Knee complaints and prognosis of osteoarthritis at 10 years : impact of ACL ruptures, meniscal tears, genetic predisposition and surgery

Huetink, K.

Knee complaints and prognosis of osteoarthritis at 10 years

Impact of ACL ruptures, Meniscal tears, Genetic predisposition and Surgery

Kasper Huétink

ISBN: 978-94-6169-737-0

Printed by: Optima Grafische Communicatie, Rotterdam

Cover design: Wouter van de Maat

Knee complaints and prognosis of osteoarthritis at 10 years

Impact of ACL ruptures, Meniscal tears, Genetic predisposition and Surgery

Poefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 23 september 2015
klokke 13.45 uur

door

Kasper Huétink
geboren te Borne in 1975

Promotores

Prof. Dr. R.G.H.H. Nelissen

Prof. Dr. J.L. Bloem

Co-promotor

Dr. A.R. van Erkel

Promotiecommissie

Dr. I. Meulenbelt

Prof. dr. C.N. van Dijk, Academisch Medisch Centrum te Amsterdam

Prof. dr . S.M.A. Bierma-Zeinstra, Erasmus Medisch Centrum te Rotterdam

Publication of this thesis was financially supported by the Dutch Arthritis Association (Reumafonds).

Aan Lena, Bram en Teun

Aan mijn ouders

Contents

Chapter 1

General Introduction

Of musculoskeletal disorders, knee complaints are the second most frequent reason (after spine related pain) for consulting the general practitioner (1). Knee Osteoarthritis (OA) is a common chronic medical condition leading to progressive structural damage of the joints and subsequent functional disability (2). Until the age of 45 knee OA is rarely diagnosed and knee complaints are often related to(sports)injury and patellofemoral knee pain (1). In older adults, there is a significant increase of the incidence and prevalence of knee OA (incidence in the age groups of 45 to 64 years, from 65 to 74 years and 75 years and older in men: 1.9, 4.1 and 7.3, respectively in women; 3.2 , 10.9 and 13.9 per 1000 people per year). Above the age of 74 years, the prevalence in men is 47.3 and 19.7 in women per 1,000 persons per year (1).

Knee OA may develop after knee injury (3), whereas in other patients knee OA develops in a more generalized way without specific trauma, affecting multiple other joints. Known risk factors for the development of OA are mechanical forces including trauma, age, female gender, family history of OA, genetics, obesity, morphologic changes and OA localization in another joint (2;4-9). To date no effective disease modifying medical therapy is available (10).

Since OA is a disease affecting the elderly, studies investigating factors involved in OA development are usually performed in older populations with mean ages ranging from 50 to 80 years (5;11-13). Determining which risk-factors of OA development can be distinguished early in life may help to define high-risk knee patients for the development of knee OA. This could be of clinical importance because high risk patients may benefit from slowing down or even stopping the OA process by early preventive exercise therapy or in the future to develop disease modifying medication, since to date no effective disease modifying medical therapy is available (10;14-16).

To identify risk factors for OA early in life, we conducted a study to investigate knee function and knee OA development after 10 years in 326 patients (mean age 32, SD 7.7) with a history of sub-acute knee complaints. Inclusion criteria 10 years ago were: persistent knee complaints e.g. pain, swelling and instability lasting for more than four weeks. Exclusion criteria were: knee complaints lasting less than four weeks, clinical symptoms of a locked knee, known inflammatory diseases such as rheumatoid arthritis, moderate to severe radiographic knee OA and a history of knee surgery. All patients were part of a cohort of 855 knee patients who participated in a study on the cost-effectiveness of 0.5T magnetic resonance (MR) imaging relative to diagnostic arthroscopy

(17). The main objective of the study was to determine which prognostic factors for knee OA development could be identified in this relatively young population with a history of knee complaints. Identifying these specific prognostic factors may help to distinguish high-risk knee patients for the development of knee OA early in life, and to develop ways to slow down OA progression towards end stage disease.

In **Chapter 2** we investigated the role of anterior cruciate ligament (ACL) and meniscal lesions and subsequent change in biomechanics of knee movement in the development of osteoarthritic changes visible on radiographs and MR imaging. Until recently, knee OA has been primarily visualized and assessed on radiographs by using the Kellgren and Lawrence (KL) scoring system (18). Investigators in large prospective studies have used radiographs with follow-up times of 10–22 years to assess the effect of meniscal and anterior cruciate ligament (ACL) lesions on the development and progression of knee OA (19-22). Magnetic resonance (MR) imaging, owing to its ability to depict cartilage damage, subchondral bone, and bone marrow lesions, has however potential advantages in assessing the development of OA (23;24). Being a relatively new imaging modality, most MR imaging studies have been cross-sectional or have involved a maximal follow-up time of only 3 years (25-28). Since no long-term MR studies were available, we wanted to determine the relationship between knee OA development detected on both radiographs and 3.0-T MR images after 10 years and the presence of ACL ruptures or meniscal tears and the effect on OA development of surgical management of these lesions. The advantages of MR imaging could be useful in determining early OA changes in a relatively young study population.

In **Chapter 3** the accuracy and sensitivity to change in hand joint space width (JSW) measurements by a newly developed quantification method is investigated.
Being a multi-factorial disease, relationships between knee OA development and the presence of OA in other joints, especially the hands have been described (29). Hand radiographs are used commonly to diagnose and monitor hand OA because of their wide availability and the relatively low costs. Since cartilage cannot be visualized by radiography, decrease of joint space width (JSW) is used as a surrogate marker for cartilage defects. Semi-quantitative methods with standard

atlases are the bench tools used by clinicians to determine changes in JSW (18;30). However, there is a limitation in reproducibility due to the difficulty to standardize the scoring between different readers. Since OA is a slowly progressive disease, an accurate and reproducible method is needed to detect subtle changes throughout follow-up, especially when evaluating new therapies. A newly developed JSW quantification method automatically detects the interphalangeal (IP) and metacarpophalangeal (MCP) joints and quantifies the JSW in hand radiographs (31). We assessed the accuracy and sensitivity to change in JSW of this quantification method by comparing the automatically determined JSW to the true distance between bony contours of the finger joints. Being able to detect small changes in JSW would make this method ideal for determining early OA changes in the hand and relate these changes to knee OA development in our relatively young study population.

In **Chapter 4** we investigated which of the following OA risk factors: ACL and /or meniscal lesions, age, female gender, body mass index (BMI), activity level before knee complaints, a family history of OA and the presence of hand OA could be related to OA development in our relatively young study population. Furthermore, subjective knee function 10 years after knee complaints was determined in relation to osteoarthritic changes, age, gender BMI and activity level before the knee complaints.

In **Chapter 5** the effect of surgical intervention on OA development shown on radiographs and MR imaging is reported in Chapter 2. Additionally, we investigated the short-term and long-term clinical effects of surgical management of the knee complaints in knee patients with traumatic knee complaints but without knee locking. Meniscetomy is commonly performed in patients with knee complaints and meniscal tears (32). Recent publications showed no benefits of meniscectomy compared to conservative therapy in patients with degenerative meniscal tears (33-35). It is suggested that knee locking in patients with meniscal tears could be considered an indication for surgical treatment but there remains controversy on the surgical management of traumatic meniscal lesions, especially in those patients without locking symptoms (36). We evaluated the long term clinical effect of meniscectomy in patients with knee complaints without

ACL lesions and with at least one traumatic tear but without symptoms of knee locking. Differences in knee function and symptoms scores at ten year follow-up were compared between surgically and non-surgically treated patients.

The purpose of this study described in **Chapter 6** was to examine the contribution of the OA susceptibility genes *ASPN, GDF5, DIO2* and the 7q22 region to radiographic development of knee osteoarthritis (OA) in patients with a mean age of 40.6 years ± 7.9 (SD) who suffered from non-acute knee complaints a decade earlier. A dose response association of 4 SNP's on the susceptibility genes *ASPN, GDF5, DIO2* and the *7q22 locus* were determined by comparing 36 patients who showed development of OA on radiographs with 88 patients who had no development of OA on radiographs and normal cartilage on MRI. OA development was defined as a Kellgren and Lawrence (K&L) score >1. Multivariate logistic regression analysis including the variables age, gender, body mass index (BMI) and reported knee trauma was performed to determine associations between OA development and the presence of the risk alleles.

Reference List

1. vd Linden MW, Westert GP, de Bakker DH, Schellevis FG. Second national study to disaeses and actions in general practice: complaints and disorders in the population and in general practice (in Dutch). 2004. Utrecht, Bilthoven, NIVEL/RIVM. Ref Type: Report

2. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann.Intern.Med. 2000;635-46.

3. Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis.Cartilage. 2011;1286-93.

4. Bierma-Zeinstra SM, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. Nat.Clin.Pract.Rheumatol. 2007;78-85.

5. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis.Cartilage. 2010;24-33.

6. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC.Musculoskelet.Disord. 2008;132.

7. Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK, Felson DT. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann.Rheum.Dis. 2011;1581-6.

8. Kalichman L, Hernandez-Molina G. Hand osteoarthritis: an epidemiological perspective. Semin.Arthritis Rheum. 2010;465-76.

9. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum.Dis.Clin.North Am. 2013;1-19.

10. Martel-Pelletier J, Wildi LM, Pelletier JP. Future therapeutics for osteoarthritis. Bone 2012;297-311.

11. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, Zhao Y, Wang C. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;291-7.

12. Jonsson H, Helgadottir GP, Aspelund T, Eiriksdottir G, Sigurdsson S, Siggeirsdottir K, Ingvarsson T, Harris TB, Launer L, Gudnason V. Hand Osteoarthritis Severity is

Associated with Total Knee Joint Replacements Independently of BMI. The Ages-Reykjavik Study. Open.Rheumatol.J. 2011;7-12.

13. Riyazi N, Meulenbelt I, Kroon HM, Ronday KH, Hellio Le Graverand MP, Rosendaal FR, Breedveld FC, Slagboom PE, Kloppenburg M. Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: the GARP study. Ann.Rheum.Dis. 2005;438-43.

14. Hunter DJ, Hellio Le Graverand-Gastineau MP. How close are we to having structure-modifying drugs available? Med.Clin.North Am. 2009;223-34, xiii.

15. Rannou F, Poiraudeau S. Non-pharmacological approaches for the treatment of osteoarthritis. Best.Pract.Res.Clin.Rheumatol. 2010;93-106.

16. Smink AJ, van den Ende CH, Vliet Vlieland TP, Swierstra BA, Kortland JH, Bijlsma JW, Voorn TB, Schers HJ, Bierma-Zeinstra SM, Dekker J. "Beating osteoARThritis": development of a stepped care strategy to optimize utilization and timing of non-surgical treatment modalities for patients with hip or knee osteoarthritis. Clin.Rheumatol. 2011;1623-9.

17. Vincken PW, ter Braak AP, van Erkel AR, Coerkamp EG, de Rooy TP, de LS, Mallens WM, Coene LN, Bloem RM, van Luijt PA, van den Hout WB, van Houwelingen HC, Bloem JL. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 2007;85-93.

18. Kilgoren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann.Rheum.Dis. 1957;494-502.

19. Chan WP, Huang GS, Hsu SM, Chang YC, Ho WP. Radiographic joint space narrowing in osteoarthritis of the knee: relationship to meniscal tears and duration of pain. Skeletal Radiol. 2008;917-22.

20. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum. 2003;2178-87.

21. Kessler MA, Behrend H, Henz S, Stutz G, Rukavina A, Kuster MS. Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. Knee.Surg.Sports Traumatol.Arthrosc. 2008;442-8.

22. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004;3145-52.

23. Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H, Roemer FW. Imaging in osteoarthritis. Rheum.Dis.Clin.North Am. 2008;645-87.

24. Hunter DJ, Arden N, Conaghan PG, Eckstein F, Gold G, Grainger A, Guermazi A, Harvey W, Jones G, Hellio Le Graverand MP, Laredo JD, Lo G, Losina E, Mosher TJ, Roemer F, Zhang W. Definition of osteoarthritis on MRI: results of a Delphi exercise. Osteoarthritis.Cartilage. 2011;963-9.

25. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, Raynauld JP, Cicuttini F, Jones G. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. J.Rheumatol. 2007;776-84.

26. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M, Guermazi A, Grigorian M, Gale D, Felson DT. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum. 2006;795-801.

27. Madan-Sharma R, Kloppenburg M, Kornaat PR, Botha-Scheepers SA, Le Graverand MP, Bloem JL, Watt I. Do MRI features at baseline predict radiographic joint space narrowing in the medial compartment of the osteoarthritic knee 2 years later? Skeletal Radiol. 2008;805-11.

28. Pelletier JP, Raynauld JP, Berthiaume MJ, Abram F, Choquette D, Haraoui B, Beary JF, Cline GA, Meyer JM, Martel-Pelletier J. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. Arthritis Res.Ther. 2007;R74.

29. Doherty M, Watt I, Dieppe P. Influence of primary generalised osteoarthritis on development of secondary osteoarthritis. Lancet 1983;8-11.

30. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis Osteoarthritis.Cartilage. 1995;3-70.

31. van 't Klooster R., Hendriks EA, Watt I, Kloppenburg M, Reiber JH, Stoel BC. Automatic quantification of osteoarthritis in hand radiographs: validation of a new method to measure joint space width. Osteoarthritis.Cartilage. 2008;18-25.

32. Montgomery SR, Zhang A, Ngo SS, Wang JC, Hame SL. Cross-sectional analysis of trends in meniscectomy and meniscus repair. Orthopedics 2013;e1007-e1013.

33. Herrlin SV, Wange PO, Lapidus G, Hallander M, Werner S, Weidenhielm L. Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up. Knee.Surg.Sports Traumatol.Arthrosc. 2013;358-64.

34. Katz JN, Losina E. Surgery versus physical therapy for meniscal tear and osteoarthritis. N.Engl.J.Med. 2013;677-8.

35. Sihvonen R, Paavola M, Malmivaara A, Itala A, Joukainen A, Nurmi H, Kalske J, Jarvinen TL. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N.Engl.J.Med. 2013;2515-24.

36. Lyman S, Oh LS, Reinhardt KR, Mandl LA, Katz JN, Levy BA, Marx RG. Surgical decision making for arthroscopic partial meniscectomy in patients aged over 40 years. Arthroscopy 2012;492-501.

37. Evangelou E, Kerkhof HJ, Styrkarsdottir U, et al. A meta-analysis of genome-wide association studies identifies novel variants associated with osteoarthritis of the hip. Ann.Rheum.Dis. 2014;2130-6.

38. Cooper C, Snow S, McAlindon TE, Kellingray S, Stuart B, Coggon D, Dieppe PA. Risk factors for the incidence and progression of radiographic knee osteoarthritis. Arthritis Rheum. 2000;995-1000.

39. Meulenbelt I, Min JL, Bos S, Riyazi N. et al. Identification of DIO2 as a new susceptibility locus for symptomatic osteoarthritis. Hum.Mol.Genet. 2008;1867-75.

40. Bomer N, den Hollander W, Ramos YF, et al. Underlying molecular mechanisms of DIO2 susceptibility in symptomatic osteoarthritis. Ann.Rheum.Dis. 2014.

Chapter 2

Localized development of knee osteoarthritis (OA) can be predicted from MRI findings a decade earlier

Kasper Huétink

Rob G.H.H. Nelissen

Iain Watt

Arian R. van Erkel

Johan L. Bloem

Radiology August 2010

Abstract

Purpose

To define localized development of knee osteoarthritis (OA) that arises from anterior cruciate ligament (ACL) and meniscal injuries identified at magnetic resonance (MR) imaging performed a decade ago and the subsequent management of those findings in patients with subacute knee symptoms.

Materials and Methods

The present study was approved by local medical ethics review boards, and written informed consent was obtained. Three hundred twenty-six patients (mean age, 42 years; 108 female) from a previously reported series of 855 patients were followed up with regard to the effect of MR imaging–guided treatment for subacute knee problems. The mean follow-up period was 10 years. Initial findings and treatment were compared with the follow-up radiograph and 3.0-T MR image findings. Odds ratios (ORs), with corresponding 95% confidence intervals, were used to identify the effects between variables.

Results

Patients with ACL ruptures had an increased risk of developing joint space narrowing (JSN), cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts medially or laterally (OR, 2.4–9.8). Patients with medial meniscal tears had an increased risk of developing JSN, cartilaginous defects, osteophytes, and bone marrow lesions medially (OR, 2.0–15.3). Patients with lateral meniscal tears had an increased risk of developing JSN, cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts laterally (OR, 2.1–10.5). Meniscectomy had no effect on the risk of developing OA.

Conclusion

Localized knee OA developed from risk factors identified from the findings of MR imaging performed a decade ago in patients with subacute knee symptoms and did not depend on the surgical treatment of those findings.

Introduction

Osteoarthritis (OA) of the knee is a common public health problem. More than 30% of the population that is aged 60 years or older has radiographically detectable knee OA (1). Knee OA has been primarily visualized and assessed on radiographs by using the Kellgren and Lawrence (KL) scoring system (2). Investigators in large prospective studies have used radiographs with follow-up times of 10–22 years to assess the effect of meniscal and anterior cruciate ligament (ACL) lesions on the development and progression of knee OA (3–10).

Magnetic resonance (MR) imaging, owing to its ability to depict cartilage damage, subchondral bone, and bone marrow lesions, has potential advantages in assessing the development of OA (11,12). Recently published MR imaging studies, however, have been cross-sectional or have involved a maximal follow-up time of only 3 years (13–16).

Ten years ago, the effect of MR imaging–guided treatment on the outcomes of 855 patients with subacute knee problems was studied (17). The aim of the present study was to define localized knee OA detected at radiography and 3.0-T MR imaging that developed from risk factors identified on MR images obtained a decade ago and the subsequent management of those findings in patients with subacute knee symptoms 10 years ago.

Material and Methods

Study population

The current study was approved by the medical ethics review boards of the three participating hospitals, and written informed consent was obtained from each participant. Patient records were retrieved from the database of a previous prospective study, which was performed in 1996 and 1997 in three different hospitals. The study sponsor (Dutch Arthritis Association) had no involvement in the study design, data collection, data analysis, or results interpretation.

The objective of the previous study was to evaluate the diagnostic value of knee MR imaging relative to arthroscopy in patients with subacute knee problems (17). Subacute knee problems were defined as persistent knee problems lasting for more than 4 weeks. Only patients with

persistent knee problems lasting for more than 4 weeks who sought physician attention were included. A total of 855 patients between the ages of 16 and 45 years (mean age, 31 years ± 8.0 [standard deviation]) participated. Exclusion criteria were knee problems lasting less than 4 weeks, clinical symptoms of a locked knee, known inflammatory diseases such as rheumatoid arthritis, known OA (KL score≥4), or history of knee surgery. All participants underwent physical knee examination, MR imaging, and radiography of the knee. Knee arthroscopy was performed randomly in 161 (50%) of 321 patients with abnormal clinical examination results and normal MR findings.

The current study is a follow-up of the above described study population (mean follow-up, 10 years ± 0.90). All 855 patients from the original cohort were invited by mail for follow-up. A total of 326 patients (38%) were included. Of the 529 excluded subjects, five patients had died, 21 patients were excluded because of MR imaging or radiographic contraindications, 87 patients refused participation, and 416 patients did not respond to the contact letter sent by mail, a second letter sent after 2 months, or the three contact attempts by telephone. To assess for selection bias in the follow-up study, the patient characteristics of the follow-up study population were compared with those of the initial study (Table 1).

Table 1

Differences in Patient Characteristics between Original and Current Study

	Patients not included in the current study population (n = 529)	Current populati-on (n = 326)	P-Value
Age distribution	30 (median age)	32 (median age)	0.006* (Mann-Whitney)
Number of women	173 (33%)	108 (33%)	1.000 (Chi-square test)
ACL ruptures	50 (10%)	48 (15%)	0.021* (Chi-square test)
MM tears	162 (31%)	119 (37%)	0.072 (Chi-square test)
LM tears	104 (20%)	68 (21%)	0.725 (Chi-square test)
No meniscus tears or ACL rupture	283 (54%)	151 (47%)	0.048* (Chi-square test)

*LM = lateral meniscus, MM = medial meniscus. *Significant difference.*

Clinical data regarding the length and severity of symptoms were measured by using the Noyes knee scoring system for function and symptoms (18,19). Noyes scores were determined at the time of inclusion, after 3 and 6 months, and after 10 years.

Radiographs and MR images of the knee that was symptomatic 10 years ago were acquired. The time interval between these follow-up examinations was less than 2 weeks. ACL and meniscal injuries detected on the initial 0.5-T MR and/or arthroscopic images were compared with findings on the follow-up radiographs and 3.0-T MR images.

Radiographic knee examination and assessment

Standardized weight-bearing posterior-anterior knee radiographs were obtained with the knee in a semi-flexed position (20). Supine lateral radiographs of the knee were also obtained. An

experienced musculoskeletal radiologist (I.W., 30 years of musculoskeletal radiology experience) and a research fellow (K.H.) scored the radiographs for features of OA. Overall severity was scored by using the KL system (2). Radiographs were also scored on a scale of 0–3 for joint space narrowing (JSN) assigned to three regions: the medial tibiofemoral compartment, the lateral tibiofemoral compartment, and the patellofemoral compartment. Osteophytes were assigned to five regions: the medial femoral compartment, the medial tibiofemoral compartment, the lateral femoral compartment, the lateral tibiofemoral compartment, and the patellofemoral compartment. JSN and osteophytes were scored by using the Osteoarthritis Research Society International atlas (21). A lesion was considered to be present when a score of 1–3 was given.

