment, pain at passive extension, crepitus at active flexion, floating patella and bony swelling of the joint were independently associated with clinical OA (AUC of 0.69). Adding items from physical examination to the patient and symptom characteristics increased the AUC by 0.02 to 0.79. Age, instability of the knee, valgus alignment and bony swelling of the joint no longer remained in the model (p >0.10).

Radiographic OA

The patient characteristics age and body mass index (BMI) >27 showed an independent association with radiographic OA at 6-year follow-up (AUC of 0.74). From the symptom characteristics, self-reported swollen knee, history of traumatic knee complaints and limitation during daily function were independently associated with radiographic OA (AUC of 0.74). Adding the symptom characteristics to the patient characteristics, the AUC increased by 0.07 to 0.81. Limitation during daily function no longer remained in the model (p >0.10). From physical examination pain at passive flexion, crepitus at active extension and tenderness of the joint space were independently associated with radiographic OA (AUC of 0.73). Adding items from physical examination to the patient and symptom characteristics increased the AUC by 0.04 to 0.85. Limitation during daily function no longer remained in the model (p >0.10).

Clinical and radiographic OA

The patient characteristics age and BMI >27 showed an independent association with clinical & radiographic OA at 6-year follow-up (AUC of 0.74). From the symptom characteristics, self-reported swollen knee, history of non-traumatic knee complaints and instability of the knee were independently associated with clinical & radiographic OA (AUC of 0.74). Adding the symptom characteristics to the patient characteristics, the AUC increased by 0.07 to 0.81. All five variables remained in the model (p ≤0.10). From

physical examination, only pain at passive flexion was independently associated with clinical & radiographic OA (AUC of 0.65). Adding items from physical examination to the patient and symptom characteristics increased the AUC by 0.01 to 0.82. Self-reported swollen knee and instability of the knee no longer remained in the model (p >0.10).

Discussion

This study investigated how to identify which patients with knee complaints in general practice will develop knee OA at 6-year follow-up, in order to improve their prognosis.

There are doubts about the usefulness of the existing clinical ACR criteria for examining knee OA in general practice.[7,8] Our earlier study in patients with non-traumatic knee complaints showed that fulfilling the clinical ACR criteria for knee OA at baseline was not significantly related with persistent knee complaints at 1-year follow-up[7] or with an unfavorable outcome at 6-year follow up.[28] A similar study also showed that the clinical ACR criteria for knee OA are not useful for early detection of knee OA in general practice.[8] The present study also confirms that the clinical ACR criteria for knee OA are not useful to predict which patients with knee complaints will have knee OA at 6-year follow-up. This is because, of the six clinical ACR items for knee OA, only age at baseline was independently and significantly associated with clinical OA, radiographic OA, and clinical & radiographic OA of the knee at 6-year follow-up. The other clinical ACR items, crepitus of the knee and tenderness of the joint space, were only associated with clinical OA or radiographic OA of the knee at 6-year follow-up, and not with clinical & radiographic OA. The three remaining clinical ACR items (stiffness of the knee < 30 min, bony enlargement of the joint and no palpable warmth of the knee) were not associated with any of the criteria at 6-year follow-up.

In the present study, 39% of the patients who were presented in general practice with a new episode of non-traumatic knee complaints suffer from knee OA at 6-year follow-up, according to the clinical ACR criteria and/or the K&L score on radiograph. According to the clinical & radiographic ACR criteria, 31% of the patients suffered from knee OA at 6-year follow-up. These percentages are largely in concordance with an earlier study.[8]

In the present study, all three criteria sets were significantly related with an unfavorable outcome at 6-year follow-up, but radiographic OA showed the weakest relationship. Furthermore, as also reported by Peat et al.,[8] we found a weak positive predictive value and a reasonably good negative predictive value of the clinical ACR criteria compared with the clinical & radiographic OA. Consequently, the clinical ACR criteria seem more useful for excluding knee OA than for confirming knee OA in general practice at an early stage. Therefore, in the present study, the clinical & radiographic ACR criteria for knee OA are the most effective to use as an outcome measurement to draw conclusions as to which baseline factors are suitable to predict which patients with knee complaints in general practice will have knee OA at 6-year follow-up.

Regarding which baseline factors are suitable to predict which patients with knee complaints in general practice will have knee OA at 6-year follow-up, according to the clinical & radiographic ACR criteria, it is noteworthy that physical examination had no additional; this was also reported in our earlier study.[29]

Therefore, only the following five patient and symptom characteristics are suitable to reasonably predict (AUC 0.81) which patients with knee complaints in general practice will have knee OA at 6-year follow-up: age, BMI >27, self-reported swollen knee, history of non-traumatic knee complaints, and instability of the knee.

It is difficult to compare these results with other studies, because (to our knowledge) similar research is lacking in general practice. However, our results are mainly in concordance with studies on risk/prognostic factors for knee OA[30,31], prognostic factors for persistent complaints in patients with non-traumatic knee complaints [29,32-34] and prognostic factors for other musculoskeletal disorders.[24]

A limitation of the present study is that a relatively large percentage of patients were lost to follow-up. This was mainly due to lack of contact, change of address and/or loss of interest, because initially a 1-year follow-up, rather than a 6-year follow-up, was discussed with the patients. Other reasons were severe illness and/or death between 1 and 6-year follow-up. Another limitation was that only about 50% of the patients available at 6-year follow-up were willing to undergo a radiograph of their knee. However, patients lost to follow-up and patients who were not willing to undergo additional radiographic examination of their knee did not appear to be a selected group of patients.

The results of the present study demonstrate that the clinical ACR criteria for knee OA are not suitable for predicting which patients with knee complaints in general practice will have knee OA at 6-year follow-up. Instead of the clinical ACR criteria we identified five patient and symptom characteristics that can be used by the GP to reasonably predict which patients will have knee OA at 6-year follow-up. However, these results should be validated in similar studies in primary care, before they are implemented in daily practice.

Predicting which patients with knee complaints in general practice will have knee OA at 6-year follow-up may encourage the development and testing of interventions for knee OA in an early stage, with the aim to diminish the burden of knee OA. Because BMI >27 was associated with knee OA at follow-up, an effective intervention in these patients could be loss of weight at an early stage. As the remaining factors are not easily modifiable, they cannot be directly used to develop or test an intervention. However, these factors can be used to select patients at high risk of developing knee OA at follow-up, and to test existing treatments for preventing knee OA in these patients (e.g. exercise therapy [35]).

Conclusions

Of the patients presenting with a new episode of non-traumatic knee complaints in general practice, 31-39% (depending on the definition used) suffer from knee OA at 6-year follow-up.

The clinical ACR criteria are not suitable to predict which patients with knee complaints in general practice will have knee OA at 6-year follow-up. Instead, the five baseline patient and symptom characteristics (age, BMI >27, self-reported swollen knee, history of non-traumatic knee complaints, and instability of the knee) are more appropriate to predict which patients with knee complaints in general practice will have knee OA at follow-up. Baseline factors from physical examination offer no additional value in this prognosis.

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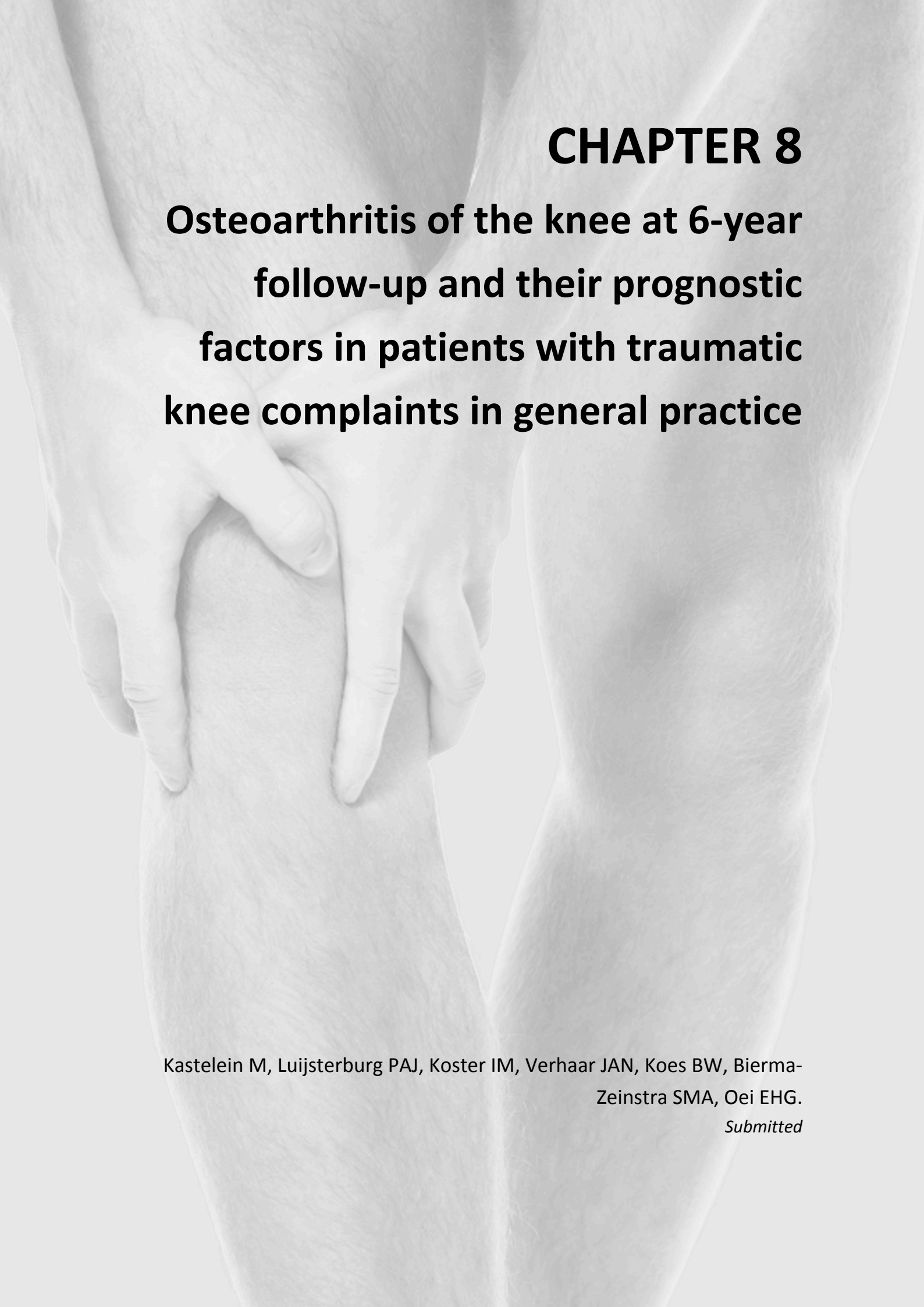

CHAPTER 8

Osteoarthritis of the knee at 6-year follow-up and their prognostic factors in patients with traumatic knee complaints in general practice

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Submitted

Abstract

Objective: To identify degenerative abnormalities of the knee on magnetic resonance imaging (MRI) and radiography 6 years after knee trauma, and their relation with persistent knee complaints and prognostic factors at baseline (including MRI findings).