MRI knee examination and assessment

For the first MR study, a 0.5-T system (Gyroscan T5; Philips Medical Systems, Best, The Netherlands) was used. The MR imaging protocol consisted of three sequences: sagittal and coronal dual spin-echo sequences and a sagittal T1-weighted three-dimensional gradient-echo sequence with frequency-selective fat suppression. Ten years ago, one of six radiologists (including J.L.B.) with at least 4 years of experience with musculoskeletal MR imaging evaluated the initial 0.5-T MR images in each patient. The locations and types of meniscal tears and ACL ruptures were scored. For the follow-up study, the initial 0.5-T MR images were compared with the follow-up 3.0-T MR images and were reinterpreted in consensus by an experienced musculoskeletal radiologist (I.W.) with more than 20 years of MR imaging experience and a research fellow (K.H.). In 51 subjects who received a diagnosis of meniscal degeneration 10 years ago and in three subjects who initially received a diagnosis of meniscal tear, the 0.5-T MR images were considered to be normal in the current consensus reading. The corrected interpretations for these 54 patients were used for analysis in the current follow-up study.

The follow-up MR imaging examinations were performed by using a 3.0-T system (Achieva 3T; Philips Medical Systems). The MR imaging protocol comprised six sequences: coronal and transverse fast spin echo with fat suppression, coronal and sagittal fast spin echo with driven equilibrium, and transverse and sagittal gradient echo with water excitation.

The parameters for coronal and transverse fat-suppressed fast spin-echo MR imaging were repetition times of 2625 and 1247 msec for the coronal and transverse planes, respectively. For both planes, the echo time was 34 msec, the field of view was 150 mm, and the matrix was 304 × 238. A 3-mm section thickness with a 0.60-mm intersection gap for coronal imaging and a 4-mm section thickness with a 0.80-mm intersection gap for transverse imaging were used. The parameters for sagittal and coronal fast spin-echo imaging with driven equilibrium were 3000/34 (repetition time msec/echo time msec) and a field of view of 150 mm. In the sagittal plane, a matrix of 304 × 238 and a 3.5-mm section thickness with a 0.70-mm intersection gap were used, and in the coronal plane, a matrix of 304 × 242 and a 3-mm section thickness with a 0.60-mm intersection gap were used. The parameters for sagittal and transverse three-dimensional gradient-echo imaging with water excitation were a 35° flip angle, 16/9.21, a 150-mm field of view, a matrix of 304 × 512, and 0.75-mm section thickness. The imaging time for the entire MR imaging protocol was 28 minutes 22 seconds.

Two experienced musculoskeletal radiologists (J.L.B., I.W., more than 20 years of MR experience) and a research fellow (K.H.), who were blinded to the patient characteristics, scored all of the acquired data in consensus by using the validated knee osteoarthritis scoring system (22). Lesions were localized to any of five regions: medial femoral compartment, medial tibiofemoral compartment, lateral femoral compartment, lateral tibiofemoral compartment, and patellofemoral compartment.

The scored parameters were focal and diffuse cartilaginous defects. A focal cartilaginous defect was defined as an abrupt transition (acute angle) between the cartilage defect and the surrounding cartilage. A diffuse cartilaginous defect was defined as a smooth and gradual transition between normal and thinned cartilage. When a focal chondral defect was superimposed on diffuse cartilage loss, both defects were scored. Other scored parameters were meniscal tears (Fig 1) and subluxations, osteophyte formation, bone marrow lesions, and subchondral cysts (Figs 2 and 3). With the knee osteoarthritis scoring system, values of 0 (absent) to 3 (severe) are assigned to the MR imaging–depicted features (22). A lesion was considered to be present when a score in the range of 1–3 was given.

Figure 1:

Sagittal 0.5-T intermediate-weighted spin-echo MR image (2250/20) shows MM tear in 29-year-old man after traumatic knee injury. This isolated MM tear was treated with partial meniscectomy 10 years ago.

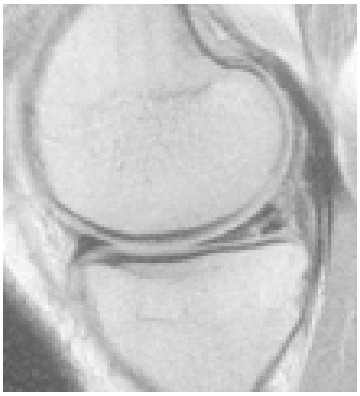


Figure 2:

Sagittal three-dimensional gradient-echo MR image shows cartilaginous defect (arrow) and bone marrow lesion in lateral femoral condyle in 54-year-old woman with ACL rupture and meniscal tears 10 years ago. This sequence was used to score the cartilage lesions. Fat-suppressed fast spin-echo sequence was used to score the bone marrow lesion. The ACL rupture was not reconstructed, and the MM tear was treated with partial meniscectomy.

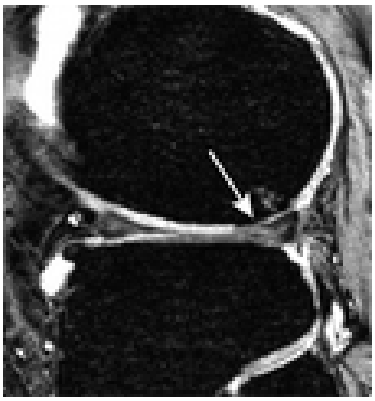
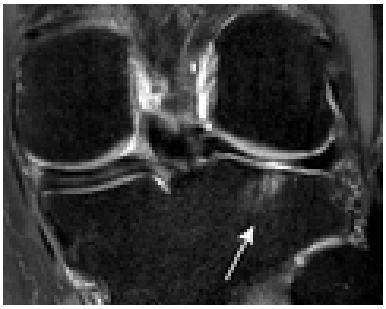


Figure 3:

Coronal fat-suppressed fast spin-echo MR image in 46-year-old man shows ill-defined bone marrow edema–like pattern in lateral tibial condyle (arrow) and cartilage loss in lateral tibia. Patient had torn LM and was treated with partial meniscectomy.



Data Analysis

To determine the prevalence of structural abnormalities, the arthroscopic and MR imaging findings from the initial study were used; in the patients who did not undergo arthroscopy, the MR findings were used. The follow-up radiographic and MR results were categorized in a binary fashion as normal or abnormal.

The Mann-Whitney test was used to compare differences in age distribution, and the $\chi 2$ test was used to compare differences in sex and structural abnormalities between the current study population and the patients who participated in the initial study but were not included in the current study population. The $\chi 2$ test was used to determine if there were differences in OA development among the knees with different structural abnormalities detected with MR imaging or arthroscopy. One-way analysis of variance was used to compare the Noyes knee function and symptom scores among five groups: patients with ACL ruptures, patients with medial meniscal tears, patients with lateral meniscal tears, patients with combined ACL ruptures and/or meniscal tears, and patients without ACL ruptures or meniscal tears.

Odds ratios (ORs), with 95% confidence intervals (CIs), were used to show the association between different risk factors and presence of OA features 10 years after subacute knee problems.

Multivariate logistic regression models were used to assess the association between MR imaging findings 10 years earlier and subsets of knee OA based on current MR imaging results while adjusting for age, sex, and body mass index. Age and body mass index were analyzed as continuous variables. When the odds ratio estimates were zero, exact logistic regression was used to obtain upper 95% CI limits.

All tests were two tailed, and $P < .05$ was considered to indicate statistical significance. All statistical analyses were performed by using SPSS, version 16.0.2, for Windows (SPSS, Chicago, Ill) and SAS Statistics, version 9.1 (SAS, Cary, NC), software.

Results

Population characteristics

The median age of the 326 patients whose data were included in the follow-up study was 42 years (mean age, 42 years ± 7.6 [standard deviation]). At the time of their inclusion in the initial study 10 years ago, their median age was 32 years (mean age, 32 years ± 7.7), which differed from the median age of the 529 patients not included in the current study population (30 years; mean age, 30 years ± 8.1, P = .006) (Table 1). At the current follow-up, 108 (33%) patients were female; this was the same percentage of female patients as that in the original study (n = 281[33%]) and in the cohort of patients not included in the current study (n = 173 [33%]) (Table 1). More ACL ruptures were found in the current study population (48 [15%]) than in the group of patients not included (50 [9%]) (P = .021) (Table 1). Furthermore, the frequency distribution of meniscal lesions found 10 years ago among the patients not included in the current study was similar to that in the current study population (Table 1).

The follow-up population can also be considered representative of the initial study population in terms of surgical history. The partial meniscectomies performed in 263 (31%) patients in the original study population within 6 months after inclusion 10 years ago were not significantly different from the 115 (35%) meniscectomies performed 10 years ago in the follow-up population

within 6 months after inclusion. An additional 14 (4%) patients in the follow-up population underwent a partial meniscectomy after 6 months but within 10 years of follow-up. Because of the nonresponders, the number of partial meniscectomies performed after 6 months in the complete initial population is not available.

The Noyes knee function and symptom scores (18,19) at the time of inclusion, after 3 and 6 months, and after 10 years were not significantly different between patients with an ACL rupture, patients with a medial meniscal tear, patients with a lateral meniscal tear, patients with combined ACL ruptures and/or meniscal tears, and patients without ACL ruptures or meniscal tears ($P \geq .05$ for all comparisons). No major trauma was reported by any patient during the 10-year interval; no information about minor injuries was available.

Ten years ago, most meniscal tears—110 (94%) of 117 MM tears and 48 (73%) of 66 LM tears—were found in the posterior horn and body. Of the 117 MM tears, two (2%) were smaller than 0.5 cm, 90 (77%) were larger than 0.5 cm, and 25 (21%) were bucket-handle tears. Of the 66 LM tears, 14 (21%) were smaller than 0.5 cm, 47 (71%) were larger than 0.5 cm, and five (8%) were bucket-handle tears.

Surgical treatment

In the knees with ACL rupture, 16 ACLs (33%) were reconstructed. The majority of these reconstructions (13 [81%]) were performed within 2 years after inclusion in the initial study. Partial meniscectomy was performed in 129 (71%) (86 MM, 43 LM) of the 183 knees with meniscal tears. The other 54 (29%) (31 MM, 23 LM) tears were treated conservatively. The majority (115 [89%])of the meniscectomies were performed within 6 months after inclusion in the initial study. Meniscectomy was performed in 25% of the 16 meniscal tears smaller than 0.5 cm (0 MM, four LM), in 71% of the 137 meniscal tears larger than 0.5 cm (62 MM, 35 LM), and in 93% of the 30 bucket-handle tears (24 MM, four LM).

Radiographic sequelae

ACL lesions.—In patients with ACL ruptures, an increased risk of advancing more than one point in the KL score over 10 years was found (OR, 2.8). There was an increased risk of developing JSN in the medial tibiofemoral compartment (OR, 5.5) and an increased risk of developing osteophytes in the medial femoral (OR, 7.0) and medial tibiofemoral (OR, 2.0) compartments (Table 2) (Fig 4a).

MM lesions.—In the knees with torn MMs, there was an increased risk of advancing more than one point in the KL score (OR, 2.0). There was an increased risk of developing JSN (OR, 15.3) and of developing osteophytes (OR, 3.9) in the medial tibiofemoral compartment (Table 2) (Fig 5a). Differences in the size and location of the MM tears had no significant effect on the risk of developing these radiographic features.

LM lesions.—Patients with LM tears had an increased risk of advancing more than one point in the KL score over 10 years (OR, 2.3). There was an increased risk of developing JSN in the lateral medial tibiofemoral compartment (OR, 10.7) and an increased risk of developing osteophytes in the lateral tibiofemoral (OR, 4.8) and patellofemoral (OR, 2.1) compartments (Table 2) (Fig 6a). Differences in the size and location of the LM tears had no significant effect on the risk of developing these radiographic features.

Table 2 *Radiographic Sequelae in Relation to Old Meniscal Tears and ACL Ruptures*

	ACL rupture n = 48			MM tear n = 117			LM tear n = 66		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
K&L Difference >1	2.8	1.2-6.4	0.013*	2.0	1.0-4.1	0.047*	2.3	1.1-4.8	0.023*
JSN Medial TFC	5.5	1.6-18.6	0.006*	15.3	3.3-71.8	0.001*	0.8	0.2-2.6	0.673
JSN Lateral TFC	1.4	0.5-4.4	0.516	0.5	0.2-1.4	0.158	10.7	3.8-29.8	<0.001*
JSN PFC	0.5	0.0-3.7	0.569	0.3	0.0-2.5	0.286	2.9	0.4-21.6	0.287
Osteophytes MFC	7.0	1.5-33.6	0.015*	3.9	0.7-21.2	0.111	1.4	0.3-7.0	0.659
Osteophytes MTC	2.0	1.1-5.7	0.032*	4.2	2.1-8.7	<0.001*	1.1	0.5-2.5	0.742
Osteophytes LFC	0.4	0.0-2.5	0.365	2.0	0.4-11.0	0.445	3.2	0.6-16.1	0.166
Osteophytes LTC	1.7	0.7-4.4	0.282	1.0	0.5-2.3	0.967	4.8	2.2-10.6	<0.001*
Osteophytes PFC	0.9	0.4-2.0	0.720	1.0	0.5-1.9	0.964	2.1	1.1-4.1	0.034*

*LFC = lateral femoral compartment, LTC = lateral tibial compartment, MFC = medial femoral compartment, MTC = medial tibial compartment, PFC = patellofemoral compartment. *Significant difference.*

MR Imaging sequelae

ACL lesions.—Patients with an ACL tear 10 years ago had an increased risk of developing diffuse cartilaginous lesions in the medial tibiofemoral compartment (OR, 4.1) and/or focal cartilaginous

lesions in the lateral femoral (OR, 3.0) and/or lateral tibiofemoral (OR, 3.1) compartment. They also had an increased risk of developing a subluxation of the MM (OR, 6.7) and of developing osteophytes in the medial femoral (OR, 3.8), medial tibiofemoral (OR, 3.0), and/or lateral tibiofemoral (OR, 2.7) compartment. Patients with ACL ruptures had an increased risk of developing bone marrow lesions (OR, 5.5) and subchondral cysts (OR, 9.8) in the lateral femoral compartment (Tables 3–7, Fig 4b).

MM lesions.—Patients with MM tears had an increased risk of developing MR imaging–detectable diffuse cartilaginous defects in the medial femoral (OR, 2.8) and/or medial tibiofemoral (OR, 3.6) compartment. There was an increased risk of developing MM subluxations (OR, 2.9) and a reduced risk of developing LM subluxation (OR, 0.2). There was an increased risk of developing osteophytes (OR, 2.8) and bone marrow lesions (OR, 4.1) in the medial tibiofemoral compartment. Patients with MM tears did not have an increased risk of developing subchondral cysts in any compartment (Tables 3–7) (Fig 5b). Differences in the size and location of the MM tears had no significant effect on the risk of developing these MR features.

LM lesions.—Patients with LM tears had an increased risk of developing focal cartilaginous lesions in the lateral tibiofemoral (OR, 2.9) and/or lateral femoral (OR, 3.3) compartment. There was an increased risk of developing a subluxation of the LM (OR, 10.5) and osteophytes in the lateral femoral compartment (OR, 2.5). Patients with LM tears had an increased risk of developing bone marrow lesions in the lateral tibiofemoral compartment (OR, 4.4) and a decreased risk of developing bone marrow lesions in the patellofemoral compartment (OR, 0.2). There was an increased risk of developing subchondral cysts in the lateral tibiofemoral compartment (OR, 4.1) (Tables 3–7) (Fig 6b). Two patients with LM bucket-handle tears developed bone marrow lesions in the lateral femoral compartment. None of the patients with smaller LM tears developed bone marrow lesions in the lateral femoral compartment, and the difference between these two groups was significant (P = .008). No other differences related to the size or location of the LM lesions were observed.

Figure 4:(a) *Drawing shows characteristic abnormalities, as seen on radiographs, that have increased risk of developing after rupture of ACL: JSN and osteophytes medially.* **(b)** *Drawing shows characteristic abnormalities, as seen on MR images, that have increased risk of developing after rupture of ACL: diffuse cartilaginous defects and osteophytes medially, and focal cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts laterally.*

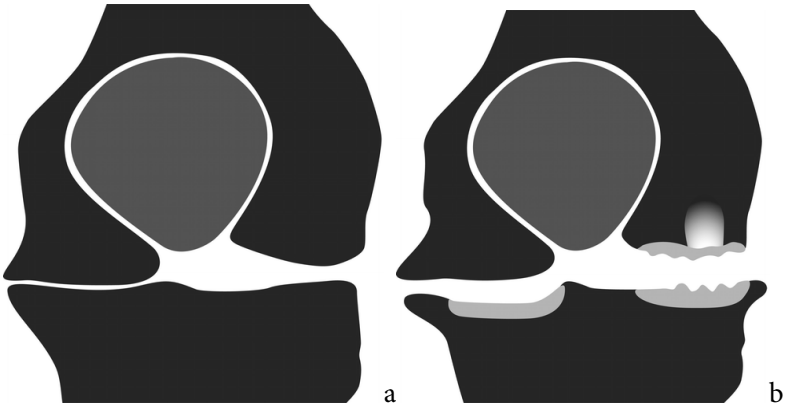


Figure 5:(a) *Drawing shows characteristic abnormalities, as seen on radiographs, that have increased risk of developing after MM tear: JSN and osteophytes medially.* **(b)** *Drawing shows characteristic abnormalities, as seen on MR images, that have increased risk of developing after MM rupture: diffuse cartilage defects, osteophytes, and bone marrow lesions medially.*

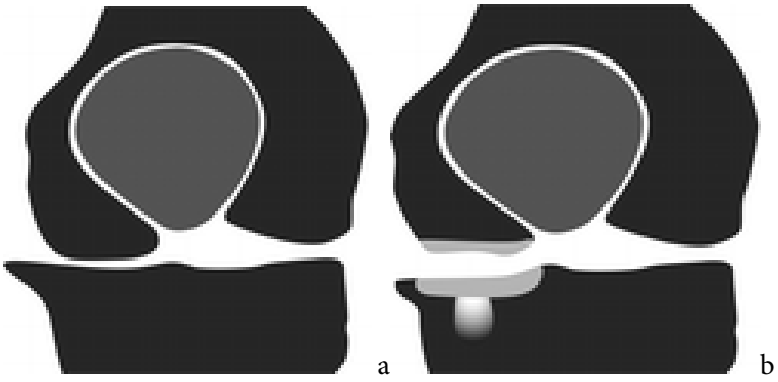
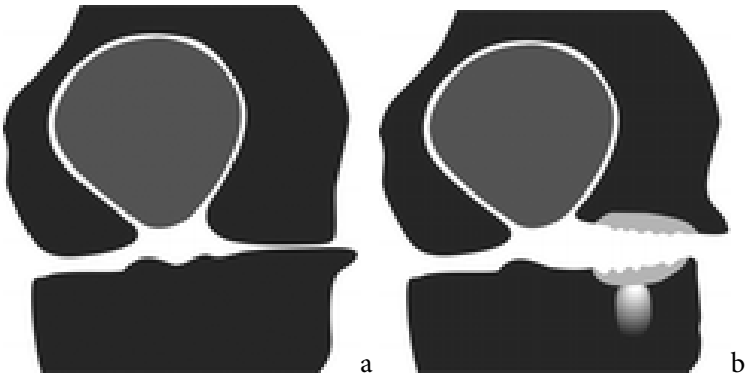


Figure 6a:(a) *Drawing shows characteristic abnormalities, as seen on radiographs, that have increased risk of developing after LM tear: JSN and osteophytes laterally.* **(b)** *Drawing shows characteristic abnormalities, as seen on MR images, that have increased risk of developing after LM rupture: focal cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts laterally.*



a b

Table 3 *Focal and Diffuse Cartilage Defects in Relation to Old Meniscal Tears and ACL Ruptures*

		ACL rupture n = 48			MM tear n = 117			LM tear n = 66		
Compartment	Cartilage Defects	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
MFC	Focal	1.2	0.7-2.1	0.242	0.9	0.5-1.6	0.755	0.7	0.3-1.4	0.284
	Diffuse	1.7	0.7-4.2	0.274	2.8	1.4-5.8	0.006*	0.8	0.3-1.8	0.537
MTC	Focal	1.3	0.3-4.9	0.725	0.5	0.2-1.5	0.216	1.0	0.3-3.3	0.999
	Diffuse	4.1	1.5-11.2	0.006*	3.6	1.4-8.9	0.006*	0.5	0.2-1.5	0.218
LFC	Focal	3.0	1.4-6.4	0.004*	0.7	0.4-1.5	0.393	2.9	1.5-5.7	0.002*
	Diffuse	1.4	0.6-3.6	0.453	0.7	0.3-1.6	0.440	0.5	0.2-1.5	0.218
LTC	Focal	3.1	1.3-7.3	0.009*	0.2	0.1-0.6	0.004*	3.3	1.5-7.3	0.002*
	Diffuse	0.8	0.1-4.0	0.738	2.0	0.7-5.9	0.231	1.6	0.5-5.1	0.397
PFC	Focal	0.8	0.4-1.6	0.574	1.2	0.7-2.1	0.406	0.7	0.4-1.2	0.213
	Diffuse	1.0	0.4-2.5	0.921	1.1	0.6-2.2	0.783	0.7	0.4-2.5	0.921

**Significant difference. LFC = lateral femoral compartment, LTC = lateral tibial compartment, MFC = medial femoral compartment, MTC = medial tibial compartment, PFC = patellofemoral compartment.*

Table 4 *Meniscal Subluxation and Newly Developed Meniscal Tears in Relation to Old Meniscal Tears and ACL Ruptures*

Meniscal findings	ACL rupture n = 48			MM tear n = 117			LM tear n = 66		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
MM subluxation	6.7	2.1-21.0	<0.001*	2.9	1.0-8.3	0.049*	1.1	0.4- 3.4	0.886
LM subluxation	0.5	0.1-2.0	0.312	0.2	0.06-0.7	0.009*	10.5	3.8-28.7	<0.001*
New MM tear	2.9	1,0-9.3	0.069	0.1	0.0-2.7	<0.001*	0.3	0.1-1.4	0.114
New LM tear	2.1	0.5-9.1	0.303	0.1	0.02-1.0	0.052	0.2	0.0-1.1	0.066

**Significant difference. MM=medial meniscus, LM=lateral meniscus*

Table 5 *MR Imaging–depicted Osteophytes in Relation to Old Meniscal Tears and ACL Ruptures*

Osteophytes	ACL rupture n = 48			MM tear n = 117			LM tear n = 66		
Compartment	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
MFC	3.8	1.8-8.1	<0.001*	1.9	1.0-3.6	0.065	1.5	0.7-3.0	0.305
MTC	3.0	1.2-7.2	0.014*	2.8	1.3-6.1	0.007*	1.4	0.6-3.2	0.408
LFC	1.1	0.4-3.4	0.819	1.0	0.4-2.5	0.980	2.5	1.0-6.2	0.040*
LTC	2.7	1.1-6.4	0.024*	0.5	0.2-1.2	0.106	2.1	0.9-4.7	0.073
PFC	1.5	0.7-2.9	0.276	1.1	0.6-1.9	0.775	1.0	0.6-1.9	0.928

**Significant difference. LFC = lateral femoral compartment, LTC = lateral tibial compartment, MFC = medial femoral compartment, MTC = medial tibial compartment, PFC = patellofemoral compartment.*

Surgical treatment and differences in Radiographic and MRI sequelae

The ORs for all structural abnormalities in the patients treated with ACL reconstruction or partial meniscectomy were not significantly different from those for the patients who were not treated. (All 95% CIs for ORs included an OR equal to 1.) In terms of the manifestation of all OA features in all compartments after 10 years, it made no difference if the initial ACL, MM, or LM lesion was detected at MR imaging or arthroscopy (P≥.05 for all comparisons).

Meniscal tears were also present in 31 (65%) knees with ACL ruptures. Logistic regression analysis revealed that the increased risk of developing OA was not dependent on meniscal lesions, but rather it could be attributed to ACL rupture only. None of the structural abnormalities evaluated 10 years ago indicated an increased risk of developing meniscal tears. (All 95% CIs for ORs included an OR equal to 1 [Table 4].)

Discussion

Localized knee OA developed, irrespective of treatment, from ACL and meniscal injuries identified at MR imaging performed a decade ago in patients with subacute knee symptoms. Patients who have had an ACL rupture and/or a meniscal tear have a significantly increased risk of developing JSN, cartilage lesions, osteophytes, and/or bone marrow lesions.

Treatment, partial meniscectomy and ACL reconstruction in particular, did not decrease the risk of developing the features of OA demonstrated on radiographs or MR images. This is in contrast to results reported previously (4). Englund et al (4) examined 155 patients with isolated meniscal tears who were treated with meniscectomy. Their results showed that, 16 years later there was an increased risk of developing radiographically detectable knee OA in patients whose meniscal tears were treated with meniscectomy as compared with this risk in a control group. The results of our study, however, show that, after 10 years, patients with meniscal tears have an increased risk of developing radiographic OA, but partial meniscectomy has no significant effect (positive or negative) on the development of radiographically detectable OA. Because Englund et al (4) examined patients who had undergone meniscectomy only, it is not clear to what extent the

development of OA in that study population could be attributed to the meniscal tear and to what extent it could be attributed to meniscectomy.

More abnormalities were found on the MR images than on the radiographs, in accordance with previously reported observations that MR imaging enables a more detailed and comprehensive display of OA-related changes than does radiography (11,12).

With rupture of the ACL, increased internal tibial rotation and anterior tibial translation occur (23–28). This leads to a higher point rotation pressure in the medial knee compartment and higher shearing forces in the medial and lateral compartments. Shearing forces are important in developing cartilaginous defects, because cartilage is known not to withstand shear stress as well as compressive forces (29–31). As a consequence, 10 years after ACL rupture, MR images depict diffuse cartilaginous lesions in the medial tibiofemoral compartment (OR, 4.1) and focal cartilaginous lesions in the lateral femoral (OR, 3.0) and lateral tibiofemoral (OR, 3.1) compartments. Our result of an increased risk of OA development in the patients with isolated ACL ruptures differed from the findings of Neuman et al (9). They found that 15 years after ACL rupture, only those patients who were also treated with meniscectomy developed radiographically detectable OA. However, as stated by Neuman et al, because of the low incidence of knee OA and the small sample size, multivariate modeling of multiple risk factors was not performed in their statistical analysis. In our study, multivariate modeling was used to compare the risks of developing OA after ACL and meniscal lesions. The effect of surgical treatment on the development of OA in these groups was analyzed separately. This makes it difficult to compare the outcomes of both studies.

Menisci are important load transmitters (32). The results of our study show that there is an increased risk of developing cartilaginous lesions after meniscal tears. This is in concordance with the results of other MR imaging studies (4,13,14,16). Our results show that there is an increased risk of developing diffuse cartilaginous defects medially in patients who have had MM tears and an increased risk of developing focal cartilaginous defects laterally after LM tears. A possible explanation for these findings is that with normal knee movements, rotation occurs mainly around a medially positioned axis, resulting in shear stress at the lateral articular surface and

point rotation pressure at the medial surface (33,34). Because cartilage is less tolerant to shearing forces, the impaired load transmission of torn menisci has a greater effect on the lateral compartment, increasing the risk of developing focal cartilaginous defects. The increased point rotation pressure in combination with the increased joint load medially during walking (35) might cause the anatomically vulnerable MM (32) to tear and increase the risk of developing diffuse cartilaginous defects medially.

Radiographically depicted JSN is reportedly influenced by meniscal position, meniscal degeneration, and cartilaginous defects (36). The results of our study show that after ACL rupture, there is an increased risk of developing medial JSN, which can contribute to the increased risk of developing cartilage lesions in the medial tibiofemoral compartment (OR, 4.1) and/or MM subluxations (OR, 6.7). The increased risk of developing JSN meniscal tears in the ipsilateral tibiofemoral compartment can be explained by the increased risk of developing cartilaginous lesions (OR range, 2.8–3.6 [Table 3]), the increased risk of developing meniscal subluxations (OR: 2.9 for MM, 10.5 for LM), and/or the meniscal tear itself. Although osteophytes can develop without explicit cartilage damage (37), the increased risk of developing radiographically and MR imaging–detectable osteophytes seems to be related to the presence of cartilaginous defects. In three of four radiographically determined locations and four of five MR imaging–determined locations with an increased risk of developing osteophytes, there was also an increased risk of developing cartilaginous lesions.

The development of MR imaging–detectable patellofemoral OA features was not related to ACL or MM lesions, but the risk of developing radiographically detectable osteophytes in the patellofemoral joint after LM tearing was increased (OR, 2.1). These results are in accordance with previous study findings that indicated that other risk factors may be involved in patellofemoral OA as opposed to tibiofemoral OA (38–41). The increased risk of radiographically detectable patellofemoral osteophytes and the decreased risk of bone marrow lesions in knees with LM tears might be explained by varus malalignment and erratic rotational movements at the femorotibial articulation with subsequent abnormal patellofemoral stresses (42).

The main limitation of the present study was the large number of patients lost to follow-up (529 [62%] of 855 patients). There are some possible reasons for this limited response rate. The study originally was not designed to be a follow-up investigation, and all patients had to be traced and asked to participate. Because the study population was relatively young, it was difficult to trace all patients: Often, their addresses and phone numbers had changed during the 10 years. Another limitation of the study was that only those patients with persistent knee problems might have been interested in participating in the follow-up study, possibly biasing the results. To investigate this, all 87 subjects who refused participation were asked if they still had knee problems. The majority of these subjects, 49 (56%) patients, had knee problems, but they also had other reasons for not participating in the study. Furthermore, no significant differences in population characteristics between the complete initial (n = 855) and current study (n = 326) populations were found (P≥.05 for all comparisons). However, when the current study population was compared with the 529 patients who participated in the initial study but were not included in the current study population, there were some significant differences. The current population was slightly older at the time of inclusion 10 years ago (mean age, 32 years ± 7.7) compared with the initial study subgroup (mean age, 30 years ± 8.1) (P = .006) and had more ACL lesions (48 [15%] compared with 50 [9%] in the initial study subgroup [P = .021]) (Table 1). There were no significant differences in meniscal tears (P≥.005). These results suggest that the current population could be considered representative of the initial study group; only the age and frequency of the ACL ruptures were different; therefore, selection bias for these two items cannot be excluded.

In summary, irrespective of treatment, the risk factors seen on knee MR images resulted in localized development of OA 10 years later. The different patterns of developing OA are determined according to the initial ACL and meniscal injuries and can be explained by ensuing changes in biomechanical loading. The hallmark finding of OA development after MM tears is diffuse medial cartilage loss, and after LM tears, it is focal lateral cartilage loss. After ACL rupture, OA characteristics are seen medially and laterally.

Reference List

1. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Rheum.Dis.Clin.North Am. 2008 Aug;34(3):515-29.

2. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann.Rheum.Dis. 1957 Dec;16(4):494-502.

3. Chan WP, Huang GS, Hsu SM, Chang YC, Ho WP. Radiographic joint space narrowing in osteoarthritis of the knee: relationship to meniscal tears and duration of pain. Skeletal Radiol. 2008 Oct;37(10):917-22.

4. Englund M, Roos EM, Lohmander LS. Impact of type of meniscal tear on radiographic and symptomatic knee osteoarthritis: a sixteen-year followup of meniscectomy with matched controls. Arthritis Rheum. 2003 Aug;48(8):2178-87.

5. Englund M, Lohmander LS. Risk factors for symptomatic knee osteoarthritis fifteen to twenty-two years after meniscectomy. Arthritis Rheum. 2004 Sep;50(9):2811-9.

6. Kessler MA, Behrend H, Henz S, Stutz G, Rukavina A, Kuster MS. Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. Knee.Surg.Sports Traumatol.Arthrosc. 2008 May;16(5):442-8.

7. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum. 2004 Oct;50(10):3145-52.

8. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am.J.Sports Med. 2007 Oct;35(10):1756-69.

9. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. Am.J.Sports Med. 2008 Sep;36(9):1717-25.

10. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual.Life Outcomes. 2003;1:64.

11. Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H, Roemer FW. Imaging in osteoarthritis. Rheum.Dis.Clin.North Am. 2008 Aug;34(3):645-87.

12. Hunter DJ. Advanced imaging in osteoarthritis. Bull.NYU.Hosp.Jt.Dis. 2008;66(3):251-60.

13. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, Raynauld JP, Cicuttini F, Jones G. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. J.Rheumatol. 2007 Apr;34(4):776-84.

14. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M, Guermazi A, Grigorian M, Gale D, Felson DT. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum. 2006 Mar;54(3):795-801.

15. Madan-Sharma R, Kloppenburg M, Kornaat PR, Botha-Scheepers SA, Le Graverand MP, Bloem JL, Watt I. Do MRI features at baseline predict radiographic joint space narrowing in the medial compartment of the osteoarthritic knee 2 years later? Skeletal Radiol. 2008 Sep;37(9):805-11.

16. Pelletier JP, Raynauld JP, Berthiaume MJ, Abram F, Choquette D, Haraoui B, Beary JF, Cline GA, Meyer JM, Martel-Pelletier J. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. Arthritis Res.Ther. 2007;9(4):R74.

17. Vincken PW, ter Braak AP, van Erkel AR, et al. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 2007;242(1):85–93.

18. Barber SD, Noyes FR, Mangine RE, McCloskey JW, Hartman W. Quantitative assessment of functional limitations in normal and anterior cruciate ligament-deficient knees. Clin.Orthop.Relat Res. 1990 Jun;(255):204-14.

19. Noyes FR, Barber SD, Mooar LA. A rationale for assessing sports activity levels and limitations in knee disorders. Clin.Orthop.Relat Res. 1989 Sep;(246):238-49.

20. Kothari M, Guermazi A, von IG, Miaux Y, Sieffert M, Block JE, Stevens R, Peterfy CG. Fixed-flexion radiography of the knee provides reproducible joint space width measurements in osteoarthritis. Eur.Radiol. 2004 Sep;14(9):1568-73.

21. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis.Cartilage. 1995 Sep;3 Suppl A:3-70.

22. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO, Woodworth TG, Bloem JL. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol. 2005 Feb;34(2):95-102.

23. Andriacchi TP, Mundermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann.Biomed.Eng 2004 Mar;32(3):447-57.

24. Andriacchi TP, Briant PL, Bevill SL, Koo S. Rotational changes at the knee after ACL injury cause cartilage thinning. Clin.Orthop.Relat Res. 2006 Jan;442:39-44.

25. Chaudhari AM, Briant PL, Bevill SL, Koo S, Andriacchi TP. Knee kinematics, cartilage morphology, and osteoarthritis after ACL injury. Med.Sci.Sports Exerc. 2008 Feb;40(2):215-22.

26. Georgoulis AD, Papadonikolakis A, Papageorgiou CD, Mitsou A, Stergiou N. Three-dimensional tibiofemoral kinematics of the anterior cruciate ligament-deficient and reconstructed knee during walking. Am.J.Sports Med. 2003 Jan;31(1):75-9.

27. Kvist J, Gillquist J. Anterior positioning of tibia during motion after anterior cruciate ligament injury. Med.Sci.Sports Exerc. 2001 Jul;33(7):1063-72.

28. Logan M, Dunstan E, Robinson J, Williams A, Gedroyc W, Freeman M. Tibiofemoral kinematics of the anterior cruciate ligament (ACL)-deficient weightbearing, living knee employing vertical access open "interventional" multiple resonance imaging. Am.J.Sports Med. 2004 Apr;32(3):720-6.

29. Carter DR, Beaupre GS, Wong M, Smith RL, Andriacchi TP, Schurman DJ. The mechanobiology of articular cartilage development and degeneration. Clin.Orthop.Relat Res. 2004 Oct;(427 Suppl):S69-S77.

30. Martin JA, Buckwalter JA. Post-traumatic osteoarthritis: the role of stress induced chondrocyte damage. Biorheology 2006;43(3-4):517-21.

31. Smith RL, Carter DR, Schurman DJ. Pressure and shear differentially alter human articular chondrocyte metabolism: a review. Clin.Orthop.Relat Res. 2004 Oct;(427 Suppl):S89-S95.

32. Rath E, Richmond JC. The menisci: basic science and advances in treatment. Br.J.Sports Med. 2000 Aug;34(4):252-7.

33. Freeman MA, Pinskerova V. The movement of the knee studied by magnetic resonance imaging. Clin.Orthop.Relat Res. 2003 May;(410):35-43.

34. Johal P, Williams A, Wragg P, Hunt D, Gedroyc W. Tibio-femoral movement in the living knee. A study of weight bearing and non-weight bearing knee kinematics using 'interventional' MRI. J.Biomech. 2005 Feb;38(2):269-76.

35. Hsu RW, Himeno S, Coventry MB, Chao EY. Normal axial alignment of the lower extremity and load-bearing distribution at the knee. Clin.Orthop.Relat Res. 1990 Jun;(255):215-27.

36. Hunter DJ, Zhang YQ, Tu X, Lavalley M, Niu JB, Amin S, Guermazi A, Genant H, Gale D, Felson DT. Change in joint space width: hyaline articular cartilage loss or alteration in meniscus? Arthritis Rheum. 2006 Aug;54(8):2488-95.

37. van der Kraan PM, van den Berg WB. Osteophytes: relevance and biology. Osteoarthritis.Cartilage. 2007 Mar;15(3):237-44.

38. Cicuttini FM, Spector T, Baker J. Risk factors for osteoarthritis in the tibiofemoral and patellofemoral joints of the knee. J.Rheumatol. 1997 Jun;24(6):1164-7.

39. Cooper C, McAlindon T, Snow S, Vines K, Young P, Kirwan J, Dieppe P. Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. J.Rheumatol. 1994 Feb;21(2):307-13.

40. Kornaat PR, Watt I, Riyazi N, Kloppenburg M, Bloem JL. The relationship between the MRI features of mild osteoarthritis in the patellofemoral and tibiofemoral compartments of the knee. Eur.Radiol. 2005 Aug;15(8):1538-43.

41. Neuman P, Kostogiannis I, Friden T, Roos H, Dahlberg LE, Englund M. Patellofemoral osteoarthritis 15 years after anterior cruciate ligament injury--a prospective cohort study. Osteoarthritis.Cartilage. 2009 Mar;17(3):284-90.

42. Hinman RS, Crossley KM. Patellofemoral joint osteoarthritis: an important subgroup of knee osteoarthritis. Rheumatology.(Oxford) 2007 Jul;46(7):1057-62.

Chapter 3

Automatic radiographic quantification of hand osteoarthritis; accuracy and sensitivity to change in joint space width in a phantom and cadaver study

Kasper Huétink

Ronald van 't Klooster

Bart L. Kaptein

Iain Watt

Margreet Kloppenburg

Rob G. H. H. Nelissen

Johan H. C. Reiber

Berend C. Stoel

Skeletal Radiology January 2012

Abstract

Objective. To validate a newly developed quantification method that automatically detects and quantifies the joint space width (JSW) in hand radiographs. Repeatability, accuracy and sensitivity to changes in JSW were determined. The influence of joint location and joint shape on the measurements was tested.

Methods. A mechanical micrometer set-up was developed to define and adjust the true JSW in an acrylic phantom joint and in human cadaver-derived phalangeal joints. Radiographic measurements of the JSW were compared to the true JSW. Repeatability, systematic error (accuracy) and sensitivity (defined as the smallest detectable difference (SDD)) were determined. The influence of joint position on the JSW measurement was assessed by varying the location of the acrylic phantom on the X-ray detector with respect to the X-ray beam and the influence of joint shape was determined by using morphologically different human cadaver joints.

Results. The mean systematic error was 0.052 mm in the phantom joint and 0.210 mm in the cadaver experiment. In the phantom experiments, the repeatability was high (SDD = 0.028 mm), but differed slightly between joint locations ($p = 0.046$), and a change in JSW of 0.037 mm could be detected. Dependent of the joint shape in the cadaver hand, a change in JSW between 0.018 and 0.047 mm could be detected.

Conclusion. The automatic quantification method is sensitive to small changes in JSW. Considering the published data of JSW decline in the normal and osteoarthritic population, the first signs of OA progression with this method can be detected within one or two years.

Introduction

Osteoarthritis (OA) is a common chronic medical condition in older adults, leading to progressive structural damage of the joints and subsequent functional disability(1-3). Although the hand is frequently involved in OA patients, leading to pain and impaired hand function, osteoarthritis research is focused predominantly on the hip and knee(4-7). Besides patient-reported outcomes (i.e. pain, physical function and patient global assessment), progressive decrease of radiographic joint space width (JSW) is an important parameter in clinical trials on hand OA(8-10). Hand radiographs are used commonly to diagnose and monitor hand OA because of their wide availability and the relatively low costs. Semi-quantitative methods with standard atlases are the bench tools used by clinicians to determine changes in JSW(11-13). Although radiographic OA features scored by these methods are widely performed(14;15), there is a limitation in reproducibility due to the difficulty to standardize the scoring between different readers. The use of an ordinal scale is a limitation to measurement accuracy, which could be improved by assessment of structural damage on a continuous metric scale(16).

At the moment, only symptomatic treatment is available(17), and the development of new structure modifying trials on hand OA is hampered by limitations in outcome measures(18). Since OA is a slowly progressive disease, an accurate and reproducible method is needed to detect subtle changes throughout follow-up, especially when evaluating new therapies.

Currently, radiography is usually digital, facilitating implementation of computerized quantitative JSW measurements. Different software tools have been developed to measure JSW in radiographs(19-25). These are mainly semi-automatic tools requiring manual detection of articular margins or joint space by the user. A newly developed JSW quantification method automatically detects the interphalangeal (IP) and metacarpophalangeal (MCP) joints and quantifies the JSW in hand radiographs(26). In a recent cross-sectional study good agreement was found between measured JSW by this method and the atlas-based ordinal scores according to the OARSI system(26).

Because the decrease in radiographic JSW is an important surrogate marker in clinical trials on hand OA, the primary aim was to assess the accuracy and sensitivity to change in JSW by comparing the automatically determined JSW to true distance between bony contours of the finger

joints. Since JSW cannot be adjusted in human subjects, this gold standard was obtained by varying the true JSW in an acrylic phantom and in cadaver finger joints, using an attached mechanical micrometer. The second aim of the study was to evaluate the influence of joint location and joint shape on the measured JSW.

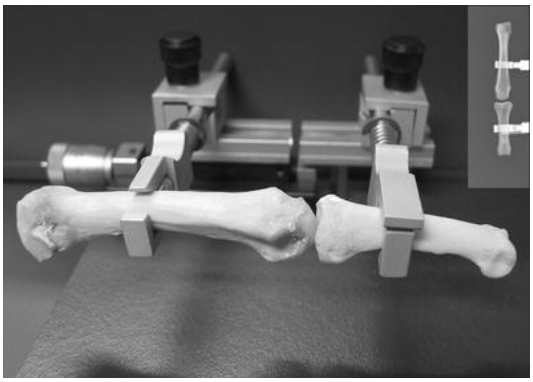
Materials and methods

Three experiments were composed to validate the automated quantification method. In all experiments a specially developed micrometer device was used to define and adjust the true JSW. Plain digital radiographs were acquired by a standard digital X-ray imaging system (Canon Inc., Tokyo, Japan) and the resulting images were analyzed by our developed software(26). Subsequently, the differences between the measured and true JSW were evaluated.