Methods: Adults (18-65 years) with incident traumatic knee complaints who visited their general practitioner were followed for 6 years. To identify degenerative abnormalities, an MRI was made at baseline and at 6-year follow-up, and a radiograph was made at 6-year follow-up. Logistic regression analysis was used to calculate associations between the various degenerative abnormalities on the 6-year MRI and the 6-year radiograph, their relation with persistent knee complaints, and to identify baseline prognostic factors associated with knee osteoarthritis (OA) at the 6-year MRI.

Results: On the 6-year radiograph, 60% of the patients showed no OA, 28% OA with a Kellgren & Lawrence (K&L) grade 1 and 13% had a K&L grade 2. On the 6-year MRI, 55% of the patients showed cartilage defect(s), 45% osteophyte(s), 36% subchondral cyst(s), 40% bone marrow edema, 21% meniscal subluxation, 83% meniscal degeneration, 11% effusion and 11% a Baker's cyst. Most degenerative abnormalities on the 6-year MRI were significantly related with the K&L score on the 6-year radiograph. Only a few abnormalities [lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation] were also significantly related with persistent knee complaints at 6-year follow-up. For knee OA seen on the 6-year MRI, 32% of the patients showed new onset or progressive knee OA. Age, history of non-traumatic knee complaints and bone marrow edema on the baseline MRI were independently related with new onset or progressive knee OA on the 6-year MRI.

Conclusions: Degenerative abnormalities on MRI of the knee are related to the K&L score on knee radiography; however, not all abnormalities are reflected in clinical outcome. Six years after knee trauma, knee OA is present in 32% of the patients. Age, history of non-traumatic knee complaints and bone marrow edema are possible predictors for new onset or progressive knee OA 6 years after knee trauma.

Introduction

General practitioners (GPs) are frequently consulted by patients with traumatic knee complaints. The incidence of traumatic knee lesions (including contusion, distortion, collateral ligament lesions, cruciate ligament lesions and meniscal tears) in Dutch general practice is about 5.3 per 1000 patients per year.[1]

Our earlier study investigating the natural course and prognostic factors of traumatic knee complaints in general practice, showed that 17% of these patients who participated in an additional MRI study suffer from persistent knee complaints at 1-year follow-up,[2] and that 27% and 33% of all patients with traumatic knee complaints who participated in the cohort study suffer from persistent knee complaints at 1 and 6-year follow-up, respectively (submitted data). Because knee trauma is an established risk factor for new and progression of existing knee osteoarthritis (OA),[3-6] knee OA could play a role in this relatively high percentage of persistent knee complaints in these patients at 6-year follow-up. Moreover, because knee OA is a chronic disorder with a major burden,[7] knowledge on prognostic factors for knee OA in patients with traumatic knee complaints could be helpful to diminish this burden of knee OA in these patients in the future.

However, data on developing knee OA and its related prognostic factors in patients with traumatic knee complaints are scarce. From primary care, the only information on this subject is available from the 1-year follow-up of our HONEUR knee cohort, which 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, and an association of only bone marrow edema on baseline MRI with knee OA.[8] From secondary care, there is evidence that about 50% of patients with a traumatic meniscal lesion or an anterior cruciate ligament (ACL) lesion develop knee OA at a younger age than expected (probably 10-20 years after onset of the trauma), and that age, sex, genetics, obesity, muscle strength, activity level and repeated injury are associated with knee OA in these patients.[9] Bone marrow edema may also be a risk factor for structural deterioration and progression of knee OA in secondary care.[10,11]

Research on developing knee OA and related prognostic factors in patients with traumatic knee complaints is complicated by the fact that it is difficult to diagnose OA of the knee in an early stage; also, there is no gold standard and radiographic changes are insensitive (particularly in an early stage of the disease) and have a poor correlation with symptoms.[12] Magnetic resonance imaging (MRI) is suggested to be the best currently available imaging technique for the detection of early osteoarthritic changes.[13] Although a consensus-based definition for OA has been published, is not yet validated.[14]

This study investigates the occurrence of knee OA in patients with traumatic knee complaints who consulted their GP. We assessed the 1) presence of degenerative abnormalities in the knee of these patients with radiography and MRI at 6-year follow-up, 2) the relationship between these imaging techniques, 3) their correlation with persistent

knee complaints at 6-year follow-up, and 4) their relationship with prognostic factors at baseline (including MRI findings).

Methods

Design

The present study was conducted within the HONEUR network (including 40 GPs) established by the Dept. of General Practice of Erasmus Medical Center Rotterdam.[15] It is part of a prospective, observational cohort study in which 1068 consecutive patients visiting their GP with a new episode of knee complaints were initially followed for 1 year.[15] Because of the high percentage of patients with persistent knee complaints at 1-year follow-up, the follow-up period was extended to 6 years. At baseline, new knee complaints were defined as episodes of complaints presented to the GP for the first time. Recurrent symptoms for which the GP was not consulted within the past 3 months were also considered as new complaints. Traumatic knee complaints were defined as those caused by a sudden impact or wrong movement occurring within 1 year before consulting their GP; all other knee complaints were considered as non-traumatic ones.

Patients were eligible for the present study if they were aged 18-65 years, had consulted their GP with traumatic knee complaints within 5 weeks after the trauma, and signed informed consent for an additional MRI of their knee. Exclusion criteria were knee symptoms that required urgent medical attention (e.g. fractures, infection), patients with malignancies, neurologic disorders or systematic musculoskeletal diseases (e.g. Parkinson's disease, rheumatoid arthritis, amyotrophic lateral sclerosis), as well as patients with insufficient understanding of the Dutch language and/or incapability of understanding the ramifications of participation. The study protocol was approved by the Medical Ethics committee of Erasmus MC Rotterdam.

Data collection

Patients filled out a questionnaire at baseline, and at 1 and 6-year follow-up. The questionnaires provided data on demographics (e.g. age, gender, composition of household, educational level and co-morbidity), on knee complaints [e.g. history of previous knee injuries or operations, duration and recurrence of knee complaints, 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 [16-18]], and on treatment. For the Lysholm score, higher scores represent better function/outcome.

In addition, the questionnaires at 1 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 complaints were defined as knee complaints that were "slightly improved", "not changed", "slightly worsened", "much

worsened" or "worse than ever". Clinically important recovery was defined as knee complaints that were "completely recovered" or "much improved".

A standardized 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 effusion, passive range of motion in flexion and extension, meniscal tests, and knee stability tests.[19,20]

MRI of the knee was performed within 3-6 weeks of the trauma and was repeated after 6 years. At baseline a 1.0 Tesla whole body MRI unit was used, whereas at 6-year follow-up, MRI was performed on a 1.5 Tesla 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).[21] 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.[14], i.e. the presence of both group A features (definite osteophyte formation; full thickness cartilage loss) or one group A feature and two or more group B features [subchondral bone marrow lesion or cyst not associated with meniscal or ligamentous attachments; meniscal subluxation, maceration or degenerative (horizontal) tear; partial thickness cartilage loss (where full thickness loss is not present); bone attrition].

In addition to degenerative abnormalities, we also assessed the presence of ligamentous lesions, meniscal lesions and bone marrow edema on MRI. To reflect clinical practice, both 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. Therefore the treatment strategy of the GP was not influenced by the MRI findings. If a patient was referred to a medical specialist, the initial MRI report was provided on request to avoid unnecessary repetition of an MRI examination.

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 Kellgren and Lawrence (K&L) grading (0-4) system[22], unaware of the clinical status of the patients. Grade 0: no knee OA, grade 1: doubtful knee OA (doubtful narrowing of joint space and possible osteophytic lipping), grade 2: mild knee OA (definite osteophytes and possible narrowing of joint space), grade 3: moderate knee OA (multiple osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone ends) and grade 4: severe knee

OA (large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends).
In the case of any difference in the K&L grade, the two readers met to read the radiograph together and a consensus score was determined.

Statistical analysis

Descriptive statistics were used to describe patient characteristics, type and severity of complaints, MRI findings, loss to follow-up, patient-reported persistent knee complaints, and the K&L score on radiograph. Odds ratios (OR) were used to calculate the association between the various degenerative abnormalities on the 6-year MRI, and the K&L score on the 6-year radiograph of the knee. ORs were also used to calculate the relation between the various degenerative abnormalities on the 6-year MRI and patient-reported persistent knee complaints at 6-year follow-up.
Univariate logistic regression analysis was performed to determine which baseline variables from history taking and MRI are associated with the presence of knee OA seen on the 6-year MRI (new onset knee OA or progression of existing knee OA), expressed as ORs. The baseline variables used as eligible prognostic factors for the univariate analysis were based on literature [23] and clinical relevance. The eligible factors were divided into three domains: patient characteristics, complaint characteristics and MRI findings. To enable easy interpretation of prognostic factors in a clinical setting we chose to dichotomize most of the variables. Imputation of missing data was carried out by multiple imputation, creating a total of 5 imputed databases.[24-26] All analyses were performed separately on all 5 imputed databases. 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 ($p \leq 0.20$), were analyzed 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 version 17.02 (SPSS Inc., Chicago, Ill, 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 male. MRI of the knee showed 15 patients (11.2%) without lesion or effusion, 37 patients (27.6%) with a contusion (joint effusion without ligamentous of meniscal lesion), 35 patients (26.1%) with medial collateral ligament lesion, 8 patients (6.0%) with lateral collateral ligament lesion, 28 patients (20.9%) with an ACL lesion, and 47 patients (35.1%) with meniscal tear. A total of 61 patients (45.5%) reported that their traumatic knee complaints were caused during

sports activity. 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).