In the first experiment, the repeatability of the JSW measurement was tested using an acrylic phantom joint, which mimics an MCP joint, attached to the micrometer (Figure 1) with a fixed JSW. In the second experiment, the sensitivity to progression was tested by varying the JSW in the acrylic phantom and measuring this simulated progression by the automated quantification method. In the final experiment, the MCP, the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints of human cadaver bones were attached to the micrometer (Figure 2) in order to study the influence of differences in joint shapes on the sensitivity to progression of Joint Space Narrowing (JSN). All experiments were repeated for different locations of the joint, determined by a standardized hand template, which is used to position the hand in research settings.

Fig. 1 *The acrylic phantom joint connected to a micrometer*

Fig. 2 *The micrometer set-up showing the cadaver metacarpal-phalangeal joint of the 3rd digit. Middle and distal phalangeal bones of the 3rd and 5th digit were also used in experiment 3*



Experiment 1, Repeatability, phantom joint

In order to test repeatability the acrylic phantom was placed on the hand template at the location of the MCP of the 3rd digit (middle finger), to which the X-ray focus was projected, perpendicularly to the receptor plate. In order to simulate conditions comparative to (follow-up) clinical trials, in which user dependent focus-film distance and (re)positioning differences may appear, 10 exposures were made with focus-film distances of 110, 115 and 120 cm (n = 4, 3 and 3, respectively), on each occasion repositioning the phantom, table and X-ray focus between exposures. The true JSW was set at 1.00mm. The experiment was repeated using the standard

anatomical location of the DIP of the 5th digit on the template, which produces the most angulated projection.

Experiment 2, Sensitivity to progression, influence of joint location

The phantom joint was placed at the positions of the MCP III, PIP III, DIP III, and DIP V on the hand template, where the MCP III location is the centre point of the x-ray beam. True JSW was varied between 0.20 and 2.40mm. In the intervals (0.20; 0.80) and (1.20; 2.40), this was done with an increment of 0.20mm. In the interval (0.90;1.20) a smaller increment of 0.02mm was used, to simulate subtle progression rates as probably encountered at the onset of OA (22;23;26). A total of 88 measurements were performed, 22 for each joint.

Experiment 3, Sensitivity to progression, influence of joint shape

In order to study the influence of different joint shapes, we used human cadaver matched metacarpal and phalangeal bones of the 3rd and 5th finger, from which all hyaline cartilage and soft tissues were dissected. JSW was varied in the same way as described in Experiment 2. The X-ray focus was centered at the location of the MCP III, PIP III, DIP III and DIP V joint. A total of 88 measurements were performed, 22 for each joint.

Image Analysis

The automatic quantification method first identifies the individual joints in the standard hand radiographs(26). Subsequently, the proximal and distal margins and the measurement interval are determined in each joint, thereby defining the joint space. Finally the JSW was calculated as the average distance between the joint margins enclosed by the measurement interval. In order to analyze the radiographs containing the phantom joints, the first step of the program was omitted and an observer had to locate the position of the phantom joint manually.

Statistical analysis

In the first experiment the standard deviation (SD) of the paired differences between measured and true JSW was defined as a measure of repeatability (random error). The smallest detectable difference (SDD) or the smallest detectable chance (SDC) is used in OA research as a threshold

for detection of JSN, and is defined as 1.96 x SD (27-29). SDs were compared between DIP and MCP joints, with the Levene's test for homogeneity. The mean of the differences gives the systematic error. To test the statistical significance of this systematic error in these clustered data, we used a Generalized Linear Model (GLM), with the error in JSW as dependent variable, and location and exposure number as random factors. Differences in systematic errors between two morphologically different joints like the DIP and MCP joint were tested with an unpaired T-test, assuming equal variances. Normal distribution of the differences was confirmed with the Kolmogorov-Smirnov Test.

In the second and third experiment, a Bland-Altman plot was made to investigate whether the systematic error was dependent on the size of the JSW measurement and to calculate the repeatability (SD of differences).
Differences in systematic errors between joint locations (Experiment 2) and between joint shapes (Experiment 3) were analyzed with a GLM model, as described above, with location and joint type as random factors, respectively, by testing whether the corresponding coefficients were significantly different from 0. Differences in random errors between locations and joint types were tested with a Levene's test.
To test the statistical significance of the systematic error for the entire group, we tested whether the intercept in the GLM analysis was significantly different from 0.
A significance level of 0.05 was used for all statistical tests.

Results

Experiment 1, Repeatability, phantom joint

The results (Table 1 and Figure 3) show a systematic error of 0.052 mm (5% over-estimation). The systematic error was independent of focus-film distance and not significantly different between the DIP V and MCP III location. We found a significant difference in the repeatability between the measurement at the DIP V location and the measurement at the MCP III location (both P-values 0.046). Highest repeatability was found at the location of the MCP of the 3rd digit.

Table 1 *Systematic error and repeatability in the phantom joint at different locations. The true JSW (micrometer) was set at 1.00 mm*

		Location		
	Entire group (n=20)	DIP V (n=10)	MCP III (n=10)	P-value
Mean difference [mm]	0.052*	0.047	0.056	0.17 a
SD of the differences [mm]	0.014	0.016	0.011	0.05 b
SDD [mm]	0.028	0.032	0.021	0.05 b

SD: standard deviation, SDD, smallest detectable difference. aStudent T-test; b Levene's test.

**Generalized Linear Model: intercept was significantly different from 0, p<<0.01.*

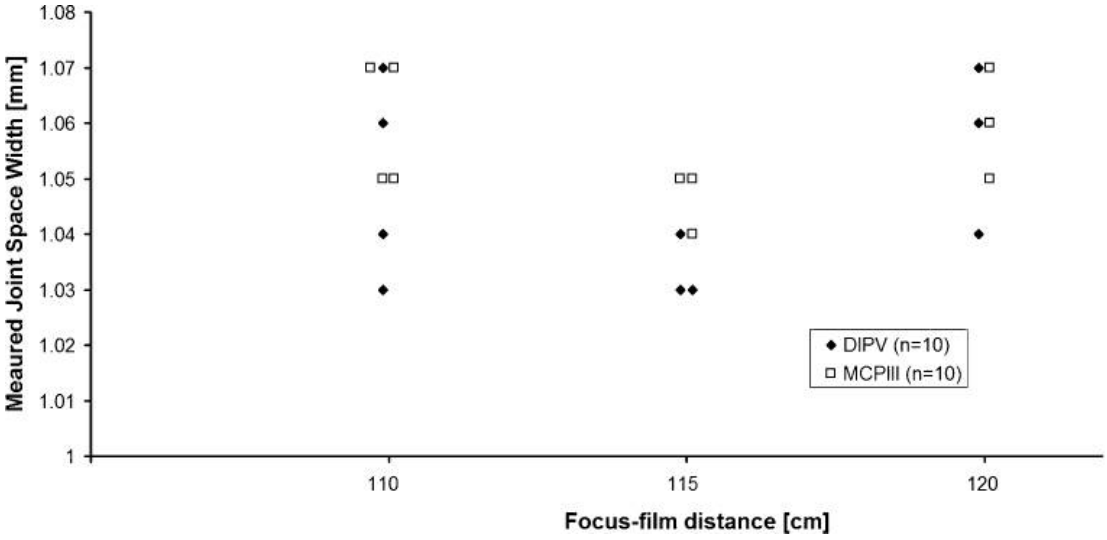


Fig. 3 *Measured JSW by automatic quantification and true JSW for two joint locations*

Experiment 2, Sensitivity to progression, influence of joint location

The results (Table 2 and Figure 4) show that the systematic and random errors were 0.054 mm and 0.037 mm respectively and both were independent of the size of JSW. These errors were slightly higher than in Experiment 1. Again highest repeatability was found at the MCP of the 3rd

digit, but no statistically significant differences in random errors were found between the four different joint locations (i.e. MCPIII, PIPIII, DIP III and V). Progression of JSN was estimated without any systematic error and with a random error of 0.016 mm (Table 3 and Figure 5). Therefore progression of 0.032 mm, as defined by the smallest detectable difference, was measured in this phantom experiment.

Table 2 *Systematic error and SDDs in the phantom joint on different locations*

		Location				
	Entire group (n=88)	DIP III (n=22)	DIP V (n=22)	MCP III (n=22)	PIP III (n=22)	P-value
Mean difference [mm]	0.054*	0.050	0.056	0.061	0.050	0. 141
SD of the differences [mm]	0.019	0.020	0.019	0.011	0.022	0.352
SDD [mm]	0.037	0.038	0.038	0.022	0.043	0.352

*SD: standard deviation, SDD, smallest detectable difference. 1Generalized Linear Model (GLM), location contribution; 2 Levene's test. *GLM: intercept significantly different from 0, p<<0.01.*

Table 3 *Systematic error and SDDs in the measurement of progression in the phantom joint from a true JSW of 1.1 mm at baseline*

		Location			
Progression	Entire group (n=88)	DIP III (n=22)	DIP V (n=22)	MCP III (n=22)	PIP III (n=22)
Mean difference [mm]	-0.002	-0.002	0.008	-0.009	-0.007
SD of the differences [mm]	0.016	0.018	0.014	0.012	0.017
SDD [mm]	0.032	0.035	0.027	0.024	0.033

SD standard deviation, SDD smallest detectable difference

Fig. 4 *Measured JSW by automatic quantification and true JSW for two joint locations*

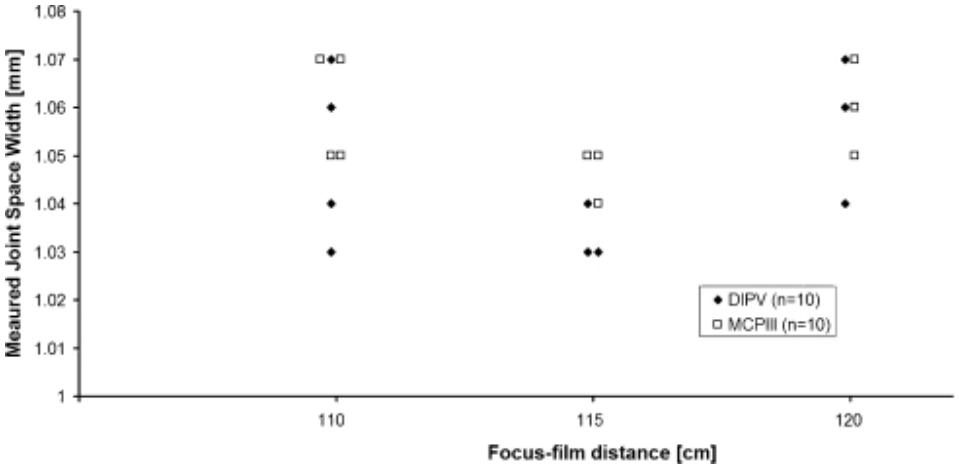
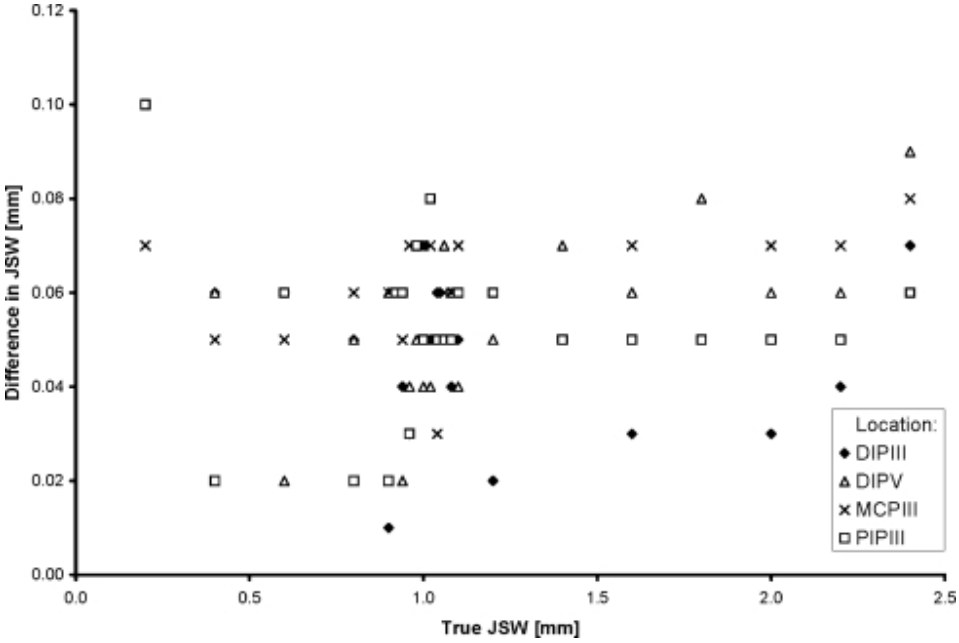


Fig. 5 *The difference between true and measured JSW against the true JSW*



Experiment 3, Sensitivity to progression, influence of joint shape

The mean systematic error was 0.210 mm (Table 4 and Figure 6) and there was a significant difference in the systematic errors between the different joints. The systematic error was smallest in DIP V (0.050mm) and highest in PIP III (0.354mm). Progression of JSN in the different joints was estimated without any systematic errors (Table 5 and Figure 7). The overall precision in detecting progression as defined by the smallest detectable difference was 0.031 mm, being smallest in DIP V (0.018mm) and highest in PIP III (0.047mm) (Table 5 and Figure 7).

Table 4 *Systematic error and SDDs in the cadaver derived joints*

JSW	Joint type					
	Entire group (n=88)	DIP III (n=22)	DIP V (n=22)	MCP III (n=22)	PIP III (n=22)	P-value
Mean difference [mm]	0.210*	0.268	0.050	0.167	0.354	<<0.01 a
SD of the diff's [mm]	0.115	0.011	0.015	0.011	0.024	<0.01 b
SDD [mm]	0.226	0.022	0.029	0.021	0.047	<<0.01 b

*SD standard deviation, SDD smallest detectable difference aGeneralized linear model (GLM), location contribution bLevene's test *GLM: intercept significantly different from 0, p < <0.01*

Table 5 *Systematic error and SDDs in the measurement of progression in the cadaver derived joint from a true JSW of 1.1 mm at baseline*

Progression	Entire group (n=88)	DIP III (n=22)	DIP V (n=22)	MCP III (n=22)	PIP III (n=22)
Mean difference [mm]	-0.007	-0.013	-0.005	0.005	-0.017
SD of the diff's [mm]	0.016	0.009	0.006	0.008	0.024
SDD [mm]	0.031	0.018	0.012	0.015	0.047

SD standard deviation, SDD smallest detectable difference

Fig. 6 *The difference between true and measured JWS is plotted against the true JSW*

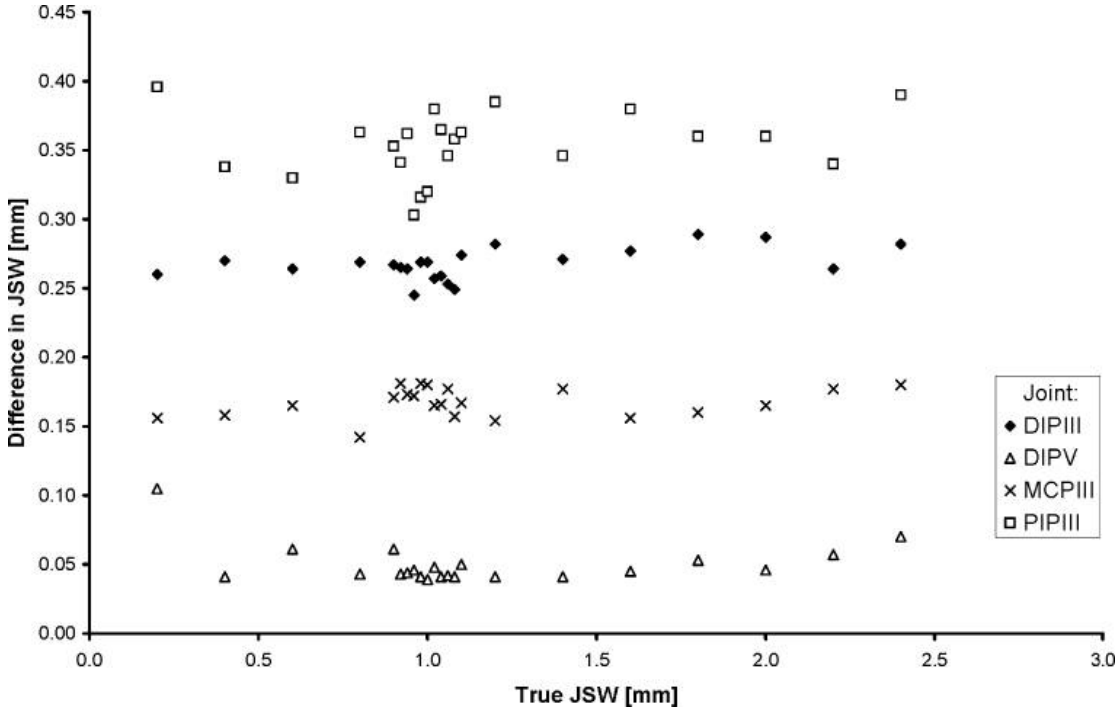
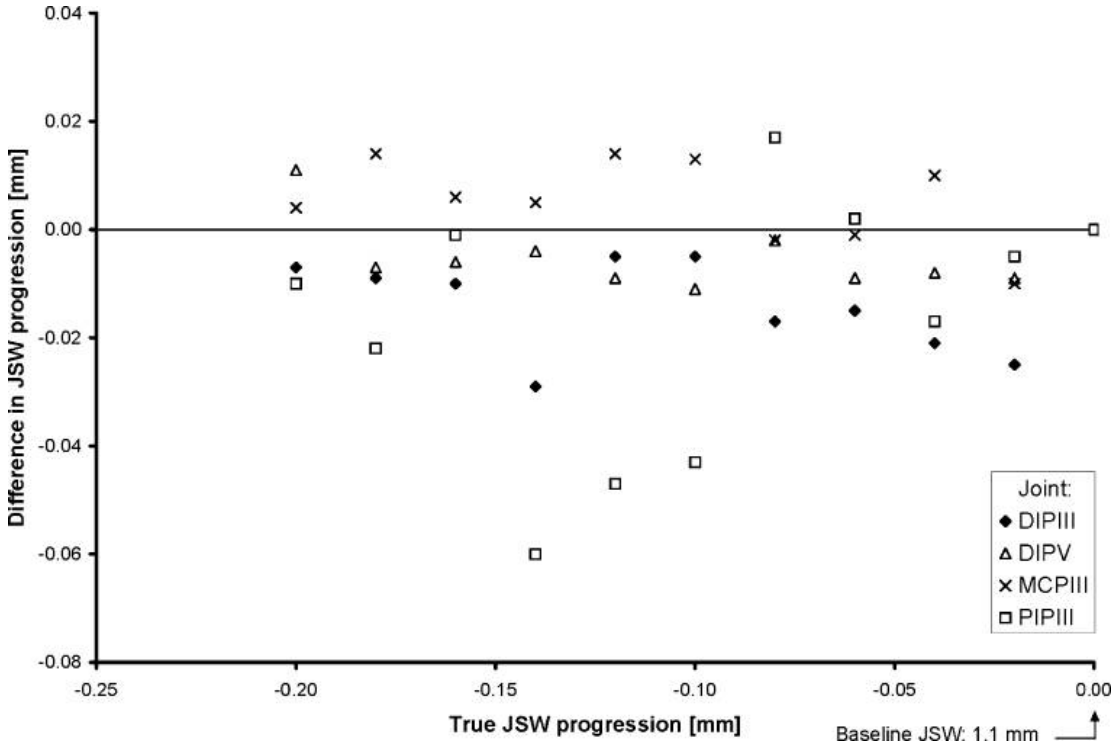


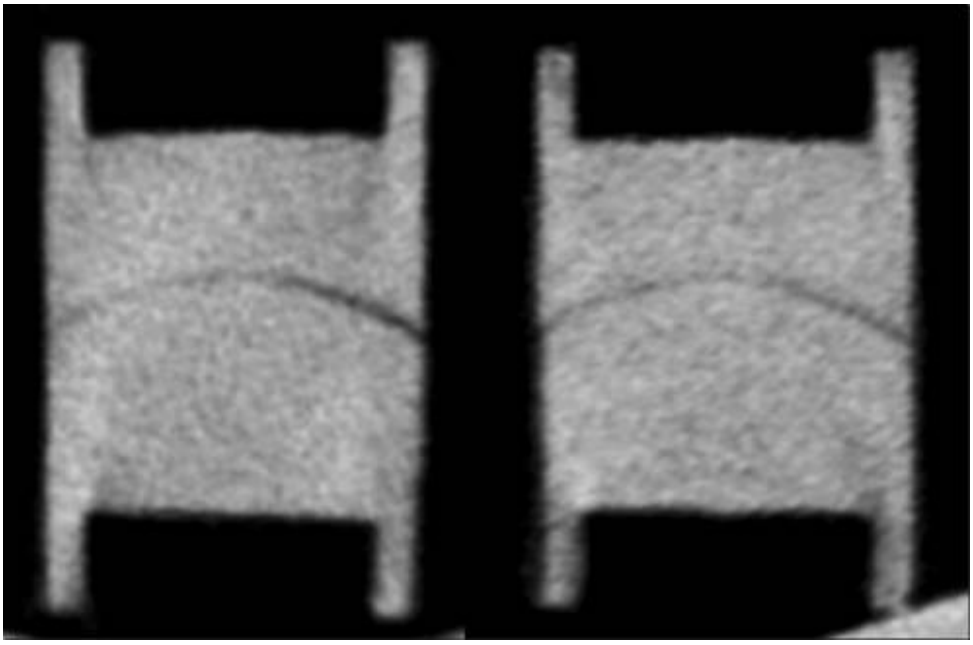
Fig. 7 *The difference between true and measured progression against the true progression, where a true JSW of 1.1 mm was taken as baseline*



Systematic error in the phantom experiments

The systematic error of 0.052 mm, found in the phantom studies, did not differ between the various focus-film distances. To test if the over-estimation was caused by the software or by the phantom design we determined the exact shape and fitting of the phantom joint, by scanning the phantom in a micro-CT scanner. This revealed that the distal and proximal surfaces did not fit perfectly, leaving a small asymmetric gap (Figure 8). This small additional space was being measured by the automatic quantification method.

Fig. 8 *Sagittal and coronal view of a Micro-CT scan of the acrylic phantom, showing a small asymmetric gap between ball and socket*



Discussion

We validated an automatic method to measure radiographic JSW of the finger joints, for which we previously found a good agreement with the atlas-based ordinal score according to the OARSI system(26). Results of the current study show that this automatic method has a high accuracy in measuring the JSW. We also found a high repeatability (SDD between 0.021 and 0.032), which varied slightly between the different hand joint locations. Measured systematic errors were between 0.056 mm and 0.047 mm and a progression of JSN between 0.012 and 0.047 mm could be detected. Both systematic errors and precision of progression estimation were dependent on the joint type, implying that the morphology differences between the MCP, PIP and DIP joints influenced the accuracy of JSW measurement.

Repeatability and systematic errors

The results of Experiment 1 showed that centering the X-ray beam to the location of a particular joint improves the repeatability slightly. The differences in repeatability may be explained by x-ray beam angulation, since the SDD of the measurements on the DIP V location was significantly higher than the SDD of the measurements on the MCP III location. The systematic error of 0.052 mm, found in the phantom studies, was caused by the phantom and not by the measurement software.

A similar phantom experiment was executed by Angwin et al, who studied the sensitivity and reliability of mean computerized JSW measurements in standard clinical hand radiographs in healthy subjects (19). They used a phantom MCP joint consisting of a gold plated aluminum ball and socket mounted on a micrometer to investigate the errors of their measurements method. In their phantom experiment an overestimation of JSW of 0.018 mm was found, which is smaller than the overestimation in our experiment. It is likely that their overestimation was also caused by the phantom model design, leaving a gap between the two components. In the same study, Angwin et al. used hand radiographs of healthy subjects to determine the smallest detectable difference, where they consequently assumed that repeatability was independent of the size of the JSW. In our experiment we could confirm that this is indeed the case. We found however that

repeatability is influenced by the shape of the joint and slightly by the joint location, as shown in Experiment 2 and 3.

The results of Experiment 3 showed that systematic errors were different between joint types. The automatic quantification software calculates a mean JSW depending on the measured area between two bony contours, whereas the micrometer device is calibrated on the minimal distance between two phalangeal bones. It is likely that the shape of the different joints influences the definition of JSW as implemented in the automatic quantification method compared to the minimal measured space by the micrometer. This may explain the differences in measured systematic errors between the various types of joints. For example, the small systematic error in DIP V may be related to the relatively flat shape of the articular surfaces. Although systematic errors differ between the different joint shapes, this may be of less relevance in future clinical trials, in which progression is being measured and the smallest detectable difference (SDD) would be more important than the systematic error.

Applicability of the automatic quantification method in clinical trials

In clinical trials progressive reduction in JSW from a patient given baseline would be assessed by the automated program. We used a micrometer determined baseline of 1.1 mm, based on results of a previous study in which JSW values were between 1.6 mm (MCP healthy subjects) and 0.6 mm (DIP OA patients)(26).

Angwin et al. studied the sensitivity and reliability of mean computerized JSW measurements in standard clinical hand radiographs of healthy subjects and the effect of hand position and joint angulation on measurement reliability(19). They found that a change > 0.11 mm in JSW in an individual joint would represent an actual physical change in JSW (outside the 95% confidence interval), and that the smallest detectable change decreased to 0.05mm when different measurements across fingers of a single subject where averaged. In our study we also investigated the influence of joint location, joint shape and JSW size on the smallest detectable difference. The results of our study show that the smallest detectable change in JSW of our quantification method ranges from 0.012mm to 0.047mm per individual finger joint. The differences in outcomes

between the two studies might be explained by the different measurements methods used, or by the fact that Angwin et al. used digitalized images captured from standard film radiographs.

In order to assess the applicability of the quantification method in future clinical trials, an indication of the expected rate of decline in JSW in the normal and OA population is needed. Pfeil et al (22-24) published a set of normative age-related and gender-specific JSW data in 869 normal (non-OA) patients. Those results show that in the normal population, aged between 20 and 80 years, there is a decrease in JSW between 0.1 and 0.2 mm every 20 years, depending on age and type of finger joint. This corresponds to an annual decrease between 0.005mm and 0.01mm. Our SDD results show that normal JSW reduction in non-OA patients could thus be detected in the DIP joints within two to four years, especially when measurements of different fingers and hands are averaged. The rate of JSW decline in hand OA patients is not known exactly, but a recently published prospective observational study showed that the semi-quantitative OARSI atlas scoring method was able to detect JSN progression after two years in 33 (19.2%) of 172 hand OA patients (30). Because rapid decrease of JSW is one of the main factors in hand OA, it is to be expected that the first signs of progression can be detected within one or two years with this automatic quantification method.

A few limitations apply to our study. The influence of finger joint flexion and extension in the measurement of JSW was not tested. Angwin et al (19) have demonstrated that this influences JSW measurements slightly. However, in contrast to rheumatoid arthritis, deformity of the hand joints is not as marked in OA. Only in a late stage of OA, full extension of the hand is limited by joint destruction. As stated by Angwin et al, the value of a sensitive measurement method lies in the detection of early progression in order to test possible benefits of newly developed methods to arrest or slow down the OA process. Therefore, it is expected that limited finger extension will not play a significant role in future OA research.
It is possible that in vivo both systematic error and SDD may be different from the values that we found in the cadaver derived bone experiment, since the actual radiographic contrast between bone, cartilage and synovial fluid is lower than between bone and air in our experiment. However,

conducting a study in vivo in humans using induced progression of JSN is practically and ethically impossible.

In hand OA research, progression of JSN is one of the most important parameters. The results of this study show that, dependent on the type of joint, a decrease in JSW of 0.01 to 0.05 mm can be detected with our automatic quantification method. It is to be expected that with this method the first signs of OA progression can be detected within one or two years, making it a sensitive tool in future hand OA research.

Reference List

1 Elders MJ. The increasing impact of arthritis on public health. J Rheumatol Suppl 2000 October;60:6-8.

2 Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994 March;84(3):351-8.

3 Center for Disease Control and Prevention (CDC). Prevalence of disabilities and associated health conditions among adults--United States, 1999. MMWR Morb Mortal Wkly Rep 2001 February 23;50(7):120-5.

4 Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). Ann Rheum Dis 2005 May;64(5):682-7.

5 Dominick KL, Jordan JM, Renner JB, Kraus VB. Relationship of radiographic and clinical variables to pinch and grip strength among individuals with osteoarthritis. Arthritis Rheum 2005 May;52(5):1424-30.

6 Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliabadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol 2002 December 1;156(11):1021-7.

7 Dillon CF, Hirsch R, Rasch EK, Gu Q. Symptomatic hand osteoarthritis in the United States: prevalence and functional impairment estimates from the third U.S. National Health and Nutrition Examination Survey, 1991-1994. Am J Phys Med Rehabil 2007 January;86(1):12-21.

8 Dougados M. Monitoring osteoarthritis progression and therapy. Osteoarthritis Cartilage 2004;12 Suppl A:S55-S60.

9 Emrani PS, Katz JN, Kessler CL, et al. Joint space narrowing and Kellgren-Lawrence progression in knee osteoarthritis: an analytic literature synthesis. Osteoarthritis Cartilage 2008 August;16(8):873-82.

10 Maheu E, Altman RD, Bloch DA, et al. Design and conduct of clinical trials in patients with osteoarthritis of the hand: recommendations from a task force of the Osteoarthritis Research Society International. Osteoarthritis Cartilage 2006 April;14(4):303-22.

11 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957 December;16(4):494-502.

12 Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995 September;3 Suppl A:3-70.

13 Kallman DA, Wigley FM, Scott WW, Jr., Hochberg MC, Tobin JD. New radiographic grading scales for osteoarthritis of the hand. Reliability for determining prevalence and progression. Arthritis Rheum 1989 December;32(12):1584-91.

14 Bellamy N, Tesar P, Walker D, et al. Perceptual variation in grading hand, hip and knee radiographs: observations based on an Australian twin registry study of osteoarthritis. Ann Rheum Dis 1999 December;58(12):766-9.

15 Maheu E, Cadet C, Gueneugues S, Ravaud P, Dougados M. Reproducibility and sensitivity to change of four scoring methods for the radiological assessment of osteoarthritis of the hand. Ann Rheum Dis 2007 April;66(4):464-9.

16 Lukas C, Sharp JT, Angwin J, et al. Automated measurement of joint space width in small joints of patients with rheumatoid arthritis. J Rheumatol 2008 July;35(7):1288-93.

17 Zhang W, Doherty M, Leeb BF, et al. EULAR evidence based recommendations for the management of hand osteoarthritis: report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007 March;66(3):377-88.

18 Maheu E, Berenbaum F. Time for new outcome measures in hand osteoarthritis? Nat Clin Pract Rheumatol 2009 March;5(3):136-8.

19 Angwin J, Heald G, Lloyd A, Howland K, Davy M, James MF. Reliability and sensitivity of joint space measurements in hand radiographs using computerized image analysis. J Rheumatol 2001 August;28(8):1825-36.

20 Sharp JT, Angwin J, Boers M, et al. Computer based methods for measurement of joint space width: update of an ongoing OMERACT project. J Rheumatol 2007 April;34(4):874-83.

21 Sharp JT, Gardner JC, Bennett EM. Computer-based methods for measuring joint space and estimating erosion volume in the finger and wrist joints of patients with rheumatoid arthritis. Arthritis Rheum 2000 June;43(6):1378-86.

22 Pfeil A, Bottcher J, Schafer ML, et al. Normative reference values of joint space width estimated by computer-aided joint space analysis (CAJSA): the distal interphalangeal joint. J Digit Imaging 2008 October;21 Suppl 1:104-12.

23 Pfeil A, Bottcher J, Seidl BE, et al. Computer-aided joint space analysis of the metacarpal-phalangeal and proximal-interphalangeal finger joint: normative age-related and gender-specific data. Skeletal Radiol 2007 September;36(9):853-64.

24 Pfeil A, Bottcher J, Seidl BE, et al. Computer-aided joint space analysis (CAJSA) of the proximal-interphalangeal joint-normative age-related and gender specific data. Acad Radiol 2007 May;14(5):594-602.

25 Langs G, Peloschek P, Bischof H, Kainberger F. Automatic quantification of joint space narrowing and erosions in rheumatoid arthritis. IEEE Trans Med Imaging. 2009 Jan;28(1):151-64.

26 van 't Klooster R., Hendriks EA, Watt I, Kloppenburg M, Reiber JH, Stoel BC. Automatic quantification of osteoarthritis in hand radiographs: validation of a new method to measure joint space width. Osteoarthritis Cartilage 2008 January;16(1):18-25.

27 Bland JM, Altman DG. Measurement error. BMJ 1996 June 29;312(7047):1654.

28 Botha-Scheepers S, Dougados M, Ravaud P, et al. Effect of medial tibial plateau alignment on serial radiographs on the capacity to predict progression of knee osteoarthritis. Osteoarthritis Cartilage 2008 February;16(2):272-6.

29 Maillefert JF, Sharp JT, Aho LS, Dougados M. Comparison of a computer based method and the classical manual method for radiographic joint space width assessment in hip osteoarthritis. J Rheumatol 2002 December;29(12):2592-6.

30 Botha-Scheepers S, Riyazi N, Watt I, et al. Progression of hand osteoarthritis over two years: a clinical and radiological follow-up study. Ann Rheum Dis 2008 August 26.

Chapter 4

Identification of factors associated with the development of knee osteoarthritis in a young to middle-aged cohort of patients with knee complaints

Kasper Huétink

Berend C. Stoel

Iain Watt

Margreet Kloppenburg

Johan L. Bloem

Steve H. Malm

Ronald van't Klooster

Rob G. H. H. Nelissen

Clinical Rheumatology September 2014

Abstract

The objective of this study was to identify risk factors for knee osteoarthritis (OA) development in a young to middle-aged population with sub-acute knee complaints. This, in order to define high risk patients who may benefit from early preventive or future disease modifying therapies. Knee OA development visible on radiographs and MR in 319 patients (mean age 41.5 years) 10 years after sub-acute knee complaints and subjective knee function (KOOS score) was studied. Associations between OA development and age, gender, activity level, BMI, meniscal or anterior cruciate ligament (ACL) lesions, OA in first-degree relatives and radiographic hand OA were determined using multivariable logistic regression analysis. OA on radiographs and MR in the TFC is associated with increased age (OR: 1.10, 95 % 1.04–1.16 and OR: 1.07, 95 % 1.02–1.13). TFC OA on radiographs only is associated with ACL and/or meniscal lesions (OR: 5.01, 95% CI 2.14–11.73), presence of hand OA (OR: 4.69, 95 % 1.35–16.32) and higher Tegner activity scores at baseline before the complaints (OR: 1.20, 95% CI 1.01–1.43). The presence of OA in the TFC diagnosed only on MRI is associated with a family history of OA (OR: 2.44, 95% CI 1.18–5.06) and a higher BMI (OR: 1.13, 95% CI 1.04–1.23). OA in the PFC diagnosed on both radiographs and MR is associated with an increased age (OR: 1.06, 95% CI 1.02–1.12 and OR: 1.05, 95% CI 1.00–1.09). PFC OA diagnosed on radiographs only is associated with a higher BMI (OR: 1.12, 95% CI 1.02–1.22). The presence of OA in the PFC diagnosed on MR only is associated with the presence of hand OA (OR: 3.39, 95% CI 1.10–10.50). Compared to normal reference values, the study population had significantly lower KOOS scores in the different subscales. These results show that knee OA development in young to middle aged patients with a history of sub-acute knee complaints is associated with the presence of known risk factors for knee OA. OA is already visible on radiographs and MRI after 10 years. These high risk patients may benefit from adequate OA management early in life.

Introduction

Osteoarthritis (OA) is a multi-factorial disease and predominantly involves the middle aged and older population (1). Risk factors for the development of OA are mechanical forces including trauma, age, female gender, family history of OA, obesity, morphologic changes and OA localization in another joint (2–7). To date no effective disease modifying medical therapy is available (8).

Knee OA is one of the main causes of walking-related disability in older adults (7). In some patients knee OA develops after knee injury (9), whereas in other patients knee OA develops in a more generalized way without specific trauma, affecting multiple other joints. It has been suggested that these two forms of OA cannot be seen as distinct from each other and that genetic predisposition may play a role in the development of knee OA after trauma (4, 5, 10–17). Studies investigating factors involved in OA development are usually performed in older populations with mean ages ranging from 50 to 80 years (5, 18–20).

The objective of the current study was to determine which risk factors could be identified for knee OA development in a specific population aged 24 to 55 years with a history of sub-acute knee complaints. Identifying these specific risk-factors may help to distinguish high-risk knee patients for the development of knee OA. Identifying these risk-factors in young patients with knee complaints could be of clinical importance. It is likely that these high risk patients will benefit from slowing down or even stopping the OA process by early preventive exercise therapy or eventually disease modifying medication (8, 21–23).

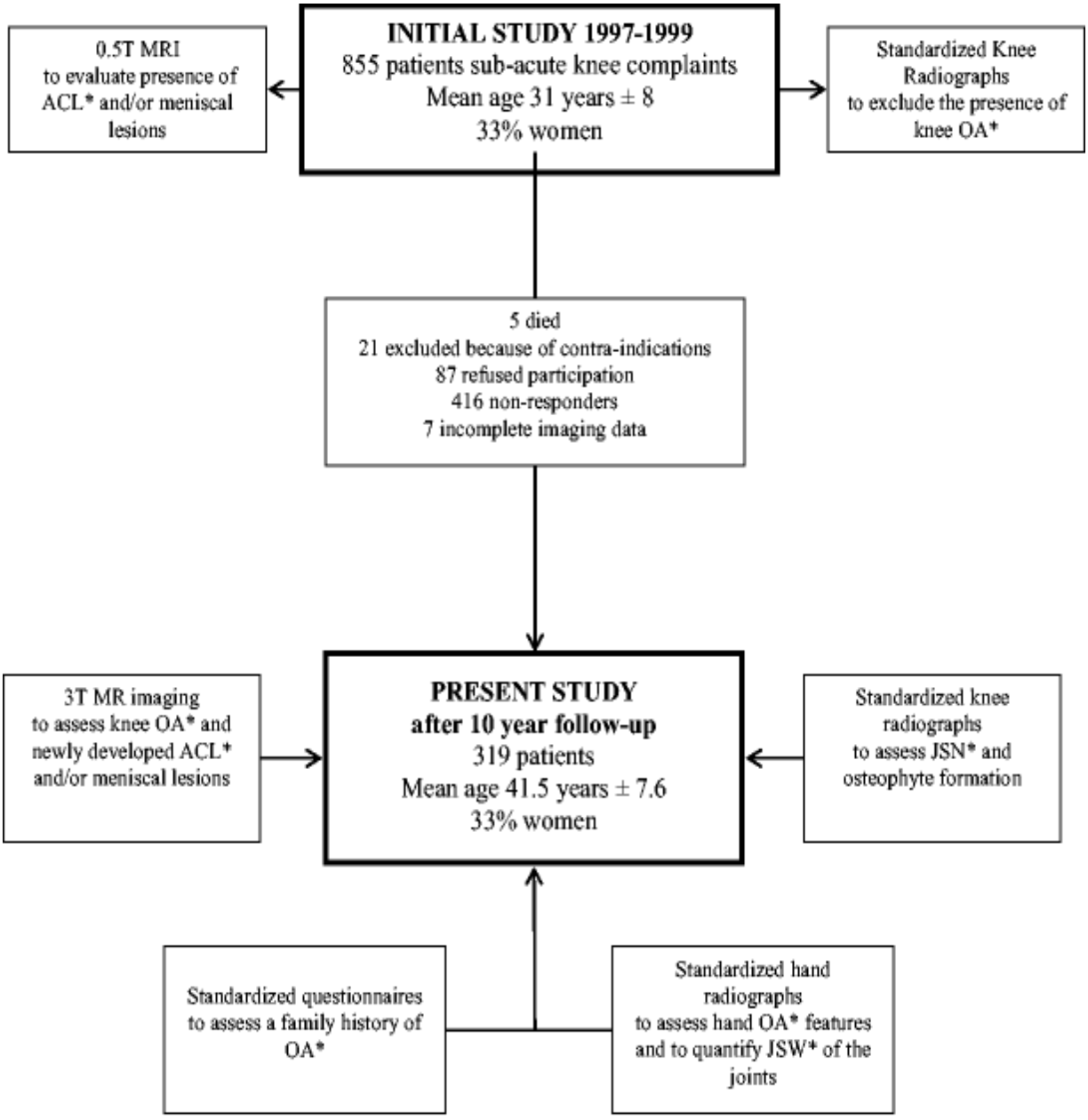
We investigated the following OA risk factors: anterior cruciate ligament (ACL) and / or meniscal lesions, age, female gender, body mass index (BMI), activity level before knee complaints, a family history of OA and the presence of hand OA.

Materials and methods

Study design

We studied a group of patients with a mean age of 41.5 years (SD 7.6) with a history of sub-acute knee complaints 10 years ago who had been the subject of a previous study of possible internal derangement of the knee (24). Subjects who were invited for this current study had participated between March 1997 and October 1999 in a prospective observational cohort study of 855 sub-acute knee patients to evaluate the cost effectiveness of magnetic resonance (MR) relative to diagnostic arthroscopy in patients with sub-acute knee complaints (24). Sub-acute knee complaints were defined as persistent knee complaints e.g. pain, swelling and instability lasting for more than four weeks. Patients between 15 and 45 years of age were included. Exclusion criteria were: knee complaints lasting less than four weeks, clinical symptoms of a locked knee, known inflammatory diseases such as rheumatoid arthritis, severe radiographic OA (Kellgren grade 4) and a history of knee surgery (24). After inclusion in the initial study all patients underwent 0.5 T MR imaging. Patients with a clinical suspicion of structural damage underwent arthroscopy if the MR result also showed structural defects needing surgical treatment. Patients with a clinical suspicion of structural damage, but no such damage visible on MR imaging were randomly assigned to a conservatively treated group and a diagnostic arthroscopy group. Knee function outcomes between the conservative and arthroscopy group were evaluated after three and six months follow up (24). Therefore, all patients received usual orthopaedic care while some patients underwent an additional diagnostic arthroscopy besides knee MR imaging. This study design was chosen for the initial study to allow evaluation of effectiveness and costs of MR imaging compared to diagnostic arthroscopy(24). All 855 subjects were invited by mail and telephone to participate in the current study and 319 patients (37 %) could ultimately be included (Fig. 1).