Table 1 Baseline characteristics of the total group of patients and those available at 6-year follow-up.

Baseline characteristic	**Total group (n=134)**	**Available at 6-year follow-up (n=78)**	**Agreed to 6-year MRI and X-ray (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 complaints			
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

After 6 years, 78 patients (58.2%) were still available for follow-up; their baseline characteristics are shown in Table 1. The patients lost to follow-up showed no significant or clinically relevant differences compared with those available at 6-year follow-up regarding baseline age, gender, diagnosis on baseline MRI, cause of the knee complaints, pain score (NRS) and Lysholm knee function score. Patients lost to follow-up also showed no difference compared with those available at 6-year follow-up regarding self-reported persistent knee complaints at 1-year follow-up (OR 0.80, 95% CI 0.31-2.09). 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. Also, at 6-year follow-up, of the 78 available patients 31 (39.7%) did not give permission for an additional MRI and/or radiograph of their knee; also these 31 patients showed no relevant differences compared with those who did agree to an additional MRI and/or radiography regarding baseline characteristics and self-reported persistent knee complaints at 6-year follow-up (OR 1.08, 95% CI 0.42-2.85).

Clinical outcome

At 6-year follow-up, of the 78 available patients 26 (33.3%) reported persistent knee complaints; 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 (listed in Table 1) was significantly associated with persistent knee complaints at 6-year follow-up (data not shown).

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

During the 6-year follow-up, of the 78 patients 11 (14.1%) underwent surgery of the knee; of these 11 patients, 6 (54.5%) reported persistent knee complaints 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 grade 0 knee OA, 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 edema, 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 edema, 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 (i.e. lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation) had a significant relation with the self-reported persistent knee complaints 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.[14]) 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 4.8-112). A significant relationship was also found with the reported persistent knee complaints (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 5 patients with existing knee OA at baseline, 3 (60.0%) showed progression.

Table 2 Signs of osteoarthritis (OA; based on the KOSS scoring system) and presence of knee OA on the 6-year MRI, compared with the K&L score for knee OA on the 6-year radiograph, their relation with the K&L score (grade 0 vs. grade 1 and 2) and their relation with persistent knee complaints at 6-year follow-up (n=47).

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

$ ≥ 2 minimal osteophytes or ≥ 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.

* $p \leq 0.05$

Table 3 Cross-tabulation of knee osteoarthritis (OA) at baseline versus the 6-year MRI.

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

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

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

* = $p \leq 0.20$ (to be included in the multivariate analysis)

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.

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

MRI findings cartilage defect, osteophytes, bone marrow edema and meniscal degeneration were associated ($p \leq 0.20$).

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 complaints (p=0.04) and bone marrow edema (p=0.07) were independently related with progression or new onset knee OA at 6-year MRI.

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

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

Discussion

This study identified degenerative abnormalities on MRI and radiography of the knee in patients 6 years after knee trauma. The degenerative abnormalities on the 6-year MRI were compared with the K&L grade on the 6-year radiograph, and the correlation with the patients' reported persistent knee complaints at 6-year follow-up was assessed. Also assessed was the relation between eligible prognostic factors at baseline (including MRI findings) and knee OA seen on the 6-year follow-up MRI.

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 lateral subchondral cyst, lateral bone marrow edema, medial meniscal degeneration, effusion and Baker's cyst were not significantly related. Only a few of the degenerative abnormalities on the 6-year MRI, i.e. lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation, were significantly related with patients' reported persistent knee complaints at 6-year follow-up. These results are largely in accordance with similar reports.[27-30] The main difference between our study and earlier studies is that we made a distinction between medial and lateral degenerative abnormalities, because (in our population) medial degenerative abnormalities of the femorotibial joint were more common than the lateral abnormalities. Also, the medial abnormalities were more strongly associated with the K&L score on radiography and there was a difference in association with persistent knee complaints at 6-year follow-up for the medial and lateral joint compartments.

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.[8] 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 OA of the knee already showed at 1-year follow-up. Therefore, it appears that in the majority of the patients who develop new knee OA or progression of existing knee OA after knee trauma, this develops within the first year after knee trauma. However, it should be noted that we used a slightly different definition for knee OA on MRI in this 6-year study compared with our earlier 1-year study;[8] nevertheless, this had no important impact on our results. Applying the definition of Hunter et al.[14] for knee OA on MRI at 1-year MRI (as used in this 6-year study) yielded a similar percentage of patients with new onset knee OA or progression of existing knee OA at 1-year follow-up as reported in our 1-year study.[8]

In the present study age, history of non-traumatic knee complaints and bone marrow edema 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 edema were also important prognostic factors for the onset or progression of knee OA.[3,5,8-11] Although history of non-traumatic knee complaints seems a logical prognostic factor for predicting progressive or new onset knee OA, this was not investigated as a prognostic factor in most earlier studies. This factor was also found to be an important prognostic factor for persistent knee complaints 6 years after trauma (submitted data). 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 that BMI is an established risk factor for knee OA.[3,5,9,31] This relationship was also absent in our 1-year follow-up study on the development of knee OA.[8] Also, we found no significant association between meniscal lesions/cruciate ligament lesions and progression or new knee OA, whereas others suggest that these lesions are related with knee OA.[9,32,33] This might be explained by our small sample size (and resulting lack of power), and our primary care setting where severity of traumatic knee complaints is expected to be lower than in studies performed in secondary care.

The present study has some limitations. Only a small number of patients were eventually investigated because a relatively large percentage was lost to follow-up (mainly due to lack of contact details, change of address, loss of interest, severe illness and/or death between 1 and 6-year 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.[14]) has not been validated, it appears to be the best available definition at this moment. In our dataset the definition showed a strong relationship with the K&L score on 6-year follow-up. We are aware that our results refer to a heterogeneous population that includes new onset of knee OA as well as progression of existing knee OA in our analysis to establish

prognostic factors for knee OA in these traumatic knee patients. However, our sample size was too small to differentiate between these two groups.

We report percentages on the presence of the different K&L grades on the 6-year radiograph, the various degenerative abnormalities on the 6-year MRI, and on the presence of new or progression of knee OA 6 years after trauma. However, it remains unknown which part is attributable to the natural course of OA and which part to the knee trauma because radiographs and/or MRIs of the contralateral knee were not available, and there was no control group. However, this is not important when assessing the relationship between degenerative abnormalities on radiographs/MRI, their relation with persistent knee complaints, and the relationship of prognostic factors with knee OA.

The results demonstrate that in 32% of these patients progression of existing knee OA or new onset knee OA is present 6 years after knee trauma.

After knee trauma clinicians need to be aware of the presence of knee OA in these patients (particularly in older patients, because the older the patient the greater the change), and check for a history of non-traumatic knee complaints and bone marrow edema 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.

Also, to promote uniformity and comparisons in future research on knee OA, a definition of knee OA assessed on MRI (including a grading system) needs to be further developed and validated.

Conclusions

Degenerative abnormalities on MRI of the knee are associated with the K&L score on knee radiography; however, not all abnormalities are reflected in clinical outcome. Six years after knee trauma, knee OA had developed or worsened in 32% of the patients. Age, history of non-traumatic knee complaints and bone marrow edema are possible prognostic factors for new onset or progressive knee OA 6 years after knee trauma.

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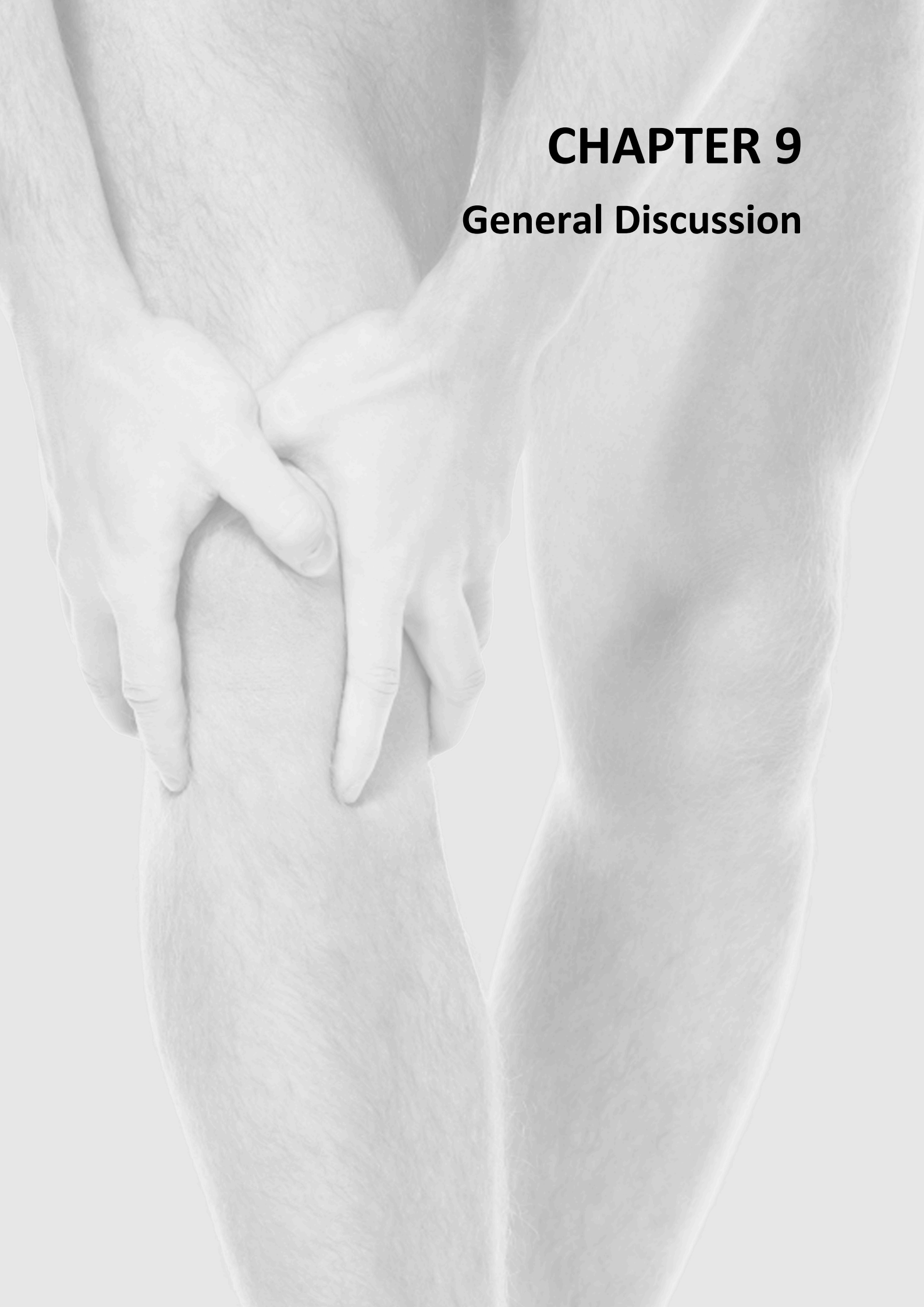