Fig. 1 Flow-chart study population



* ACL= anterior cruciate ligament
* OA=osteoarthritis
* JSN=joint space narrowing
* JSW=joint space width

Bony features of knee OA can be detected on radiographs. MR imaging adds information about soft tissues (e.g. ligamentous structures, synovium) which makes it possible to assess the knee as a whole organ (25, 26). Although the use of MR imaging is gaining more interest in daily clinical practice and in the field of OA research, conventional knee radiographs are still considered to be the standard in imaging knee OA. in both clinical and research settings (25). Therefore, in this study both radiographs and MR were used to determine knee OA development. To assess the presence of radiographic knee OA and/or knee OA on MR, standardized knee radiographs and knee MR scans were made of the initially affected knee. To determine if the ACL or menisci had been structurally damaged, both the knee MR images made 10 years ago and the recent follow-up MR data were used. To assess the presence of hand OA, routine hand radiographs were made. Questionnaires were used to obtain information about the body mass index (BMI), knee trauma and the presence of OA in first degree relatives. A family history was considered to be present when at least one first degree relative had OA. The Tegner activity scale was used to assess activity levels before the start of the knee complaints (27). The KOOS knee function questionnaire was used to determine subjective knee function after 10 years (28).

Imaging and assessment of knee OA features

Knee Radiographs

Ten years ago knee radiographs were made to identify signs of knee OA. During follow-up visit after 10 years standardized weight bearing posterior-anterior knee radiographs in a semi-flexed position and lateral radiographs of the knee were made. Knee radiographs of the initially affected knee were scored for the presence and severity of OA using the 0–4 Kellgren and Lawrence (KL) scoring system (29). Radiographic knee OA was considered to be present in patients with a KL score of 2 or higher. Joint space narrowing (JSN) and osteophyte formation in the patellofemoral compartment (PFC) were scored on the same basis of severity (0–3) compared to the skyline view radiographs described in the OARSI atlas (30). All radiographs were scored in consensus by an experienced musculoskeletal radiologist with over 30 years of experience (IW) and a research fellow (KH). The outcome scores were used in a binary fashion (absent-present) for further analysis.

Knee MR imaging

Ten years ago 0.5 T knee MR (Gyroscan T5; Philips Medical Systems, Best, the Netherlands) scans were evaluated on the presence of ACL and / or meniscal lesions by one of six radiologists involved in the initial study with at least 4 years of experience with musculoskeletal MR imaging (24).

During follow-up visit, 3.0 T MR examinations (Achieva 3 T, Philips Medical Systems, Best, the Netherlands) were performed of the initially affected knee, blinded for patient characteristics and scored in consensus by two experienced musculoskeletal radiologists (JLB, IW) each with over 20 years of MR imaging experience and a research fellow (KH). Scored items were absence or presence of ACL and / or meniscal tears, diffuse and focal cartilaginous defects, osteophytes, bone marrow edema-like abnormalities (BME), meniscal subluxations and subchondral cysts with values from absent to severe (0–3) using the validated KOSS scoring system (31). Cartilage lesions, osteophyte formation, BME and subchrondal cysts were scored in four compartments of the TFC and in five compartments of the PFC. For further analysis the outcome scores were used in a binary fashion (absent-present). To assess the presence of knee OA on MRI a Delphi exercise based definition of OA on MRI was used (26). Tibiofemoral OA was considered to be present when both definite osteophyte formation and full thickness cartilage loss are present, or when definite osteophyte formation or full thickness cartilage loss are present and two or more of the following features: 1) BME or cyst not associated with meniscal or ligamentous attachments; 2) meniscal subluxation, maceration or degenerative (horizontal) tear; 3) partial thickness cartilage loss (where full thickness loss is not present). Since bone attrition is not a specific item described in the KOSS scoring system, bone attrition could not be used as an OA scoring. Patellofemoral OA detected on MR images is considered to be present if a definite osteophyte and partial or full thickness cartilage loss involving the patella and/or anterior femur are found (26). An osteophyte with a KOSS score of 2 or higher was considered to be definite.

Radiographic OA assessment of the hand

Hand radiographs

During follow-up visit hand template assisted standardized PA radiographs were taken of both hands and scored on a scale of 0–3 for joint space narrowing in the fingers joints (H-JSN) and osteophyte formation, using the OARSI atlas (30). All radiographs were scored in consensus by an experienced musculoskeletal radiologist with over 30 years of experience (IW) and a research fellow (KH). These outcome scores were used in a binary fashion (absent-present) for further analysis. Because the study group comprised young to middle-aged patients, we expected to find only a small number of hand joints affected by OA (32). Therefore, we additionally employed an automatic joint space width (JSW) quantification method to detect subtle differences in finger JSW, since smaller JSWs reflect hyaline cartilage loss, one of the main characteristics of OA (33, 34).

Data analysis

For data analysis, SPSS version 20 was used. Chi-square tests and independent T- tests were used to compare the population characteristics of the follow-up population and the non-follow-up group. To compare knee function score outcomes and the presence of radiographic knee OA of the study population to normal population reference values (32, 35) the T-test and Chi square test were used. According to their presence or absence, both MR and radiographic detectable knee OA were categorized in a binary fashion. Binary logistic regression analysis was used to determine associations between radiographic knee OA or knee OA on MRI and the following independent variables: age, gender, a family history of OA, BMI, Tegner activity level before complaints, ACL and/or meniscal lesions, radiographic hand OA, and the mean JSW of the finger joints. All covariates were used in one model. The presence of knee OA in the TFC and PFC defined on radiographs and MR images were used as dependent variables. Odds ratios (OR) and 95 % confidence intervals were determined and adjusted for all variables. To determine associations between KOOS knee function outcomes and age, gender, BMI, activity level before complaints, ACL and/or meniscal lesions and radiographic knee OA or knee OA on MRI a multivariate analysis of covariance model was used. Effect size and 95 % confidence intervals were determined and adjusted for all variables.

Results

Population characteristics

A total of 319 patients were included in the present study. The mean age of the study population was 41.5 years (range 24-55y, SD 7.6). The percentage women was 33% (106). The mean BMI was 26.1 (SD 3.8). None of the included subjects had experienced a major knee trauma in the last decade. A family history of OA was present in 70 patients (22%). ACL and/or meniscal lesions were present in 188 patients (57 %), this was an increase of 20 patients (6%) relative to the start of the study. A total of 212 (67%) patients underwent an arthroscopy or other invasive procedure in the affected knee. Forty-nine (56%) of the 87 patients who returned the follow-up invitation letter, but refused to participate in the study had knee complaints. The main reason not to participate in the current study was a lack of time. At baseline there were no differences in radiographic knee OA severity between those who chose to participate in this current study and those who were non-responders or declined participation (P >>0.05).

Presence of knee OA on the follow-up radiographs

Radiographic tibiofemoral knee OA (KL≥2) was present in 74 patients (23%) at follow-up. The two patients with a K&L score of 2 at baseline both showed OA progression to a K&L score of 4. The remaining 18 patients had a K&L score of 1 at baseline, seven of these remained K&L 1, in the other 11 patients there was an increase of at least one grade in the K&L score after 10 years (5 patients K&L 2; 6 patients K&L 3) (Table 1). Patellofemoral JSN and/or osteophytes were present in 71 (22%) patients at follow-up. Seventy-one patients developed JSN and osteophytes in the PFC after 10 years. In seven of these (10%) JSN was also present at baseline while the other 54 patients had developed new lesions.

Table 1

Presence of radiographic Knee OA at baseline and follow-up

Number of subjects with radiographic knee OA scored with the Kellgren and Lawrence (K&L) scoring system at baseline and after 10 years follow-up.

K&L score		After 10 years follow-up				
		0	1	2	3	4
Baseline	0	13	225	37	11	13
	1	0	7	5	6	0
	2	0	0	0	0	2
	3	0	0	0	0	0
	4	0	0	0	0	0

Normal values of the prevalence of radiographic knee OA are only available for men and women aged 45 years and older (32). In the study population 109 (34 %) patients were aged 45 years or older. Only 3 patients were aged 55 years or older, due to the small sample size OA prevalence could not be compared to normal reference data. In both men and women aged between 45 and 49 years at follow-up the prevalence of knee OA was higher than in the normal population (34.9 % vs. 9.4 % and 22.7 % vs. 14.2 %), this difference was statistically significant ($p < 0.001$) only in men. Compared to the prevalence of knee OA in the normal population, in both men and women aged between 50 and 54 years the prevalence of knee OA was statistically significant higher (40 % vs. 13.5 % and 42.1 % and 18.3 %) ($p < 0.001$ and $p = 0.01$).

There were no differences in the radiographic knee OA development between patients randomly assigned to the conservatively treated group or to the diagnostic arthroscopy group.

Presence of knee OA on follow-up MR images

Knee OA on MR was present in the TFC in 73 patients (23 %) and in the PFC in 78 patients (25 %). OA progression on MR imaging could not be assessed because different types of scanners (0.5 T vs. 3.0 T) and different scoring methods were used at baseline and at follow-up.

Prevalence of radiographic hand OA

In 8 of the 319 included patients no hand radiographs were made due to late withdrawal by patients. Seventeen (5.3 %) subjects had signs of hand OA according to the OARSI atlas scoring method. A total of 56 joints had mild to moderate signs of hand OA (H-JSN or osteophyte grade 1–2). There were no patients with severe hand OA (grade 3). Most affected were the DIP joints (29; 52 %) and the CMC I joints (25; 45 %). In the majority (50 joints; 89 %) of the joints affected with OA, osteophytes as well as H-JSN were present. Few joints had isolated H-JSN (two CMC I and four DIP joints). In patients with hand OA according to the OARSI atlas there was a trend towards a smaller JSW in all measured finger joints; the mean difference in JSW for the MCP, PIP and DIP joints were 0.08 mm, 0.02 mm and 0.05 mm respectively, however none these differences were statistically significant.

Factors associated with radiographic knee OA or knee OA on MRI

Associations between risk factors and the presence of knee OA are described in Tables 2, 3, 4 and 5.

Age

Increased age was associated with the presence of radiographic knee OA in the TFC (radiographic and MR) and PFC (radiographic and MR)

Gender

There were no significant differences between men and women in the presence of knee OA.

BMI

A higher BMI was associated with the presence of OA in the PFC (radiographs only), and with the presence of OA in the TFC (MR only).

ACL and/or meniscal lesions

ACL and/or meniscal lesions were associated with the presence of OA in the TFC (radiographs and MR).

Familial OA

A family history of OA was associated with the presence of OA in the TFC (MR only).

Hand OA

The presence of radiographic hand OA was associated with the presence of OA in the TFC (radiographs only) and with the presence of OA in the PFC (MR only).

Tegner activity levels

Higher Tegner activity levels at baseline were associated with an increased risk of developing radiographic OA in the TFC.

Table 2 Radiographic findings tibiofemoral compartment

Associations between radiographic knee OA defined as a Kellgren and Lawrence score (K&L) of≥2 in the TFC and the listed independent variables. Binary logistic regression analysis was used. Outcomes were adjusted for all independent variables.

Independent variables	K&L < 2	K&L ≥ 2	Unadjusted OR	Unadjusted 95% CI	Adjusted OR	Adjusted 95% CI	Adjusted P-value
Mean age in yrs (SD)	40 (7.5)	45 (7.0)	1.09	1.05-1.13	1.10	1.04-1.16	<0.001*
Sex, number of women (%)	82 (34%)	24 (32%)	0.95	0.55-1.66	2.78	0.93-8.25	0.07
BMI, kg/m^2 (SD)	25.8 (3.9)	26.9 (3.4)	1.07	1.00-1.15	1.07	0.98-1.18	0.15
ACL or meniscal Lesions (%)	129 (53%)	59 (80%)	3.54	1.90-6.57	5.01	2.14-11.73	<0.001*
Presence of familial OA (%)	52 (22%)	16 (24%)	1.07	0.56-2.02	1.27	0.58-2.80	0.56
Tegner activity score baseline (SD)	5.9(2.4)	5.9 (2.3)	1.00	0.90-1.12	1.20	1.01-1.43	0.04*
Radiographic hand OA (%)	8 (3%)	9 (12%)	4.09	1.52-11.01	4.69	1.35-16.32	0.02*

*** Statistically significant difference, adjusted for all variables in table**

Abbreviations: TFC= tibiofemoral compartment, K&L= Kellgren and Lawrence score, OR= odds ratio, 95% CI = 95% confidence interval, SD= standard deviation, ACL=anterior cruciate ligament

Table 3 Radiographic findings patellofemoral compartment

Associations between radiographic knee OA defined as a Kellgren and Lawrence score (K&L) of≥2 in the PFC and the listed independent variables. Binary logistic regression analysis was used. Outcomes were adjusted for all independent variables.

Independent variables	No JSN or Osteophytes	JSN and or Osteophytes	Unadjusted OR	Unadjusted 95% CII	Adjusted OR	Adjusted 95% CI	Adjusted P-value
Mean age in yrs (SD)	41 (7.5)	45 (7.2)	1.08	1.04-1.12	1,06	1,02-1,12	0,01*
Sex, number of women (%)	79 (36%)	18 (26%)	0.61	0.33-1.11	0,57	0,21-1,57	0,27
BMI, kg/m^2 (SD)	25.6 (3.7)	27.3 (3.8)	1.12	1.04-1.20	1,12	1,02-1,22	0,01*
ACL or meniscal Lesions (%)	122 (56%)	49 (69%)	1.79	1.01-3.16	1,95	0,96-3,99	0,07
Presence of familial OA (%)	49 (24%)	14 (21%)	0.82	0.42-1.60	1,02	0,48-2,18	0,97
Tegner activity score baseline (SD)	5.9 (2.3)	5.7 (2.5)	0.96	0.85-1.07	1,03	0,89-1,21	0,67
Radiographic hand OA (%)	8 (4%)	8 (11%)	3.35	1.21-9.28	2,59	0,84-7,96	0,10

* **Statistically significant difference, adjusted for all variables in table** *Abbreviations: PFC= patellofemoral compartment, K&L= Kellgren and Lawrence score, OR= odds ratio, 95% CI= 95% confidence interval, SD= standard deviation, ACL=anterior cruciate ligament*

Table 4 MRI Findings tibiofemoral compartment

Associations between knee OA on MRI defined by the Delphi criteria in the TFC and the listed independent variables. Binary logistic regression analysis was used. Outcomes were adjusted for all independent variables.

	No MRI OA according to Delphi criteria	MRI OA according to Delphi criteria	Unadjusted OR	Unadjusted 95% CII	Adjusted OR	Adjusted 95% CI	Adjusted P-value
Mean age in yrs (SD)	41 (7.7)	44 (6.9)	1.06	1.03-1.10	1.07	1.02-1.13	<0.001*
Sex, number of women (%)	89 (40%)	13 (17%)	0.31	0.16-0.60	0.45	0.161.28	0.13
BMI, kg/m^2 (SD)	25.6 (3.8)	27.3 (3.7)	1.11	1.04-1.20	1.13	1.04-1.23	0.01*
ACL or meniscal Lesi-ons (%)	118 (53%)	54 (72%)	2.25	1.27-3.97	2.02	1.00-4.08	0.05
Presence of familial OA (%)	44 (21%)	20 (29%)	1.53	0.83-2.84	2.44	1.18-5.06	0.02*
Tegner activity score baseline (SD)	5.8 (2.4)	6.1 (2.3)	1.05	0.94-1.18	1.12	0.96-1.30	0.16
Radiographic hand OA (%)	9 (4%)	7 (9%)	2.41	0.87-6.73	1.69	0.52-5.47	0.38

*** Statistically significant difference, adjusted for all variables in table** *Abbreviations: TFC= tibiofemoral compartment, K&L= Kellgren and Lawrence score, OR= odds ratio, 95% CI= 95% confidence interval, SD= standard deviation, ACL=anterior cruciate ligament*

Table 5 MRI Findings patellofemoral compartment

Associations between knee OA on MRI defined by the Delphi criteria in the PFC and the listed independent variables. Binary logistic regression analysis was used. Outcomes were adjusted for all independent variables..

	No MRI OA according to Delphi criteria	MRI OA according to Delphi criteria	Unadjusted OR	Unadjusted 95% CI	Adjusted OR	Adjusted 95% CI	Adjusted P-value
Mean age in yrs (SD)	41 (7.3)	43 (8.2)	1.05	1.01-1.09	1.05	1.00-1.09	0.03*
Sex, number of women (%)	77 (35%)	25 (32%)	0.87	0.50-1.50	0.77	0.31-1.93	0.58
BMI, kg/m^2 (SD)	25.7 (3.6)	26.9 (4.3)	1.08	1.01-1.16	1.05	0.97-1.13	0.22
ACL or meniscal Lesions (%)	130 (60%)	42 (54%)	0.79	0.47-1.33	0.71	0.38-1.30	0.26
Presence of familial OA (%)	43 (21%)	21 (28%)	1.45	0.79-2.65	1.78	0.92-3.43	0.09
Tegner activity score baseline (SD)	5.9 (2.3)	5.7 (2.5)	0.97	0.86-1.08	1.04	0.91-1.20	0.56
Radiographic hand OA (%)	6 (3%)	10 (13%)	5.17	1.81-14.76	3.39	1.10-10.50	0.03*

*** Statistically significant difference, adjusted for all variables in table** *Abbreviations: PFC= patellofemoral compartment, K&L= Kellgren and Lawrence score, OR= odds ratio, 95% CI= 95% confidence interval, SD= standard deviation, ACL=anterior cruciate ligament*

Additional diagnostic arthroscopy in randomization group

There were no differences in radiographic knee OA or MR knee OA development between patients randomly assigned to the conservative treated group or to the diagnostic arthroscopy group.

Subjective Knee function after 10 years

KOOS knee function outcomes compared to normal reference data (35) are shown in Table 6. Due to the small sample size p-values for the age group above 55 years could not be determined. Generally, our study population had lower KOOS scores compared to the normal reference values. In the subscales Sports& Recreation and Quality of Life these difference were significant in all groups. Dependent on age and gender the subscales Pain, Symptoms and ADL were also significant lower in our study population compared to the normal reference values.
Lower KOOS scores in all subscales were associated with an increased BMI (Effect size reaching from 0.024- 0.064). TFC OA according to the Delphi criteria was associated with lower outcomes in the subscales Sports and Recreation and Quality of life (Effect size 0.027 and 0.021). The presence of JSN and osteophytes in the PFC was associated with lower Quality of life scores (Effect size 0.017). Higher Tegner Activity scores at baseline were associated with higher scores in the subscales Pain and Sports and recreation (Effect size 0.018 and 0.019). A higher age was associated with lower scores in the subscales ADL and Pain (Effect size 0.018 and 0.048). The presence of ACL and/or meniscal lesions was associated with lower Symptoms scores (Effect size 0.019). There were no differences in KOOS outcomes between patients randomly assigned to the conservatively treated group or to the diagnostic arthroscopy group.

Table 6

KOOS knee function outcomes 10 years after sub-acute knee complaints

Age and gender specific differences in KOOS knee function subscales scores compared between the study population outcomes and reference data published by Paradowski et al. (51)

		18–34y						35–54y						55–74y			
		male			female			male			female			male		female	
	KOOS subscales	N	Mean (SD)	p	N	Mean (SD)	p	N	Mean (SD)	p	N	Mean (SD)	p	N	Mean (SD)	N	Mean (SD)
Studypopulation	PAIN	31	79.9(17.9)	<0.001*	24	86.3(13.4)	0.078	162	82.9(18.1)	0.072	76	75.2(25.8)	<0.001*	2	36.1(35.4)	2	87.5(17.7)
Reference data	PAIN	60	92.2(11.2)		74	92.1(14.0)		78	87.4(17.9)		80	88.8(18.7)		88	87.7(17.4)	85	78.6(25.5)
Studypopulation	SYMPTOMS	31	73.2(20.6)	<0.001*	25	79.1(17.8)	0.005*	163	82.0(16.8)	0.053	76	75.7(19.6)	<0.001*	2	30.4(27.8)	2	89.3(15.2)
Reference data	SYMPTOMS	60	87.2(13.9)		74	89.1(13.5)		78	86.5(16.7)		82	89.5(14.6)		88	88.4(17.3)	85	77.1(24.8)
Studypopulation	ADL	31	87.8(15.5)	0.092	24	92.8 (9.7)	0.363	163	86.9(16.9)	0.352	74	80.3(23.7)	0.019*	1	11.8 (-)	2	89.0(15.6)
Reference data	ADL	60	94.2(10.0)		74	95.2(11.6)		78	89.1(17.6)		80	88.6(19.7)		88	86.3(18.8)	85	77.4(26.2)
Studypopulation	SPORT&REC	31	62.7(27.9)	<0.001*	24	62.9(25.4)	<0.001**	163	64.8(28.6)	0.006*	76	53.0(35.3)	<0.001*	2	20.0(28.3)	1	100.0 (-)
Reference data	SPORT&REC	60	85.1(20.8)		74	86.4(21.1)		76	76.0 (29.5)		80	79.3(27.7)		87	72.6(29.9)	84	61.0(36.9)
Studypopulation	QOL	31	59.5(20.3)	<0.001*	25	67.0(17.5)	<0.001**	162	63.5(22.0)	<0.001*	76	59.2(28.7)	<0.001*	2	21.9(30.9)	2	84.4(13.3)
Reference data	QOL	59	85.3(19.2)		74	83.6(20.2)		78	77.7 25.4)		80	83.4(22.0)		88	78.9(25.4)	85	68.6(31.4)

* **Statistically significant difference** *P-values were derived using Chi-square testing Abbreviations: ADL= Function (Activities) in daily living SPORT&REC = Function in sport and recreation, QOL = Knee related Quality of Life*

Discussion

The results of our study show that in this specific young to middle-aged population with a history of sub-acute knee complaints, several factors are associated with the development of knee OA on radiographs and/or MR over a 10 year period. OA on radiographs and MR in the TFC is associated with age. TFC OA on radiographs is associated with ACL and/or meniscal lesions, the presence of hand OA and higher Tegner activity scores at baseline before the complaints. The presence of OA in the TFC diagnosed only on MRI is associated with a family history of OA and a higher BMI. OA in the PFC diagnosed with both radiographs and MR is associated with an increased age. PFC OA diagnosed on radiographs only is associated with a higher BMI. The presence of OA in the PFC diagnosed with MR is associated with the presence of hand OA.