CHAPTER 9

General Discussion

General discussion

General practitioners (GPs) are frequently consulted by patients with knee complaints. The incidence of these knee complaints presented in Dutch general practice is about 13.7 per 1000 registered patients per year with a prevalence of 19.0 per 1000 patients per year.[1]

Despite this high incidence and prevalence, evidence on various aspects of non-traumatic and traumatic knee complaints is scarce, especially in general practice.

In this thesis, we report on diagnosing traumatic knee complaints in general practice, on the six-year natural course and prognostic factors for both non-traumatic and traumatic knee complaints seen in general practice, and on the prediction of which patients with non-traumatic and traumatic knee complaints in general practice will develop chronic complaints due to knee osteoarthritis (OA).

In this chapter we present the main findings of our work in relation to existing evidence and discuss their additional value. In addition, we address the study limitations and their implications for daily practice and future research.

Main findings and additional value

The prospective HONEUR knee cohort is the first study with a long-term follow-up of six years that includes patients with both incident non-traumatic and traumatic knee complaints presenting in general practice. This makes the HONEUR knee cohort a unique and representative study of patients with knee complaints in general practice.

Diagnosing traumatic knee complaints

Concerning the diagnostic value of history taking and physical examination in patients with a traumatic knee complaint, to our knowledge no other studies (other than those in the HONEUR knee cohort) [2,3] have been performed in general practice. A few studies on this subject have been performed in secondary care.[4-8] However, the results emerging from secondary care are not necessarily applicable in general practice, because patients seen in secondary care are a selection with a higher incidence of actual knee lesions and different predictive values of items on history taking and physical examination. Moreover, most studies performed in secondary care have reported on meniscal and cruciate lesions [4-8] and not on medial collateral ligament (MCL) lesions and effusion of the knee, as in this thesis. Therefore, the studies in this thesis provide new information for the GP on diagnosing MCL lesions (Chapter 2) and effusion of the knee (Chapter 3) in patients with traumatic knee complaints.

We found that MCL lesions and effusion of the knee can be reasonably excluded by the GP based on history taking and physical examination in patients with traumatic knee complaints seen in general practice (Chapters 2 and 3). In contrast, predicting the

presence of an MCL lesion or effusion of the knee in these patients by the GP is more difficult based on history taking and physical examination. Although both history taking and physical examination increased the probability of the presence of both MCL lesion and effusion of the knee, the positive predictive values did not exceed 63% (Chapters 2 and 3). In addition, we found a positive relationship between effusion and an intra-articular lesion(s) of the knee (Chapter 3), which is in accordance with earlier studies performed in secondary care.[9,10]

Natural course and prognostic factors of knee complaints

Besides the HONEUR knee cohort, a few studies have examined the course and prognosis of knee complaints in general practice. However, these studies differed from our knee cohort in that all had a shorter term of follow-up, with a maximum of three years.[11-14] Also, compared with our knee cohort, van der Waal et al. did not include physical examination and only investigated the course of non-traumatic knee complaints.[13] Peat et al. performed their study in the general population, but only in patients aged 50 years and older with non-traumatic knee complaints; this represents a major difference compared with our knee cohort which includes incident non-traumatic and traumatic knee complaints in patients aged 12 years and older in general practice.[12] Therefore, our findings provide new information on the six-year course and prognostic factors of non-traumatic knee complaints in adolescents and young adults (aged 12-35 years; Chapter 4), of non-traumatic knee complaints in adults (≥ 35 years; Chapter 5) and of traumatic knee complaints in adolescents and adults (≥ 12 years; Chapter 6).

A substantial proportion of the adolescents and young adults with non-traumatic knee complaints presented in general practice reported persistent knee complaints at one and six-year follow-up, i.e. 47% and 27%, respectively (Chapter 4). Also, patients with patellofemoral pain syndrome had the worse prognosis of these patients, with 40% reporting persistent knee complaints at six-year follow-up (Chapter 4). This moderate prognosis is in contrast with the assumed good prognosis for knee complaints in adolescents and young adults as reported in the Dutch College of General Practitioners (NHG) guideline for non-traumatic knee complaints.[15] In this Dutch clinical guideline the prognosis was based on consensus rather than on evidence, because studies on this subject were totally lacking in general practice at the time of its development.

Also, we showed that non-traumatic knee complaints in adults in general practice appear to become a chronic disorder in almost 50% of the patients (Chapter 5). This is in accordance with the assumption that many of these patients probably suffer from knee OA and therefore report chronic knee complaints.[16]

We also found that traumatic knee complaints in general practice have a mean recovery period of 7.4 (SD 13.1) months and seem to become a chronic disorder in one out of three patients (Chapter 6). This prognosis is not in accordance with the reported prognosis in the NHG guideline for traumatic knee complaints.[17] The assumed good

prognosis in this guideline was based on the assumption that most patients with traumatic knee complaints in general practice suffer from a contusion or distortion and are therefore complaint-free in a few weeks; however, evidence on this subject was lacking at the time of development of the guideline.

We found several prognostic factors assessed at baseline (patient and symptom characteristics, and items from physical examination) that are associated with persistent knee complaints at one and six-year follow-up in adolescents and young adults with non-traumatic knee complaints (Chapter 4) and in patients with traumatic knee complaints (Chapter 6). Also, we found ten prognostic factors that are associated with an unfavorable outcome at six-year follow-up in adult patients with non-traumatic knee complaints, and used these prognostic factors to develop a clinical prediction rule (Chapter 5). In all three groups, patient and symptom characteristics had the highest prognostic values, while items from physical examination had little additional value (Chapters 4, 5 and 6). It is difficult to compare the prognostic factors found in our three various groups with existing literature because very few similar studies have been performed in general practice.[11-14] Moreover, the groups defined in these studies are not comparable with ours. In our three groups we mainly found different prognostic factors per group. This seems logical, because each group of patients is characterised by its own major knee problems and, therefore, also by its own prognostic factors. However, there are some similarities between the prognostic factors found in our three groups. Prognostic factors such as age, body mass index (BMI), low/middle education level, bilateral complaints, poor health/co-morbidity and history of knee complaints were associated with persistent knee complaints/unfavourable outcome in two or more of our study groups. These prognostic factors are also found in similar studies with a shorter-term follow-up [11-14,18] and/or with prognostic factors found in a systematic review on musculoskeletal pain in general practice.[19]

Osteoarthritis in patients with knee complaints

Evidence on predicting which patients with non-traumatic knee complaints will develop chronic complaints due to knee OA is scarce. The American College of Rheumatology (ACR) developed criteria for classifying knee OA (the clinical ACR criteria); however, they were developed mainly for scientific research and not for diagnosing the individual patient with knee OA.[20] Also, because these criteria were developed and validated mainly in secondary care, they are not applicable in general practice because patients from secondary care have considerable differences in the severity of their complaints. Moreover, it is reported that the clinical ACR criteria are not appropriate to identify knee OA in an early stage in patients with non-traumatic knee complaints in general practice.[21,22]

Information on predicting knee OA in patients with traumatic knee complaints is also scarce. From secondary care it is known that patients with traumatic knee complaints are

at increased risk to develop knee OA at a young age, probably 10-20 years after onset of the injury.[23] However, no other studies were found on this subject in general practice, with the exception of one study (also performed within the HONEUR knee cohort) which reported on the presence and prognostic factors of knee OA one year after onset of the traumatic knee complaints.[24] The studies in this thesis offer new information on predicting which patients with non-traumatic (Chapter 7) and traumatic knee complaints (Chapter 8) will develop chronic knee complaints due to knee OA at six-year follow-up.

We found that 31-39% of the adults with non-traumatic knee complaints seen in general practice suffer from knee OA at six-year follow-up (Chapter 7); this is in accordance with data reported by Peat et al.[22] Also, we confirmed that the clinical ACR criteria for knee OA, as earlier suggested by Peat et al. and Belo et al.[21,22], are not suitable for predicting which patients with non-traumatic knee complaints in general practice will develop chronic knee complaints due to knee OA (Chapter 7). Instead, we identified five baseline patient and symptom characteristics i.e. age, BMI >27, self-reported swollen knee, history of non-traumatic knee complaints and self-reported instability of the knee) that might be used in the future to predict which patients in general practice will develop chronic complaints due to knee OA (Chapter 7). It is not possible to compare our results with existing literature because (as far as we know) similar research is lacking in general practice. However, our findings (i.e. age, BMI, history of non-traumatic knee complaints) are largely in accordance with studies on risk factors/prognostic factors for knee OA[25,26], prognostic factors for persistent complaints in patients with non-traumatic knee complaints [11-13,18] and prognostic factors for other musculoskeletal disorders.[19]

In addition, we found that 32% of the patients with traumatic knee complaints show new knee OA or progression of existing knee OA at MRI, six years after their trauma. It seems suspicious that this percentage is almost the same as presented in our study one year after the trauma.[24] We identified age, history of non-traumatic knee complaints and bone marrow oedema (on baseline MRI) to be predictors for progression or new knee OA six years after knee trauma. These predictors (i.e. age and bone marrow oedema) are partly in accordance with the limited evidence available on this topic.[23,24,27,28]

Study limitations

The first important limitation of the six-year course of the HONEUR knee cohort is that a relatively large percentage of patients were lost to follow-up. This was mainly due to lack of contact, change of address, loss of interest, severe illness and/or death between one and six-year follow-up. However, patients lost to follow-up did not appear to be a selected group of patients, based on various baseline characteristics and self-reported persistent knee complaints at one-year follow-up. Moreover, at six-year follow-up, some of the available patients did not agree to undergo additional investigations such as physical examination, radiograph and/or MRI of their knee. However, these patients did not differ from patients who did agree to undergo the additional investigations, based on

various baseline and six-year characteristics, including self-reported persistent knee complaints at six-year follow-up. Although patients lost to follow-up and patients who did not agree to undergo additional investigation do not appear to be a selected group of patients, we cannot guarantee that these patients are missing (completely) at random and therefore have not biased our results.[29] Moreover, the relatively large percentage of patients lost to follow-up also weakened the statistical power of our study. As a result, we may have missed some results that otherwise might have been significant.