In contrast to OA development in the TFC, ACL and /or meniscal lesions are not associated with the development of knee OA in the PFC. This supports the hypothesis that underlying biomechanical factors related to knee OA development in the TFC and the PFC may be different (37-39). Lesions of the menisci and ACL may disturb adequate mechanical loading in the TFC whereas patellar misalignment causes disturbance of patella movements in the femoral trochlea (40, 41). On the other hand, our results indicate that besides mechanical factors other factors are associated with, both TFC and PFC OA development (e.g. BMI, hand OA).

Several publications have shown that the development of knee OA is related to the presence of hand OA (10, 13, 16, 42), the results of our study confirm this relationship in a young middle-aged population with knee complaints 10 years ago for both radiographic OA in the TFC and OA on MRI in the PFC.

An association between the development of knee OA and a family history of OA (17, 42, 43), has been described, whereas others did not find such a relationship (20). Our results show that in this young to middle-aged population a family history of OA is associated with OA on MRI in the TFC.

Age is related to radiographic knee OA and knee OA on MRI in both the TFC and the PFC. A higher BMI is associated with knee OA on MRI in the TFC and radiographic knee OA in the PFC. These relationships have been described in studies which investigated risk factors for the

development of knee OA in older populations (2, 5, 32, 44–49). Our results show that this effect is already visible at a relatively young age.

We found no gender-related differences in the development of radiographic knee OA or knee OA on MRI. These results are in contrast to most publications which reported an increased risk of developing knee OA in women compared to men (5, 32, 50). This may be explained by the fact that the female participants in the present study were mostly pre-menopausal, in contrast to older and post-menopausal women in the other publications.

Higher Tegner activity levels before the start of the knee complaints at baseline are associated with radiographic TFC OA development. This is in agreement with previous published data, in which the relationships between sports and TFC OA development is described (36).

Compared to reference data published by Paradowski et al. (35) our study population had lower KOOS knee function scores than the general population. This difference seems to be of clinical importance in all KOOS subscales except for ADL since the mean outcome scores differ more than 10 points, which is considered to be clinically relevant (28). Therefore, it can be concluded that patients with sub-acute knee complaints have an increased risk of poorer subjective knee functioning after 10 years. Our results also show that radiographic OA and OA on MRI are only partly related to poorer subjective knee function (only with respect to the subscales Sports & recreation and Quality of life), this is in agreement with previous published data on the relationship between radiographic and clinical OA (37). BMI, age, activity level, radiographic PFC OA and TFC OA on MRI are all associated with subjective poorer knee functions, however, non of these associations appear to be strong (effect sizes all smaller than 0.1).

Bony features of knee OA are visible on knee radiographs and MR imaging makes it possible to assess the knee as a whole organ adding information about soft tissues (e.g. ligamentous structures, synovium) (25). Several risk factors have a statistically significant association with both X-ray and MRI OA development (Age and ACL or meniscal lesions). Some factors did not reach statistical significance with OA development on both modalities, although OR's of both MRI and X ray outcomes gave a same association. The latter may be due to the fact that some of the groups were small (potential type II effect) (Tables 2, 3, 4 and 5). Although MR imaging is widely held to be more sensitive in detecting OA (51) we found a higher number of patients with radiographic

knee OA than knee OA at MRI. This is because in order to meet the Delphi criteria for OA at MRI not only osteophytes and cartilage lesions have to be present but also several other criteria linked to soft tissue injuries have to be present as well. In fact, there are significantly more patients with cartilage lesions and osteophytes detected on MR than on radiographs, mainly because small defects are easier to detect on MR imaging than on radiographs.

To date no disease modifying medication is available, however several drugs are in development which may be essential in future prevention of joint replacement surgery (52). The current study shows that in young to middle aged patients with an episode of sub-acute knee complaints risk profiling for OA can identify patients who have an increased risk of developing OA within 10 years. This may open the road to preventive or disease modifying therapies, thus preventing total knee replacement later in life

Some limitations to our study should be mentioned. Due to technical limitations, the JSW of finger joints in the first ray could not be measured with the automatic quantification method, while single most radiographic hand OA features assessed using the OARSI atlas were present in the CMC I joint. A family history of OA was self-reported using a questionnaire. There is a reasonable chance that only relatives with symptomatic OA were mentioned in the forms, which may have biased our estimations. BMI was not determined at baseline, therefore only follow-up data could be used to determine associations between an increased BMI and knee OA development. Another limitation is a comparison could not be made on the prevalence of knee radiographic changes in people without non-acute knees symptoms a decade ago. Reference data concerning the prevalence of radiographic knee OA in the general population aged < 45 years are not available. When we compare the prevalence of knee OA in the normal population older than 45 years (32), our patients appear to be more often affected with knee OA compared to these normal values.

In conclusion, the presence of certain known risk factors in young to middle aged patients with an episode of sub-acute knee complaints a decade ago are associated with the development of knee OA visible on radiographs and MR imaging. These patients also report poorer subjective knee function compared to normal reference values. Knee radiographs and MR images combined with assessment of the presence of these risk factors can be used to identify high risk patients who may

benefit from adequate OA management early in life in order to prevent eventual knee joint replacement.

Reference List

1. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum.Dis.Clin.North Am. 2013;1-19.

2. Grotle M, Hagen KB, Natvig B, Dahl FA, Kvien TK. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. BMC.Musculoskelet.Disord. 2008;132.

3. Kalichman L, Hernandez-Molina G. Hand osteoarthritis: an epidemiological perspective. Semin.Arthritis Rheum. 2010;465-76.

4. Bierma-Zeinstra SM, Koes BW. Risk factors and prognostic factors of hip and knee osteoarthritis. Nat.Clin.Pract.Rheumatol. 2007;78-85.

5. Blagojevic M, Jinks C, Jeffery A, Jordan KP. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis.Cartilage. 2010;24-33.

6. Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK, Felson DT. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann.Rheum.Dis. 2011;1581-6.

7. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, Kington RS, Lane NE, Nevitt MC, Zhang Y, Sowers M, McAlindon T, Spector TD, Poole AR, Yanovski SZ, Ateshian G, Sharma L, Buckwalter JA, Brandt KD, Fries JF. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann.Intern.Med. 2000;635-46.

8. Martel-Pelletier J, Wildi LM, Pelletier JP. Future therapeutics for osteoarthritis. Bone 2012;297-311.

9. Muthuri SG, McWilliams DF, Doherty M, Zhang W. History of knee injuries and knee osteoarthritis: a meta-analysis of observational studies. Osteoarthritis.Cartilage. 2011;1286-93.

10. Hirsch R, Lethbridge-Cejku M, Scott WW, Jr., Reichle R, Plato CC, Tobin J, Hochberg MC. Association of hand and knee osteoarthritis: evidence for a polyarticular disease subset. Ann.Rheum.Dis. 1996;25-9.

11. Lohmander LS, Felson D. Can we identify a 'high risk' patient profile to determine who will experience rapid progression of osteoarthritis? Osteoarthritis.Cartilage. 2004;S49-S52.

12. Hochberg MC, Lane NE, Pressman AR, Genant HK, Scott JC, Nevitt MC. The association of radiographic changes of osteoarthritis of the hand and hip in elderly women. J.Rheumatol. 1995;2291-4.

13. Dahaghin S, Bierma-Zeinstra SM, Reijman M, Pols HA, Hazes JM, Koes BW. Does hand osteoarthritis predict future hip or knee osteoarthritis? Arthritis Rheum. 2005;3520-7.

14. Harris PA, Hart DJ, Dacre JE, Huskisson EC, Spector TD. The progression of radiological hand osteoarthritis over ten years: a clinical follow-up study. Osteoarthritis.Cartilage. 1994;247-52.

15. Valdes AM, Spector TD. The contribution of genes to osteoarthritis. Rheum.Dis.Clin.North Am. 2008;581-603.

16. Haugen IK, Cotofana S, Englund M, Kvien TK, Dreher D, Nevitt M, Lane NE, Eckstein F. Hand joint space narrowing and osteophytes are associated with magnetic resonance imaging-defined knee cartilage thickness and radiographic knee osteoarthritis: data from the Osteoarthritis Initiative. J.Rheumatol. 2012;161-6.

17. Riyazi N, Rosendaal FR, Slagboom E, Kroon HM, Breedveld FC, Kloppenburg M. Risk factors in familial osteoarthritis: the GARP sibling study. Osteoarthritis.Cartilage. 2008;654-9.

18. Jiang L, Tian W, Wang Y, Rong J, Bao C, Liu Y, Zhao Y, Wang C. Body mass index and susceptibility to knee osteoarthritis: a systematic review and meta-analysis. Joint Bone Spine 2012;291-7.

19. Jonsson H, Helgadottir GP, Aspelund T, Eiriksdottir G, Sigurdsson S, Siggeirsdottir K, Ingvarsson T, Harris TB, Launer L, Gudnason V. Hand Osteoarthritis Severity is Associated with Total Knee Joint Replacements Independently of BMI. The Ages-Reykjavik Study. Open.Rheumatol.J. 2011;7-12.

20. Riyazi N, Meulenbelt I, Kroon HM, Ronday KH, Hellio le Graverand MP, Rosendaal FR, Breedveld FC, Slagboom PE, Kloppenburg M. Evidence for familial aggregation of hand, hip, and spine but not knee osteoarthritis in siblings with multiple joint involvement: the GARP study. Ann.Rheum.Dis. 2005;438-43.

21. Hunter DJ, Hellio Le Graverand-Gastineau MP. How close are we to having structure-modifying drugs available? Med.Clin.North Am. 2009;223-34, xiii.

22. Rannou F, Poiraudeau S. Non-pharmacological approaches for the treatment of osteoarthritis. Best.Pract.Res.Clin.Rheumatol. 2010;93-106.

23. Smink AJ, van den Ende CH, Vliet Vlieland TP, Swierstra BA, Kortland JH, Bijlsma JW, Voorn TB, Schers HJ, Bierma-Zeinstra SM, Dekker J. "Beating osteoARThritis": development of a stepped care strategy to optimize utilization and timing of non-surgical treatment modalities for patients with hip or knee osteoarthritis. Clin.Rheumatol. 2011;1623-9.

24. Vincken PW, ter Braak AP, van Erkel AR, Coerkamp EG, de Rooy TP, de LS, Mallens WM, Coene LN, Bloem RM, van Luijt PA, van den Hout WB, van Houwelingen HC,

Bloem JL. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 2007;85-93.

25. Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H, Roemer FW. Imaging in osteoarthritis. Rheum.Dis.Clin.North Am. 2008;645-87.

26. Hunter DJ, Arden N, Conaghan PG, Eckstein F, Gold G, Grainger A, Guermazi A, Harvey W, Jones G, Hellio le Graverand MP, Laredo JD, Lo G, Losina E, Mosher TJ, Roemer F, Zhang W. Definition of osteoarthritis on MRI: results of a Delphi exercise. Osteoarthritis.Cartilage. 2011;963-9.

27. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin.Orthop.Relat Res. 1985;43-9.

28. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual.Life Outcomes. 2003;64.

29. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann.Rheum.Dis. 1957;494-502.

30. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis.Cartilage. 1995;3-70.

31. Kornaat PR, Ceulemans RY, Kroon HM, Riyazi N, Kloppenburg M, Carter WO, Woodworth TG, Bloem JL. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol. 2005;95-102.

32. van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann.Rheum.Dis. 1989;271-80.

33. Huetink K, van 't KR, Kaptein BL, Watt I, Kloppenburg M, Nelissen RG, Reiber JH, Stoel BC. Automatic radiographic quantification of hand osteoarthritis; accuracy and sensitivity to change in joint space width in a phantom and cadaver study. Skeletal Radiol. 2011.

34. van 't Klooster R., Hendriks EA, Watt I, Kloppenburg M, Reiber JH, Stoel BC. Automatic quantification of osteoarthritis in hand radiographs: validation of a new method to measure joint space width. Osteoarthritis.Cartilage. 2008;18-25.

35. Paradowski PT, Bergman S, Sunden-Lundius A, Lohmander LS, Roos EM. Knee complaints vary with age and gender in the adult population. Population-based reference data for the Knee injury and Osteoarthritis Outcome Score (KOOS). BMC.Musculoskelet.Disord. 2006;38.

36. Kornaat PR, Watt I, Riyazi N, Kloppenburg M, Bloem JL. The relationship between the MRI features of mild osteoarthritis in the patellofemoral and tibiofemoral compartments of the knee. Eur.Radiol. 2005;1538-43.

37. Neuman P, Kostogiannis I, Friden T, Roos H, Dahlberg LE, Englund M. Patellofemoral osteoarthritis 15 years after anterior cruciate ligament injury--a prospective cohort study. Osteoarthritis.Cartilage. 2009;284-90.

38. Cooper C, McAlindon T, Snow S, Vines K, Young P, Kirwan J, Dieppe P. Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. J.Rheumatol. 1994;307-13.

39. Hinman RS, Crossley KM. Patellofemoral joint osteoarthritis: an important subgroup of knee osteoarthritis. Rheumatology.(Oxford) 2007;1057-62.

40. Egloff C, Hugle T, Valderrabano V. Biomechanics and pathomechanisms of osteoarthritis. Swiss.Med.Wkly. 2012;w13583.

41. Felson DT, Couropmitree NN, Chaisson CE, Hannan MT, Zhang Y, McAlindon TE, LaValley M, Levy D, Myers RH. Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: the Framingham Study. Arthritis Rheum. 1998;1064-71.

42. Haara MM, Manninen P, Kroger H, Arokoski JP, Karkkainen A, Knekt P, Aromaa A, Heliovaara M. Osteoarthritis of finger joints in Finns aged 30 or over: prevalence, determinants, and association with mortality. Ann.Rheum.Dis. 2003;151-8.

43. Wilder FV, Barrett JP, Farina EJ. Joint-specific prevalence of osteoarthritis of the hand. Osteoarthritis.Cartilage. 2006;953-7.

44. Hirsch R, Lethbridge-Cejku M, Hanson R, Scott WW, Jr., Reichle R, Plato CC, Tobin JD, Hochberg MC. Familial aggregation of osteoarthritis: data from the Baltimore Longitudinal Study on Aging. Arthritis Rheum. 1998;1227-32.

45. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman B, Aliabadi P, Levy D. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. Arthritis Rheum. 1997;728-33.

46. Franklin J, Ingvarsson T, Englund M, Lohmander LS. Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis. Ann.Rheum.Dis. 2009;536-40.

47. Goekoop RJ, Kloppenburg M, Kroon HM, Dirkse LE, Huizinga TW, Westendorp RG, Gussekloo J. Determinants of absence of osteoarthritis in old age. Scand.J.Rheumatol. 2011;68-73.

48. Holliday KL, McWilliams DF, Maciewicz RA, Muir KR, Zhang W, Doherty M. Lifetime body mass index, other anthropometric measures of obesity and risk of knee or hip osteoarthritis in the GOAL case-control study. Osteoarthritis.Cartilage. 2011;37-43.

49. Lohmander LS, Gerhardsson d, V, Rollof J, Nilsson PM, Engstrom G. Incidence of severe knee and hip osteoarthritis in relation to different measures of body mass: a population-based prospective cohort study. Ann.Rheum.Dis. 2009;490-6.

50. Mmanipphyty CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: A systematic review of prognostic studies. Arthritis Care Res.(Hoboken.) 2011.

51. Vignon E, Valat JP, Rossignol M, Avouac B, Rozenberg S, Thoumie P, Avouac J, Nordin M, Hilliquin P. Osteoarthritis of the knee and hip and activity: a systematic international review and synthesis (OASIS). Joint Bone Spine 2006;442-55.

52. Hunter DJ. Advanced imaging in osteoarthritis. Bull.NYU.Hosp.Jt.Dis. 2008;251-60.

53. Losina E, Daigle ME, Suter LG, Hunter DJ, Solomon DH, Walensky RP, Jordan JM, Burbine SA, Paltiel AD, Katz JN. Disease-modifying drugs for knee osteoarthritis: can they be cost-effective? Osteoarthritis.Cartilage. 2013;655-67.

Chapter 5

Long-term clinical effects of partial meniscectomy in patients with traumatic meniscal tears

Kasper Huétink

Samuel K. van de Velde

Johan L. Bloem

Rob G.H.H. Nelissen

Submitted

Abstract

Purpose

To determine potential differences in 10 year clinical outcome of surgically and conservatively treated traumatic meniscal lesions in patients without locking.

Methods

We performed a 10-year follow-up study of 118 patients (mean age 32 years SD 7.8) with traumatic meniscal tears without locking complaints. Clinical outcome measures of surgically and conservatively treated patients were compared using the Noyes and KOOS knee questionnaires.

Results

There were no differences in short- and long-term Noyes scores and long-term cross-sectional KOOS *Pain*, *Symptoms*, *ADL* and *Quality of life* outcomes. KOOS *Sports and Recreation* outcomes were significantly better in surgically treated patients (19.2 points, 95% CI 1.5; 36.8, p=0.033). Higher activity levels before the start of the complaints improved this effect.

Conclusions

Partial meniscectomy of traumatic meniscal tears may result in better Sports and Recreation related long-term clinical outcomes. This effect is positively associated with higher activity levels before injury. Future randomized controlled trials may elucidate the effect of surgical treatment of traumatic meniscal tears.

Introduction

Meniscal tears are common injuries and are often treated by partial meniscectomy [1]. Figures from a database representing 9% of the U.S. population under 65 years of age showed that 387.833 arthroscopic partial meniscectomies were performed between 2005 and 2011 [2].

Recent studies have questioned the benefit of partial meniscectomy in patients with degenerative meniscal tears. [3]. A recently published trial showed that knee function outcomes in patients with degenerative meniscal tears after partial meniscectomy were not better compared to outcomes after sham surgery [4]. Whereas degenerative meniscal tears result from repetitive normal forces acting upon a worn down meniscus in the older population, traumatic meniscal tears are related to excessive force applied to a normal meniscus and are mainly present in the young to middle aged population [5].

Consensus based guidelines on the management of meniscal lesiosn exist [6] and long term follow-up clinical effects after meniscectomy have been studied [7;8]. However, no comparative studies between surgical and conservative management of traumatic meniscal tears have been performed [9]. Although it has been suggested that knee locking in patients with traumatic meniscal tears can be considered to be an indication for surgical treatment, controversy remains on the surgical management of traumatic meniscal lesions especially in those patients that present without locking symptoms [10].

The aim of this study was to evaluate the long term (10 year) clinical effect of partial meniscectomy in patients with knee complaints lasting for more than four weeks without symptoms of knee locking. Ten year follow-up differences in knee function and symptoms scores were compared between surgically and non-surgically treated patients with traumatic meniscal tears.

Patients and Methods

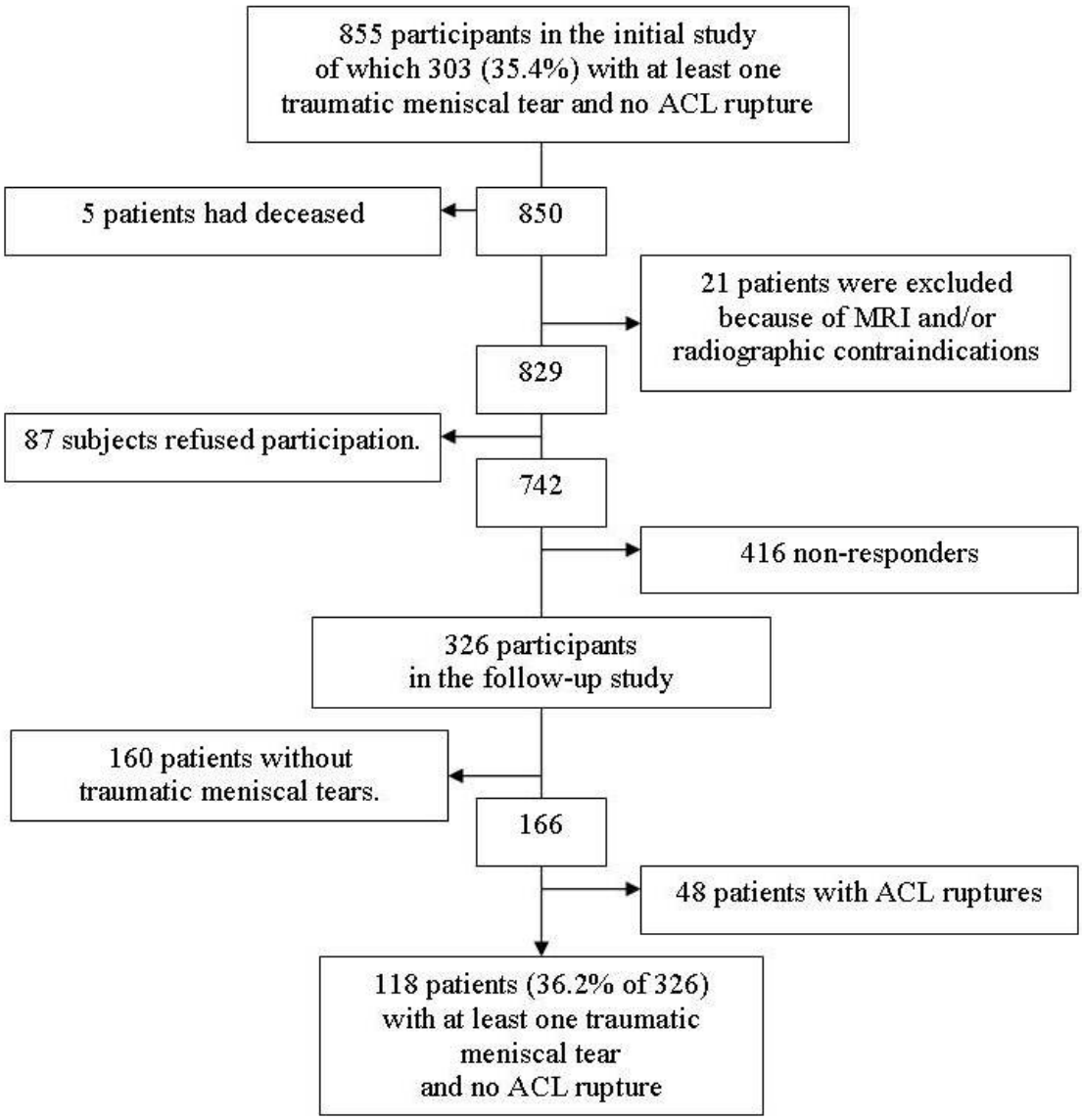
Patient selection.