Our main outcome measurement in the six-year course of the HONEUR knee cohort was persistent knee complaints as reported by the patient (Chapters 4 and 6) or persistent knee complaints combined with knee replacement surgery; unfavourable outcome (Chapter 5). It was possible to choose another outcome measurement, such as the total Western Ontario and McMaster Universities Arthritis Index (WOMAC)[30] score, or differences in the WOMAC score. However, we preferred an outcome that it is easier to use and interpret in clinical practice, rather than the total WOMAC score. Also, having persistent knee complaints was strongly associated with an unfavourable total WOMAC score (Chapter 5). Therefore, we think that the choice of our outcome measurement had no important impact on the results of our study.

For the development of knee OA in patients with traumatic knee complaints, we made an independent choice for the definition of knee OA on MRI. Although a scoring system for degenerative abnormalities on MRI is available (i.e. the Knee Osteoarthritis Scoring System; KOSS)[31] no definition for knee OA on MRI is currently available (but is being developed and validated).[32] We decided to use the definition of knee OA as reported by Hunter et al., even though it has not yet been validated; the reason for this choice is that it is currently the best available definition for knee OA on MRI. Nevertheless, this choice remains debatable.

Another limitation is the use of relatively heterogeneous study groups. Investigating the course and prognostic factors of different diagnoses is probably preferable, but requires larger study populations and confirmed diagnoses, neither of which were available for this cohort study (with the exception of patients with traumatic knee complaints who received an additional MRI). On the other hand, in daily practice GPs are generally confronted with a heterogeneous patient population and a diagnosis can seldom be made in the first consultation for knee complaints.

Most of the variables were dichotomised, because this is easier to interpret in clinical practice. However, the consequences of dichotomizing variables are loss of information, reduction of statistical power and an increased probability of a type II error.[33,34]

Also, in the various studies in this thesis, we decided to perform univariable regression analysis in a first step, using a relatively large p-value of 0.10-0.20 to determine which factors to test in multivariable analysis. This was due to the difficulty in choosing possible prognostic factors (due to the lack of evidence in this field) for direct analysis in a multivariable analysis. Consequently, we tested a relatively large number of factors in the

univariable analysis. This implies that some factors that were found to be significant may have been so due to chance (type I error).

Implications for daily practice and future research

The results reported in this thesis may have implications for the GP in daily practice and might in future be incorporated in the various Dutch NHG guidelines for knee complaints.[15-17] This seems a possibility because evidence on the long-term natural course of knee complaints in general practice and their prognostic factors is scare, and the studies in this thesis provide new and relevant information on this subject. In fact, the findings we reported on diagnosing traumatic knee complaints have already been incorporated in the Dutch NHG guideline on traumatic knee complaints.[17] Nevertheless, it is important that all the results presented in this thesis be validated in additional studies conducted in general practice, because similar research is either scarce or lacking at the moment. Preferably, our results should be validated in larger studies with fewer patients lost to follow-up.

Diagnosing traumatic knee injuries

Our results on the diagnostic value of history taking and physical examination in assessing MC lesions and effusion of the knee in patients with traumatic knee complaints in general practice can be used by the GP to reassure the patient if there is no suspicion of a MCL lesion or effusion of the knee and, therefore, only a small risk for an intra-articular lesion (Chapters 2 and 3). In case of a high risk for a MCL lesion or effusion of the knee, GPs can inform patients about this lesion (or any intra-articular lesion of the knee) and can decide to follow-up the natural course and/or refer the patient for additional investigations or treatment in secondary care (Chapters 2 and 3).

Natural course and prognostic factors of knee complaints

The prognostic information presented in this thesis on non-traumatic (Chapters 4 and 5) and traumatic knee complaints (Chapter 6) in patients in general practice can be used by the GP to identify patients at increased risk to develop chronic knee complaints. The GP can decide to follow-up these patients more carefully and adjust management accordingly. This information can also be used by the GP to better inform patients with knee complaints about their expected course, because prognostic information is known to be important for patients.[35] Also, this information can be used in future research to test the effectiveness of specific treatments (e.g. NSAIDS, physiotherapy or surgery) in patients at increased risk, and to investigate the possibility to improve the prognosis of these patients.

Osteoarthritis in patients with knee complaints

The information presented in this thesis on knee OA in adult patients with non-traumatic (Chapter 7) or traumatic knee complaints (Chapter 8) seen in general practice, can be used by the GP to predict which patients are at increased risk to develop chronic knee complaints due to knee OA. This information can be used to inform patients about their expected course. Moreover, in these patients the GP should be aware of chronic complaints due to knee OA and can consider starting treatment for OA (e.g. exercise therapy is considered effective[36]) at an early stage when signs of knee OA are presented. However, because it remains questionable whether such treatment is in fact effective at an early stage of knee OA, more research is needed to investigate the effectiveness of this treatment. Predicting which patients with knee complaints develop chronic complaints due to knee OA may also encourage the development and testing of other interventions for knee OA in an early stage and, hopefully, diminish the burden of knee OA for the patient and society.

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Summary

Summary

General practitioners (GPs) are frequently consulted by patients with various types of knee complaints. The incidence of these knee complaints presented in Dutch general practice is about 13.7 per 1000 registered patients per year with a prevalence of 19.0 per 1000 patients per year. Approximately 80% of these knee complaints are of non-traumatic cause.

In spite of that knee complaints are a common disorder in general practice, evidence on this subject in general practice is scarce. To improve the management of knee complaints in general practice, evidence is needed on diagnosis, long-term natural course and prognostic factors for persistent knee complaints and the development of knee OA. Therefore we performed a prospective observational cohort study (HONEUR knee cohort) with a six-year follow-up, aimed to assess the course of knee complaints and prognostic factors for persistent knee complaints in general practice.

In **chapter 2** we assessed the diagnostic value of history taking and physical examination of medial collateral ligament (MCL) lesions after a knee injury presenting in general practice.

Patients aged 18 to 65 years with a traumatic knee injury who consulted their general practitioner within 5 weeks after trauma filled out a questionnaire, underwent a standardized physical examination and a magnetic resonance imaging (MRI) scan. Univariate and multivariate logistic regression analysis was used to test possible associations between determinants from history taking/physical examination and MCL lesions. The diagnostic value of history taking and physical examination was determined for those variables indicating an association ($p<0.15$) with MCL lesions and was assessed by sensitivity, specificity, predictive value and likelihood ratios.

Of the 134 patients included in this study, 35 (26%) had an MCL lesion seen on MRI. From history taking the determinants “trauma by external force to leg” and “rotational trauma” showed an association with MCL lesion after multivariate analysis ($p<0.15$). From physical examination “pain valgus stress 30^{o}” and “laxity valgus stress 30^{o}” showed an association ($p<0.15$). Isolated determinants from history taking and physical examination showed some diagnostic value; the likelihood ratio positive (LR+) was 2.0 for “trauma by external force to leg” and for “pain valgus stress 30^{o}” 2.3. Adding “pain valgus stress 30^{o}” and “laxity valgus stress 30^{o}” from physical examination to history taking improved the diagnostic value to a LR+ of 6.4.

Therefore we concluded that MCL lesions are frequently seen in patients with traumatic knee injury. History taking has a diagnostic value, while adding physical examination increased the diagnostic value.

In **chapter 3** we assessed the diagnostic value of history taking and physical examination for knee joint effusion in patients with a knee injury presenting in general practice. In addition, we determined the association between effusion seen on MRI and internal derangement of the knee.
Patients aged 18 to 65 years with a traumatic knee injury who consulted their general practitioner within 5 weeks after trauma filled out a questionnaire, underwent a standardized physical examination and a MRI. Multivariate logistic regression analysis was used to determine the diagnostic value of history taking and physical examination ($p<0.15$) as assessed by sensitivity, specificity, predictive values and likelihood ratios. The relationship between effusion and internal derangement of the knee was assessed with a Chi-square test.
Of the 134 participating patients, 42 (31%) had knee joint effusion seen on MRI. Multivariate analysis showed an association with knee joint effusion for the symptom "Self-noticed swelling" (history taking) and for the "Ballottement test" (physical examination); LR+ was 1.5 and 1.6 respectively. These two combined improved the diagnostic value to an LR+ of 3.6. Effusion showed a positive association with internal derangement of the knee ($p= 0.002$); 31 (74%) of the 42 patients with knee joint effusion had internal derangement of the knee.
Consequently, we concluded that in patients with traumatic knee injury, knee joint effusion is frequently seen on MRI. The combination of self-noticed swelling and the ballottement test was of diagnostic value. Knee joint effusion seen on MRI was associated with internal derangement of the knee.

In **chapter 4** we assessed the 1 and 6-years course of non-traumatic knee complaints in adolescents and young adults presenting in general practice, and identified prognostic factors for persistent knee complaints.
Adolescents and young adults (12-35 years; n=191) with non-traumatic knee complaints were included by their general practitioner and were followed-up for 6 years. Between baseline and 6-year follow-up patients filled out questionnaires on demographics, knee symptoms and perceived recovery. A standardized physical examination was carried out at baseline and at 1-year follow-up. Descriptive statistics were used to describe the course of the knee complaints. Multivariable logistic regression analysis was used to identify prognostic factors for persistent knee complaints at 1 and 6-years follow-up and the area under the receiver operating curve (AUC) was calculated.
At 1-year follow-up, persistent knee complaints were reported by 78 (47%)_of the patients and by 29 (27%) of the available patients at 6-year follow-up. Patients with patellofemoral pain syndrome (n=45) had the worse prognosis, with 40% reporting persistent knee complaints at 6-years follow-up. There was a positive relationship, OR 4.8, 95% CI 1.8-12.8, between having persistent knee complaints at 1-year follow-up and at 6-

year follow-up. Prognostic factors assessed at baseline associated with persistent knee complaints at 1-year follow-up were body mass index (BMI) >25, low/middle education level, poor general health, bilateral complaints, self-reported swollen knee, presence of locked knee, painful patellar ligament, and absence of floating patella (AUC 0.75). At 6-year follow-up low/middle education level, self-reported swollen knee, painful patellar edges and absence of floating patella were associated with persistent knee complaints (AUC 0.76).
We concluded that the prognosis of non-traumatic knee complaints in adolescents and young adults in general practice is not as good as previously assumed. Various prognostic factors collected at baseline were associated with persistent knee complaints at follow-up

In **chapter 5** we examined the 6-years course of non-traumatic knee complaints in adults in general practice, identified prognostic factors for unfavorable outcome and to developed a clinical prediction rule.
Adults (>35 years) with incident non-traumatic knee complaints (n=549) were followed for 6 years. Multivariable logistic regression analysis was used to identify prognostic factors associated with an unfavorable outcome, the AUC was calculated to determine discriminative ability and a clinical prediction rule was developed. Unfavorable outcome was defined as persistent knee complaints at 6-year follow-up, or having undergone knee replacement surgery during follow-up.
At 6-year follow-up, 143 (42%) of the patients had an unfavorable outcome. Having persistent knee complaints (OR 5.31, 95% CI 3.27-8.61) and fulfilling the clinical ACR criteria for osteoarthritis (OA) (OR 2.65, 95% CI 1.48-4.73) at 1-year follow-up were significantly associated with unfavorable outcome, while fulfilling the clinical ACR criteria for OA at baseline was not. Baseline factors independently associated with an unfavorable outcome were low/middle education level, co-morbidity of the skeletal system, duration of knee complaints >3 months, bilateral knee complaints, self-reported warm knee, history of non-traumatic knee complaints, valgus alignment, pain at passive knee flexion/extension, and bony enlargement of the knee joint (AUC 0.80).
Therefore we concluded that non-traumatic knee complaints in adults in general practice appear to become a chronic disorder in nearly half of the patients. The developed clinical prediction rule with 10 baseline prognostic factors can be used to select high-risk patients for an unfavorable outcome at long term.

In **chapter 6** we described the 1 and 6-years course of traumatic knee complaints in adolescents and adults presenting in general practice, and identified prognostic factors for persistent knee complaints.
Adolescents (≥ 12 years) and adults with traumatic knee complaints (n=328) were included by their general practitioner and followed-up for 6 years. Patients filled out

questionnaires and underwent a standardized physical examination. Descriptive statistics were used to describe the course of the knee complaints. Multivariate logistic regression analysis was used to identify prognostic factors for persistent knee complaints at 1 and 6-years follow-up, and the AUC was calculated.
Persistent knee complaints were reported by 81 (27%) of the patients at 1 year and by 60 (33%) patients at 6 years. There was a strong relationship (OR 11.0, 95% CI 5.0-24.2) between having persistent knee complaints at 1 year and at 6-year follow-up. Patients reporting recovery during follow-up reported this in a mean time-period of 7.4 months. Prognostic factors associated with persistent knee complaints at 1 year were age, poor general health, history of non-traumatic knee complaints, absence of floating patella and laxity on the anterior drawer test (AUC 0.72). At 6-year follow-up, age, BMI > 27, non-skeletal co-morbidity, self-reported crepitus of the knee, history of non-traumatic knee complaints, and laxity on the anterior drawer test were associated with persistent knee complaints (AUC 0.82).
We concluded that traumatic knee complaints in general practice seem to become a chronic disorder in 1 of 3 patients. Having knee complaints at 1-year follow-up is an important predictor for persistent knee complaints at 6-year follow-up. Several prognostic factors assessed at baseline were associated with persistent knee complaints at 1 and 6-year follow-up.

In **chapter 7** we investigate how to identify which patients with knee complaints in general practice will develop knee osteoarthritis (OA) at 6-year follow-up.
Adults (aged >35 years) with incident non-traumatic knee complaints (n=549) were followed for 6 years for the presence of knee OA, according to the clinical ACR criteria. In addition, at 6-year follow-up the presence of knee OA was identified based on a radiograph and the clinical & radiographic ACR criteria. Multivariable logistic regression analysis was used to identify baseline prognostic factors associated with the presence of knee OA at 6-year follow-up and the AUC was calculated.
According to the clinical ACR criteria, at baseline and at 1 and 6-years follow-up, 63%, 44% and 39% of the patients suffered from knee OA, respectively. In total, 45% of the patients switched from ACR positive/negative at the different follow-up points. Also, at 6-year follow-up, 39% and 31% of the patients suffered from knee OA based on the radiographs assessed with the Kellgren&Lawrence score (K&L) and the clinical & radiographic ACR criteria, respectively. Of the clinical ACR criteria, only age was independent significantly related with clinical and radiographic knee OA at 6-year follow-up. In addition, a BMI of >27, self-reported swollen knee, history of non-traumatic knee complaints and self-reported instability of the knee were also independent significantly related with clinical and radiographic knee OA (AUC of 0.81). Physical examination had no additional value.

We concluded that of patients with non-traumatic knee complaints seen in general practice, 31%-39% suffer from knee OA at 6-year follow-up. The clinical ACR criteria for knee OA were not appropriate for predicting which patients with knee complaints in general practice will develop knee OA at follow-up. For this, five baseline patient and symptom characteristics seemed more appropriate.

In **chapter 8** we identified degenerative abnormalities of the knee on MRI and radiography 6 years after knee trauma, and their relation with persistent knee complaints and prognostic factors at baseline (including MRI findings).
Adults (18-65 years) with incident traumatic knee complaints who visited their general practitioner were followed-up for 6 years. To identify degenerative abnormalities, an MRI was made at baseline and at 6-year follow-up, and a radiograph was made at 6-year follow-up. Logistic regression analysis was used to calculate associations between the various degenerative abnormalities on the 6-year MRI and the 6-year radiograph, their relation with persistent knee complaints, and to identify baseline prognostic factors associated with knee OA at the 6-year MRI.
On the 6-year radiograph, 60% of the patients showed no OA, 28% OA with a (K&L) grade 1 and 13% had a K&L grade 2. On the 6-year MRI, 55% of the patients showed cartilage defect(s), 45% osteophyte(s), 36% subchondral cyst(s), 40% bone marrow edema, 21% meniscal subluxation, 83% meniscal degeneration, 11% effusion and 11% a Baker's cyst. Most degenerative abnormalities on the 6-year MRI were significantly related with the K&L score on the 6-year radiograph. Only a few abnormalities (lateral cartilage defect(s), medial osteophyte(s) and medial meniscal subluxation)) were also significantly related with persistent knee complaints at 6-year follow-up. For knee OA seen on the 6-year MRI, 32% of the patients showed new onset or progressive knee OA. Age, history of non-traumatic knee complaints and bone marrow edema on the baseline MRI were independently related with new onset or progressive knee OA on the 6-year MRI.
We concluded that degenerative abnormalities on MRI of the knee are related to the K&L score from knee radiography; however, not all abnormalities are reflected in clinical outcome. Six years after knee trauma, knee OA is present in 32% of the patients. Age, history of non-traumatic knee complaints and bone marrow edema on MRI are possible predictors for new onset or progressive knee OA 6 years after knee trauma.

Chapter 9 presents the main findings of this thesis in relation to existing evidence and their addictive value. Besides we reflect in this chapter on the study limitations and their implications for daily practice and future research.

Samenvatting

Samenvatting

Huisartsen worden vaak bezocht door patiënten met verschillende soorten knieklachten. De incidentie van deze knieklachten gepresenteerd in de Nederlandse huisartsenpraktijk is ongeveer 13,7 per 1000 geregistreerde patiënten per jaar met een prevalentie van 19,0 per 1000 patiënten per jaar.
Ondanks dat knieklachten in de huisartsenpraktijk een veelvoorkomende aandoening is, is wetenschappelijk bewijs omtrent dit onderwerp schaars. Om het beleid omtrent knieklachten in de huisartsenpraktijk te verbeteren, is wetenschappelijk bewijs noodzakelijk op het gebied van diagnose, lange termijn natuurlijke beloop en prognostische factoren voor aanhoudende knieklachten en de ontwikkeling van knieartrose. Daarom hebben we een prospectieve observationele cohort studie (HONEUR knie cohort) opgezet met een follow-up van 6 jaar, met als doel het beloop van knieklachten en prognostische factoren voor aanhoudende knieklachten in de huisartsenpraktijk vast te stellen.

In **hoofdstuk 2** hebben we de diagnostische waarde van anamnese en lichamelijk onderzoek bepaald voor het vaststellen van mediaal collateraal bandletsel van de knie na een knieblessure gepresenteerd in de huisartsenpraktijk.
Patiënten tussen de 18 en 65 jaar met een knieblessure die hun huisarts bezochten binnen 5 weken na de blessure vulden een vragenlijst in, ondergingen een gestandaardiseerd lichamelijk onderzoek en een magnetic resonance imaging (MRI) scan. Univariate en mutivariate logistische regressie analyse werden gebruikt om mogelijke associaties tussen determinanten van anamnese /lichamelijk onderzoek en collateraal bandletsel te testen. De diagnostische waarde van anamnese en lichamelijk onderzoek werd bepaald voor die variabelen die een associatie ($p<0,15$) met mediaal collateraal bandletsel toonden door middel van sensitiviteit, specificiteit, voorspellende waardes en likelihoodratio's.
Van de 134 patiënten die geincludeerd zijn in deze studie, hadden er 35 (26%) een mediaal collateraal bandletsel op de MRI. Van de anamnese toonden de determinanten "blessure door externe kracht op het been" en "rotatieblessure" een associatie met mediaal collateraal bandletsel na multivariate analyse ($p<0,15$). Van lichamelijk onderzoek toonden "pijn valgus stress 30^{o}" en "laxiteit valgus stress 30^{o}" een associatie ($p<0,15$). Geïsoleerde determinanten van anamnese en lichamelijk onderzoek hadden enige diagnostische waarde; de positieve likelihoodratio (LR+) was 2,0 voor "blessure door externe kracht op het been" en 2,3 voor "pijn valgus stress 30^{o}". Toevoegen van "pijn valgus stress 30^{o}" en "laxiteit valgus stress 30^{o}" van lichamelijk onderzoek aan de anamnese verhoogde de diagnostische waarde naar een LR+ van 6,4.

We concludeerden dat mediaal collateraal bandletsel frequent gezien wordt bij patiënten met een knieblessure. Anamnese heeft enige diagnostische waarde, terwijl lichamelijk onderzoek de diagnostische waarde verhoogt.

In **hoofdstuk 3** hebben we de diagnostische waarde van anamnese en lichamelijk onderzoek bepaald voor het vaststellen van effusie van de knie na een knieblessure gepresenteerd in de huisartsenpraktijk. Aanvullend bepaalden we ook de associatie tussen effusie op de MRI en intra-articulair knieletsel.
Patiënten tussen de 18 en 65 jaar met een knieblessure die hun huisarts bezochten binnen 5 weken na de blessure vulden een vragenlijst in, ondergingen een gestandaardiseerd lichamelijk onderzoek en een magnetic resonance imaging (MRI) scan. Univariate en mutivariate logistische regressie analyse werden uitgevoerd om mogelijke associaties tussen determinanten van anamnese /lichamelijk onderzoek en effusie van de knie te testen. De diagnostische waarde van anamnese en lichamelijk onderzoek werd bepaald voor die variabelen die een associatie ($p<0,15$) met effusie toonden door middel van sensitiviteit, specificiteit, voorspellende waardes en likelihoodratio's. De relatie tussen effusie en intra-articulair knieletsel werd bepaald met een Chi-squaretest.
Van de 134 patiënten die meededen aan deze studie, hadden er 42 (31%) effusie van het kniegewricht op de MRI. Multivariate analyse toonde een associatie met effusie van het kniegewricht voor het symptoom "zelf gerapporteerde zwelling" (anamnese) en voor de "ballottement test" (lichamelijk onderzoek); LR+ was 1,5 en 1,6 respectievelijk. Effusie toonde een positieve associatie met intra-articulair knieletsel ($p=0,002$); 31 (74%) van de 42 patiënten met effusie van het kniegewricht had intra-articulair letsel van de knie.
We concludeerden dat bij patiënten met een knieblessure effusie frequent wordt gezien. De combinatie van zelf gerapporteerde zwelling en de ballottement test was van diagnostische waarde. Effusie van het kniegewricht gezien op de MRI was geassocieerd met intra-articulair knieletsel.

In **hoofdstuk 4** hebben we het 1 en 6-jaar beloop van niet-traumatische knieklachten bij adolescenten en jongvolwassenen beschreven die zich presenteerden in de huisartsenpraktijk, en identificeerden we prognostische factoren voor aanhoudende knieklachten.
Adolescenten en jongvolwassenen (12-35 jaar; n=191) met niet-traumatische knieklachten werden geïncludeerd door hun huisarts en gevolgd voor 6 jaar. Tussen baseline en follow-up vulden patiënten vragenlijsten in betreffende hun knieklachten en ervaren herstel. Een gestandaardiseerd lichamelijk onderzoek werd uitgevoerd op baseline en 1-jaar follow-up. Beschrijvende statistiek werd gebruikt om het beloop van de knieklachten te beschrijven Multivariate logistische regressie analyse werd gebruikt om prognostische factoren voor aanhoudende knieklachten op 1 en 6-jaar follow-up te identificeren en de area under the receiver operating curve (AUC) werd berekend.

Op 1-jaar follow-up rapporteerde 78 (47%) van de beschikbare patiënten en op 6-jaar follow-up 29 (27%) van de beschikbare patiënten, aanhoudende knieklachten. Patiënten met patellofemoraal pijn syndroom (n=45) hadden de slechtste prognose, met een 40% rapportage van aanhoudende knieklachten op 6-jaar follow-up. Er was een positieve relatie OR 4,8, 95% BI 1,8-12,8, tussen het hebben van aanhoudende knieklachten op 1-jaar follow-up en 6-jaar follow-up. Prognostische factoren bepaald op baseline die geassocieerd waren met aanhoudende knieklachten op 1 jaar follow-up waren body mass index (BMI) >25, laag/gemiddeld opleidingsniveau, slechte algemene gezondheid, bilaterale klachten, zelf gerapporteerde gezwollen knie, aanwezigheid van slotstand van de knie, pijnlijk patellair ligament, en afwezigheid van een balloterende patella (AUC 0,75). Op 6-jaar follow-up laag/gemiddeld opleidingsniveau, zelf gerapporteerde gezwollen knie, pijnlijk patellair ligament, en afwezigheid van een balloterende patella (AUC 0,76).
We concludeerden dat de prognose van niet-traumatische knieklachten bij adolescenten en jongvolwassenen niet zo goed is als eerder verondersteld werd. Verschillende prognostische factoren verzameld op baseline waren geassocieerd met aanhoudende knieklachten bij follow-up.

In **hoofdstuk 5** hebben we het 6-jaar beloop beschreven van niet-traumatische knieklachten bij volwassenen die zich presenteerden in de huisartsenpraktijk, we identificeerden prognostische factoren voor een ongunstige uitkomst en ontwikkelden een klinische beslisregel.
Volwassenen (>35 jaar) met incidente niet-traumatische knieklachten (n=549) werden 6 jaar gevolgd. Multivariate logistische regressie analyse werd gebruikt om prognostische factoren te identificeren die geassocieerd werden met een ongunstige uitkomst, de AUC werd berekend om het onderscheidende vermogen te bepalen en een klinische beslisregel werd ontwikkeld. Een ongunstige uitkomst was gedefinieerd als aanhoudende knieklachten op 6-jaar follow-up of het hebben ondergaan van een knievervangende operatie gedurende follow-up.
Op 6-jaar follow-up hadden 143 (42%) van de patiënten een ongunstige uitkomst. Het hebben van aanhoudende knieklachten (OR 5,31, 95% BI 3,27-8,61) en het voldoen aan de ACR criteria voor knieartrose (OR 2,65, 95% BI 1,48-4,73) op 1-jaar follow-up waren beide significant geassocieerd met een ongunstige uitkomst, terwijl het voldoen aan de ACR criteria voor knieartrose op baseline dat niet was. Baseline factoren onafhankelijk geassocieerd met een ongunstige uitkomst waren laag/gemiddeld opleidingsniveau, co-morbiditeit van het skeletale systeem, duur van de knieklachten > 3 maanden, bilaterale knieklachten, zelf gerapporteerde warme knie, voorgeschiedenis van niet-traumatische knieklachten, valgus stand, pijn bij passieve flexie/extensie en benige verbreding van het kniegewricht (AUC 0,80).

We concludeerden dat niet-traumatische knieklachten bij volwassenen in de huisartsenpraktijk een chronische aandoening wordt in bijna de helft van de patiënten. De door ons ontwikkelde klinische beslisregel met 10 baseline prognostische factoren kan gebruikt worden om hoog risico patiënten voor een ongunstige uitkomst te selecteren.

In **hoofdstuk 6** hebben we het 1 en 6-jaar beloop beschreven van traumatische knieklachten bij adolescenten en volwassenen die zich in de huisartsenpraktijk presenteerden en identificeerden we prognostische factoren voor aanhoudende knieklachten.
Adolescenten (>12 jaar) en volwassenen met traumatische knieklachten (n=328) werden geïncludeerd door hun huisarts en gevolgd voor 6 jaar. Patiënten vulden vragenlijsten in en ondergingen een gestandaardiseerd lichamelijk onderzoek. Beschrijvende statistiek werd gebruikt om het beloop van de knieklachten te beschrijven. Multivariate logistische regressie analyse werd gebuikt om prognostische factoren te identificeren voor aanhoudende knieklachten op 1 en 6-jaar follow-up, en de AUC werd berekend.
Aanhoudende knieklachten werden gerapporteerd door 81 (27%) van de patiënten op 1-jaar en door 60 (33%) patiënten op 6-jaar follow-up. Er was een sterke relatie (OR 11,0, 95% BI 5,0-24,2) tussen het hebben van aanhoudende knieklachten op 1 jaar en 6-jaar follow-up. Patiënten die herstelden rapporteerden een gemiddelde hersteltijd van 7,4 maanden. Prognostische factoren geassocieerd met aanhoudende knieklachten op 1-jaar follow-up waren leeftijd, slechte algemene gezondheid, voorgeschiedenis van niet-traumatische knieklachten, afwezigheid van een balloterende patella en laxiteit bij de voorste schuiflade test (AUC 0,72). Op 6 jaar follow-up waren BMI >27, niet-skeletale comorbiditeit, zelf gerapporteerd kraken van de knie, voorgeschiedenis van niet-traumatische knieklachten en laxiteit bij de voorste schuiflade test geassocieerd met aanhoudende knieklachten (AUC 0,82).
We concludeerden dat traumatische knieklachten in de huisartsenpraktijk bij 1 op de 3 patiënten een chronische aandoening wordt. Het hebben van knieklachten op 1-jaar follow-up is een belangrijke voorspeller voor het hebben van aanhoudende knieklachten op 6-jaar follow-up. Verscheidende prognostische factoren waren geassocieerd met aanhoudende knieklachten op 1 en 6-jaar follow-up.

In **hoofdstuk 7** hebben we beschreven hoe we kunnen identificeren welke patiënten met niet-traumatische knieklachten in de huisartsenpraktijk knieartrose hebben ontwikkeld op 6 jaar follow-up.
Volwassenen (leeftijd >35 jaar) met incidente niet-traumatische knieklachten (n=549) werden 6 jaar gevold op de aanwezigheid van knieartrose volgens de klinische ACR-criteria. Aanvullend werd op 6-jaar follow-up ook de aanwezigheid van knieartrose bepaald aan de hand van een röntgenfoto en de klinische & radiologische ACR criteria. Multivariate logistische regressie analyse werd gebruikt om te identificeren welke

baseline factoren waren geassocieerd met de aanwezigheid van knieartrose op 6-jaar follow-up en de AUC werd berekend.
Volgens de klinische ACR criteria op baseline, 1 en 6-jaar follow-up, leed respectievelijk 63%, 44% en 39% van de patiënten aan knieartrose. In totaal wisselde 45% van de patiënten van ACR positief/negatief op de verschillende follow-up momenten. Op 6-jaar follow-up leed 39% en 31% van de patiënten aan knieartrose gebaseerd op respectievelijk de Kellgrenn&Lawrence (K&L) score op de röntgenfoto en de klinische & radiologische ACR criteria. Van de klinische ACR criteria was alleen leeftijd onafhankelijk geassocieerd met klinische & radiologische knieartrose op 6-jaar follow-up. Aanvullend, BMI >27, zelf gerapporteerde gezwollen knie, voorgeschiedenis van niet-traumatische knieklachten en zelf gerapporteerde instabiliteit van de knie waren onafhankelijk geassocieerd met klinische & radiologische knieartrose (AUC 0,81). Lichamelijk onderzoek had geen aanvullende waarde.
We concludeerden dat 31-39% van de volwassenen die zich presenteerden met niet-traumatische knieklachten in de huisartsenpraktijk lijden aan knieartrose op 6-jaar follow-up. De klinische ACR criteria voor knieartrose zijn niet geschikt om te voorspellen welke patiënten met knieklachten in de huisartsenpraktijk knieartrose zullen ontwikkelen. In plaats daarvan lijken 5 andere baseline patiënt en symptoom karakteristieken beter geschikt daarvoor.

In **hoofdstuk 8** hebben we de degeneratieve afwijkingen van de knie op de MRI en de röntgenfoto 6 jaar na de knieblessure, hun relatie met aanhoudende knieklachten en prognostische factoren op baseline (inclusief MRI bevindingen) beschreven.
Volwassenen (18-65 jaar) die hun huisarts bezochten met een incidente knieblessure werden gevolgd voor 6 jaar (n=134). Een MRI werd gemaakt op baseline en 6 jaar follow-up om degeneratieve afwijkingen te identificeren. Tevens werd op 6-jaar follow-up een röntgenfoto van de knie gemaakt. Logistische regressie analyse werd gebruikt om de associaties tussen de verscheidende degeneratieve afwijkingen op de 6-jaar MRI en 6-jaar röntgenfoto te berekenen, hun relatie met aanhoudende knieklachten te bepalen en om te identificeren welke baseline factoren geassocieerd waren met knieartrose op de 6-jaar MRI.
Op de 6-jaar röntgenfoto had 60% van de patiënten geen knieartrose, 28% knieartrose met een K&L score 1 en 13% met een K&L score 2. Op de 6-jaar MRI had 55% van de patiënten kraakbeendefecten, 45% osteofyten, 36% subchondrale cysten, 40% beenmergoedeem, 21% subluxatie van de meniscus, 83% meniscusdegeneratie, 11% effusie en 11% Bakerse cyste. De meeste degeneratieve afwijkingen op de 6-jaar MRI waren significant geassocieerd met de K&L score op de 6-jaar röntgenfoto. Alleen enkele afwijkingen (laterale kraakbeendefecten, mediale osteofyten en mediale meniscussubluxatie) waren ook significant geassocieerd met aanhoudende knieklachten op 6-jaar follow-up. Op de 6-jaar MRI toonde 32% van de patiënten nieuw ontstane of

progressie van bestaande knieartrose. Leeftijd, voorgeschiedenis van niet-traumatische knieklachten en beenmergoedeem op de baseline MRI waren onafhankelijk geassocieerd met nieuw ontstane of progressie van bestaande knieartrose op de 6-jaar MRI.
We concludeerden dat degeneratieve afwijkingen op de MRI van de knie gerelateerd zijn aan de K&L score op de röntgenfoto van de knie, echter worden niet alle degeneratieve afwijkingen gereflecteerd in de klinische uitkomst. Zes jaar na de knieblessure is knieartrose bij 32% van de patiënten aanwezig. Leeftijd, voorgeschiedenis van niet-traumatische knieklachten en beenmergoedeem op de MRI zijn mogelijke voorspellers van nieuw ontstane of progressie van bestaande knieartrose 6 jaar na de knieblessure.

In **hoofdstuk 9** zijn de belangrijkste bevindingen van dit proefschrift uiteengezet in relatie tot de bestaande literatuur en hun toegevoegde waarde hierop. Daarnaast wordt er in dit hoofdstuk gereflecteerd op de beperkingen van het onderzoek en de implicaties voor de dagelijkse praktijk en toekomstig onderzoek.

Dankwoord

Dankwoord

In dit dankwoord wil ik graag iedereen bedanken die bijgedragen heeft aan de totstandkoming van dit proefschrift. Zonder de patiënten en huisartsen die deelgenomen hebben aan het HONEUR kniecohort was dit onderzoek niet van de grond gekomen. Allereerst wil ik hen daar dus voor bedanken: bedankt voor jullie tijd, inzet, enthousiasme en de bereidheid om na 6 jaar nog weer mee te werken aan ons onderzoek! Het is onmogelijk om iedereen bij naam te noemen, maar een aantal personen wil ik graag specifiek bedanken.

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Curriculum Vitae

Curriculum Vitae

Marlous Kastelein is op 17 november 1983 geboren in Voorburg. Na het behalen van haar VWO diploma aan College ‘t Loo in Voorburg is zij in 2002 begonnen met de studie geneeskunde aan de Erasmus Universiteit in Rotterdam. Tijdens haar studie geneeskunde volgde zij keuzeonderwijs in de klinische genetica. In 2007/2008 deed zij bij de afdeling huisartsgeneeskunde 21 weken onderzoek naar de diagnostische waarde van anamnese en lichamelijk onderzoek bij patiënten met traumatische knieklachten in de huisartsenpraktijk. Dit resulteerde in 2 internationale en 2 nationale publicaties (waarvan 1 dubbelpublicatie). Tijdens haar coschappen volgde zij de keuze coschappen dermatologie en psychiatrie. Zij doorliep haar oudste coschap in een huisartsenpraktijk in Nootdorp. Na het behalen van het artsenexamen in 2008 werd zij in september 2008 zowel bij de huisartsenopleiding als de onderzoeksafdeling huisartsgeneeskunde van de Erasmus Universiteit Rotterdam aangenomen, wat resulteerde in een 5-jarig combinatietraject van de opleiding tot huisarts en wetenschappelijk onderzoeker (aiotho-traject). Op deze manier kon zij het onderzoek waarmee zij begonnen was tijdens de studie geneeskunde voortzetten middels een promotietraject. Zij werkte 2 jaar, namelijk in 2008/2009 en 2010/2011, aan haar promotietraject. In augustus 2009 behaalde zij haar Master of Science in de klinische epidemiologie aan het Nederlands Instituut for Health Sciences (NIHES). Het eerste jaar van de huisartsenopleiding volgde zij in 2009/2010 in een huisartsenpraktijk in Gilze, gemeente Gilze-Rijen. Vanaf 2012 is zij bezig om de laatste 2 jaar van de huisartsenopleiding te voltooien.
Zij woont samen met Alex Ruigendijk, hebben een dochter Aimee en wonen in Berkel en Rodenrijs (gemeente Lansingerland).

PhD Portfolio

PhD Portfolio

Name PhD student: Marlous Kastelein
ErasmusMC Department: General practice
PhD period: 2008-2012
Promotoren: Prof. dr. S.M.A. Bierma-Zeinstra, Prof. dr. B.W. Koes
Copromotor: Dr. P.A.J. Luijsterburg

PhD training

Research skills

- MSc training in Clinical Epidemiology, NIHES, Rotterdam, 2008-2009 (70 ECTS)
    - Erasmus Summer Programme: Principles of Research in Medicine, Clinical Decision Analysis, Methods of Public Health Research, Clinical Trials, Health Economics, Conceptual founding of epidemiologic Study Design, Cohort studies, Case-control Studies, Introduction to Public Health, Primary and Secondary Prevention Research, Introduction to Decision-making in Medicine, Topics in Health and Diseases in the Elderly
    - Core Curriculum: Study Design, Classical methods for Data-analysis, Clinical Epidemiology, Methodological Topics in Epidemiologic Research, Modern Statistical Methods.
    - Advanced Short Courses: Prognostic Research, Advanced Topics in Decision-making in Medicine, Planning and Evaluation of Screening
- Basiscursus Regelgeving en Organisatie van Klinische trials (BROK), 2009 (1 ECTS)

Professional Education

Vocational training for general practitioner, Erasmus MC, Department of General Practice, 2009 - present

Presentations

- Annual Science Conference of the Dutch College of General practitioners (NHG)
    - 2008, Rotterdam, oral presentation
    - 2011, Nijmegen, oral presentation and poster presentation
- Annual Conference of the Royal Dutch Society for Physical Therapy (KNGF)
    - 2009, Amsterdam, oral presentation
- Primary Care Musculoskeletal Research Congress (PRIMUS)
    - 2010, Rotterdam, oral presentation and poster presentation

Interviews

- Dutch Journal for Medicine (NTVG), 2009, Podcast

- Reuters Health's professional news wire, 2011, Article

Additional publication

Kastelein M, Wagemakers HPA, Luijsterburg PAJ, Berger MY, Koes BW, Bierma-Zeinstra SMA. The value of anamnesis and physical examination in the diagnosis of traumatic knee injury [in Dutch]. Huisarts Wet 2008;51(11):528-35.

Teaching activities

Supervising medical students, 2009, 2010 and 2011