The clinical effect of meniscectomy in 118 knee patients with traumatic meniscal tears 10 years after knee complaints was determined. All 118 patients were part of a prospective cohort of 855 patients with knee complaints who participated in a study on the cost-effectiveness of 0.5T magnetic resonance (MR) imaging (Gyroscan T5; Philips Medical Systems, Best, the Netherlands) relative to diagnostic arthroscopy 10 years ago [11]. All 855 participants of the initial study were invited by mail and/or by telephone call for clinical knee function evaluation, knee radiographs and 3.0T MR imaging (Achieva 3T, Philips Medical Systems, Best, the Netherlands) at 10 year follow-up.

Inclusion criteria for the original cohort study 10 years ago were knee complaints e.g. pain, swelling and instability lasting for more than four weeks. Exclusion criteria of the initial study were knee complaints lasting less than four weeks, clinical symptoms of a locked knee, known inflammatory diseases such as rheumatoid arthritis, moderate to severe radiographic knee OA and a history of knee surgery. At baseline MR images of the affected knee were made and all 855 patients received regular orthopedic care [12].

The study was approved by the Medical Ethics Review Boards of the three participating hospitals. Three hundred twenty-six patients were willing to participate in the current follow-up study (Fig. 1). Written informed consent of each participant was obtained. The mean age of the 326 patients willing to participate in the follow-up study was higher (32 years; SD 7.7) than of the 529 non-participants (31 years; SD 8.1). There were no differences in age, sex and traumatic meniscal tears without anterior cruciate ligament (ACL) injury between the follow-up group and the non-participants. Traumatic meniscal tears were more often surgically treated in the follow-up group [91 (77%)] than in the non-participants [118 (64%)], (p-value 0.016). Of the participants, patients without meniscal tears or those with an accompanying anterior cruciate ligament (ACL) ruptures were excluded from further analysis (Fig. 1).

Flow Diagram



Of the 118 patients with at least one traumatic meniscal tear and no ACL injury, 96 patients were treated by partial meniscectomy and 22 patients were treated conservatively. There was no difference in duration of the knee complaints before inclusion 10 years ago between surgically or conservatively treated patients (14 months (SD 28.2) vs. 13 months (SD 29.0), p-value 0.86) (Table 1).

Table 1

Patient characteristics of the conservatively and surgically treated patients

	Conservative treatment N=22 (44 menisci)	Meniscectomy N=96 (192 menisci)	P-Value
Mean age at baseline (SD)	32.1 (6.4)	35.3 (7.0)	0.049*
Number of women (%)	8 (36.4)	20 (20.8)	0.163
Duration of the knee complaints before inclusion in months (SD)	12.9 (28.2)	14.1 (28.9)	0.860
Tegner activity level before complaints (SD)	5.7 (2.1)	5.6 (2.3)	0.739
Number of traumatic tears < 5mm (%)	6 (13.6)	3 (1.6)	0.002*
Number of traumatic tears ≥ 5mm (%)	19 (43.2)	100 (52.4)	0.319
Traumatic tear in both menisci (%)	3 (13.6)	8 (8.3)	0.428
Traumatic tear in medial meniscus (%)	16 (72.7)	74 (77.1)	0.426
Traumatic tear in lateral meniscus (%)	9 (40.9)	29 (30.2)	0.234

*Statistically significant difference.

The independent sample T-test, the Fisher's Exact test and the Chi-square tests were used to compare means and proportions.

A traumatic meniscal tear was defined as an intrameniscal signal intensity unequivocally extending to an articular surface visible on MR images after traumatic distortion of the knee, leading to complaints.

Outcome Measures

The clinical effect of management of the traumatic meniscal tears was determined by comparing Noyes knee Function and Symptoms scores and KOOS knee function scores of the 96 patients treated with partial meniscectomy and the 22 patients treated conservatively treatment. Noyes Symptoms scores range from 0 (serious symptoms) to 400 (no symptoms), Noyes Function scores range from 200 (poor function) to 550 (good function)[13]. Noyes knee scores were obtained at inclusion, 3 months, 6 months and 10 years follow-up. At 10 year follow-up knee function was also cross-sectionally scored using the KOOS questionnaire [14].

A modified Lotysch classification system: a five-point grading scale for meniscal lesions (degenerative tears and traumatic tears, including buckethandle tears), was used to score the meniscal tears [15;16]. To determine radiographic knee OA development the Kellgren & Lawrence scoring system was used [17]. Knee OA was considered to be present in patients with a K&L score > 1. Knee OA in the patellofemoral compartment was scored on joint space narrowing (JSN) and osteophyte formation similar to the skyline view radiographs described in the OARSI atlas [18] More detailed knee radiograph and MRI results of the 10 year follow-up cohort have been published earlier [19].

The Tegner activity score before the start of symptoms at baseline 10 years ago was obtained retrospectively at the time of inclusion to determine the level of activity before the knee complaints. The Tegner activity scale ranges from 10: high level competitive sports, through 0: not working due to knee problems [20]. Factors associated with functional outcomes after meniscectomy described in literature being gender, age and activity level [21] were also compared.

Data Analysis

Longitudinal Linear Mixed Model analysis was used to compare the Noyes Function and Symptoms outcomes. Mancova analysis was used to compare the KOOS scores. All models included the variables sex, age, radiographic OA in the tibiofemoral end patellafemoral compartment, newly developed ACL lesions and Tegner activity level before the complaints. Effect estimates and 95% confidence intervals were determined. P-values < 0.05 were considered statistical significant.

Results

Management of Meniscal Tears

In the first six months after inclusion, 91 of the 118 patients (77%) with traumatic meniscal tears were surgically treated, which is significantly higher than in the non-participant group with traumatic meniscal tears and no ACL lesions (64%, p = 0.014). None of the patients were treated with meniscal repair. There were no differences in number of patients treated with meniscectomy between the three participating centers (27 (79%), 33 (89%) and 36 (77%), p = 0.319)

Of the 11 patients with traumatic tears in both the medial and the lateral meniscus a partial meniscectomy was performed in both menisci in one patient, in four patients meniscectomy was performed in only one meniscus and three patients were conservatively treated. The surgical reports of the remaining three patients were not available for analysis.

Between 6 months and 10 years follow-up, four of the initially conservatively treated patients with a traumatic tear underwent a partial meniscectomy. Ten year follow-up 3T MR images showed that three patients had developed new traumatic meniscal tears. Two of these three patients had been additionally treated with partial meniscectomy.

The mean age in the meniscectomy group was higher (3.2 years) and there were no differences in number of women or activity levels .

Knee function outcome scores

At inclusion the Noyes Function (360, SD 71 vs. 357 SD, 72) and Noyes Symptoms (268, SD 84 vs. 276, SD 86) scores were not significantly different between the surgically and conservatively treated patient groups (p>>0.05). None of the Noyes Function outcomes scores were different in surgically or conservatively treated patients with traumatic meniscal tears (Table 2) (Fig 2). Uncorrected outcomes showed a significant positive effect of meniscectomy on long term Noyes Symptoms scores. However, after correction for sex, age, radiographic knee OA, newly developed ACL lesions and Tegner activity level before the complaints no differences were present (Table 2)(Fig 2). Long term Noyes Symptoms were mainly related to sex differences (women had lower scores) and activity level before the start of the knee complaints (higher Tegner activity scores were related to higher Symptoms scores).

Figure 2

Diagram showing the differences in Noyes knee Function and Symptoms scores between conservatively and surgically treated patients with traumatic meniscal tears.

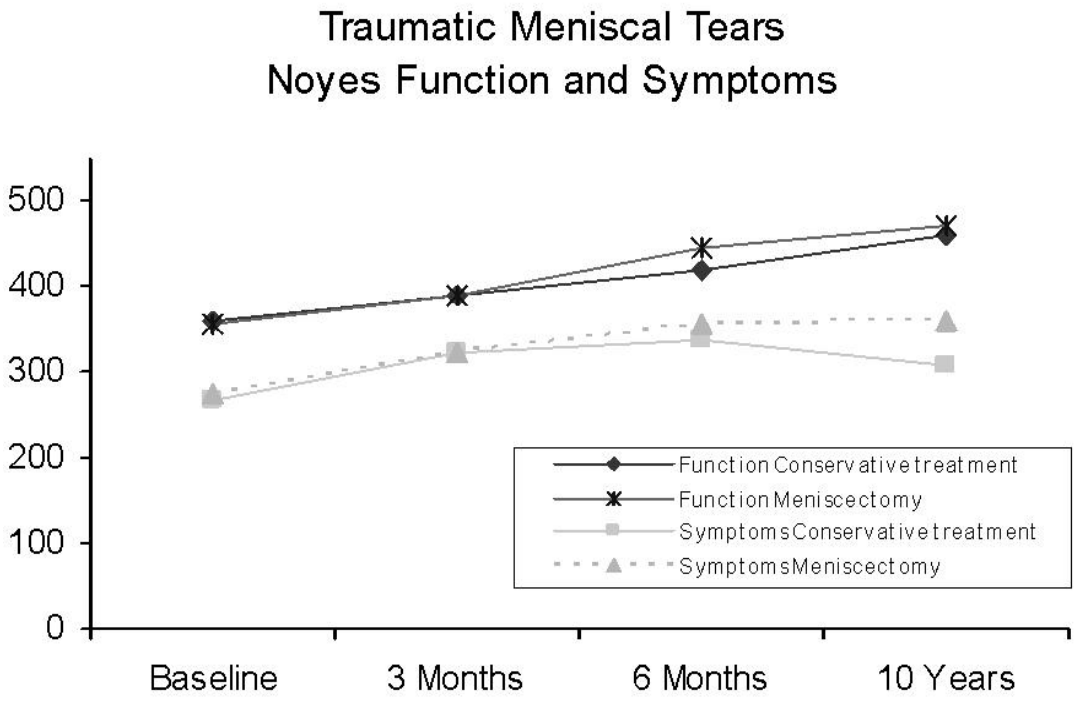


Table 2

Noyes scores throughout the 10 years follow-up

		Short term follow-up					Long term follow-up		
	Treatment	Baseline (n)	3 months (n)	6 months (n)	Effect Estimate (95% CI)	P-Value	10 years (n)	Effect Estimate (95% CI)	P-Value
Noyes Function	Conservative	360 (22)	391 (25)	421 (23)	22.2 (-11.7; 56.1)	0.20	460 (20)	1.3 (-16.1; 18.8)	0.88
	Meniscectomy	357 (96)	389 (86)	446 (85)			471 (88)		
Noyes Symptoms	Conservative	268 (22)	322 (25)	339 (23)	2.9 (-36.8; 42.7)	0.88	309 (20)	14.7 (-6.0; 35.3)	0.16
	Meniscectomy	276 (95)	324 (86)	355 (85)			360 (88)		

Longitudinal Linear Mixed Model analysis was used to compare the Noyes Function and Symptoms outcomes

In four of the five KOOS subscales there were no differences in outcome scores between surgically or conservatively treated patients with traumatic meniscal tears (Table 3) (Fig 3). In the KOOS subscale Sport & Recreations score there was a non-significant different higher mean score of 14.3 points in patients with traumatic meniscal tears treated with partial meniscectomy. This effect increased to a statistically significant 19.2 points when corrected for gender, age, knee OA, newly developed ACL lesions and Tegner activity level before the complaints (95% CI 1.5; 36.8, p 0.033). Higher Tegner activity scores had an additional positive effect on Sport & Recreations outcome scores after meniscectomy, whereas ACL lesions developed during follow-up and the presence of knee OA diminished this effect.

Figure 3

Knee injury and Osteoarthritis Outcome Score (KOOS) after 10 years in patients with traumatic meniscal tears.

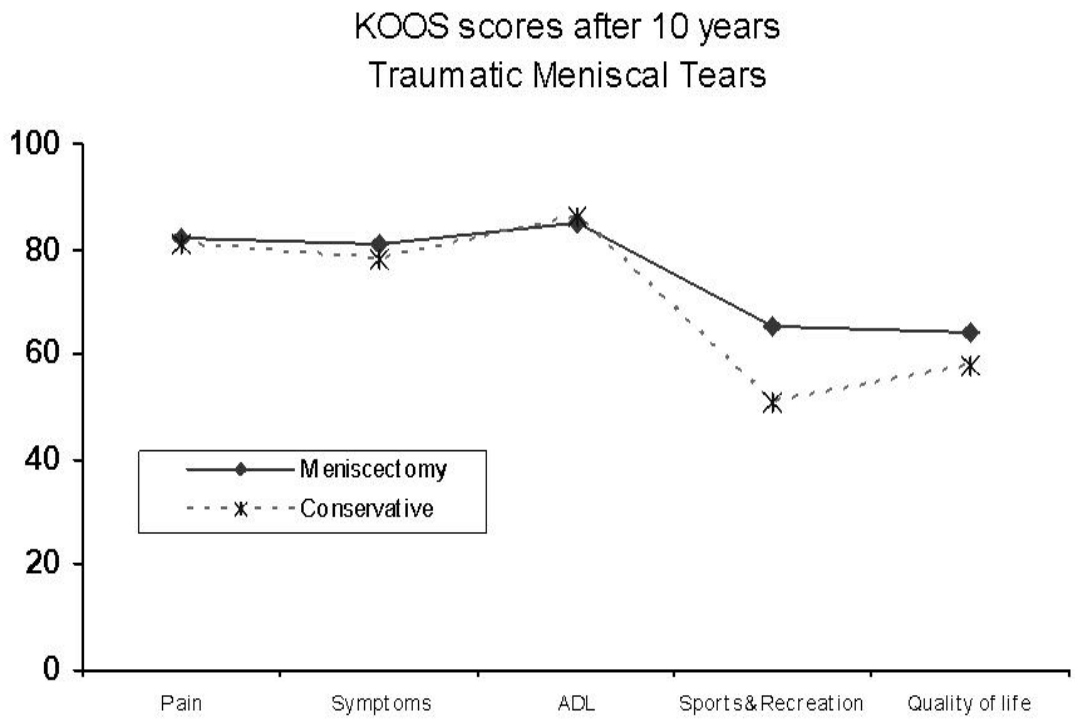


Table 3 KOOS outcomes

Treatment	N	KOOS Subscale	Score	Mean Difference (95% CI)	Uncorrected P-Value	Effect Estimate (95% CI)	Corrected P-Value
Conservative	21	Pain	80.9	1.2 (-9.1; 11.5)	0.814	5.1 (-6.6; 16.8)	0.387
Meniscectomy	89		82.2				
Conservative	21	Symptoms	78.1	3.1 (-6.5; 12.7)	0.519	5.7 (-5.0; 16.4)	0.289
Meniscectomy	90		81.2				
Conservative	21	ADL	85.9	0.7 (-10.5; 9.1)	0.880	1.8 (-9.0; 12.7)	0.738
Meniscectomy	89		85.2				
Conservative	21	Sports &	51.0	14.3 (-1.5; 30.0)	0.075	19.2 (1.5; 36.8)	0.033*
Meniscectomy	90	Recreation	65.2				
Conservative	21	Quality of Life	57.7	6.3 (-6.6; 19.2)	0.311	9.6 (-3.2; 22.4)	0.141
Meniscectomy	89		64.1				

*Statistically significant difference.

The independent T-test was used to compare the mean differences. MANCOVA was used to compare 10 year follow-up outcomes.

The mean activity levels before the start of the knee complaints were in the conservatively treated group 5.7 (SD 2.1) and in the meniscectomy group 5.6 (SD 2.3). The mean activity levels after 10 years were in the conservatively treated group 5.2 (SD 2.3) and in the meniscectomy group 4.9 (SD 2.4). These were not statistically significant differences.

Discussion

The results of this 10 year follow-up cohort study show that surgical treatment of traumatic meniscal tears in knee patients without locking complaints appears to have a positive effect on long term knee function outcomes compared to conservative treatment. Treatment with meniscectomy is related to better cross-sectional measured long term Sports and Recreation KOOS scores after 10 years, and this effect increases in patients with higher Tegner activity level scores before the complaints started. Although patients treated with meniscectomy also appear to be scoring better on long term follow-up Noyes Symptoms outcome scores, multivariate analysis shows that this effect is mainly related to gender differences (women scored worse than men).

The effect of meniscectomy in patients with degenerative tears has been investigated in several randomized controlled trials [4;22;23], but there is a void in the literature for the treatment of traumatic tears with no mechanical symptoms. The indication for surgical treatment is mainly based on clinical symptoms and supportive MR images findings [10]. The current study results show that the clinical effect of meniscectomy in relative young patients with traumatic meniscal tears and without significant knee OA is limited to better KOOS sports and recreation outcome scores. This effect is mainly present in patients who: (1) showed higher activity levels before the start of the knee complaints 10 years ago, (2) developed no ACL lesions during follow-up and (3) had no radiographic OA changes. The effect of a mean 19.2 points higher score in the KOOS Sport & Recreation scale seems to be of clinical relevance since 8-10 points is considered to be the minimal clinically important change [24].

In the conservatively treated patient group, smaller traumatic meniscal tears were more often present compared to the patient group treated with meniscectomy (6 (13.6%) vs. 3 (1.6%)). This may be due to confounding by indication in the conservative group, since the general opinion is that meniscal tears smaller than 5mm are not clinically relevant and should be treated

conservatively [25]. However, the number of larger meniscal tears was not significant different between the conservatively treated group and the meniscectomy group (19 (43.2%) vs. 100 (52.4%)) (Table 2).

Several limitations of the current study should be mentioned. The large number of patients lost to follow-up, which may be partially due to the 10 year follow-up (529; 62%). Another limitation of the study was that only patients with persistent knee complaints might have been interested in participating in the follow up study, possibly biasing the results. To investigate this, all 87 subjects who refused participation were asked if they still had knee complaints. The majority of these subjects, 49 patients (56%), had knee complaints, but had other reasons not to participate in the study. Traumatic tears were more often surgically treated in the follow-up group (77% vs. 64%, p-value 0.014)). Another limitation is that the KOOS questionnaire was used at 10 years follow-up only, because it did not exist at baseline 10 years ago. There is a chance that baseline KOOS scores would have been different between the surgically and conservatively treated patient groups, however the baseline Tegner and Noyes scores were not different between these groups. Finally, at the start of the original cohort study, meniscal repair was not yet incorporated in common clinical practice, therefore we were not able to determine the clinical effects of meniscal repair in patients with traumatic meniscal tears.

In conclusion, partial meniscectomy of traumatic meniscal tears in knee patients without locking complaints seem to result in better Sports and Recreation related long-term clinical outcomes. This effect is positively associated with higher activity levels before injury. Future randomized controlled trials may elucidate the effect of surgical treatment of traumatic meniscal tears.

Reference List

1. Montgomery SR, Zhang A, Ngo SS, Wang JC, Hame SL. Cross-sectional analysis of trends in meniscectomy and meniscus repair. Orthopedics 2013;e1007-e1013.

2. Abrams GD, Frank RM, Gupta AK, Harris JD, McCormick FM, Cole BJ. Trends in meniscus repair and meniscectomy in the United States, 2005-2011. Am.J.Sports Med. 2013;2333-9.

3. Herrlin SV, Wange PO, Lapidus G, Hallander M, Werner S, Weidenhielm L. Is arthroscopic surgery beneficial in treating non-traumatic, degenerative medial meniscal tears? A five year follow-up. Knee.Surg.Sports Traumatol.Arthrosc. 2013;358-64.

4. Sihvonen R, Paavola M, Malmivaara A, Itala A, Joukainen A, Nurmi H, Kalske J, Jarvinen TL. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N.Engl.J.Med. 2013;2515-24.

5. Howell R, Kumar NS, Patel N, Tom J. Degenerative meniscus: Pathogenesis, diagnosis, and treatment options. World J.Orthop. 2014;597-602.

6. Beaufils P, Hulet C, Dhenain M, Nizard R, Nourissat G, Pujol N. Clinical practice guidelines for the management of meniscal lesions and isolated lesions of the anterior cruciate ligament of the knee in adults. Orthop.Traumatol.Surg.Res. 2009;437-42.

7. Matsusue Y, Thomson NL. Arthroscopic partial medial meniscectomy in patients over 40 years old: a 5- to 11-year follow-up study. Arthroscopy 1996;39-44.

8. Meredith DS, Losina E, Mahomed NN, Wright J, Katz JN. Factors predicting functional and radiographic outcomes after arthroscopic partial meniscectomy: a review of the literature. Arthroscopy 2005;211-23.

9. Mordecai SC, Al Hadithy N, Ware HE, Gupte CM. Treatment of meniscal tears: An evidence based approach. World J.Orthop. 2014;233-41.

10. Lyman S, Oh LS, Reinhardt KR, Mandl LA, Katz JN, Levy BA, Marx RG. Surgical decision making for arthroscopic partial meniscectomy in patients aged over 40 years. Arthroscopy 2012;492-501.

11. Vincken PW, ter Braak AP, van Erkel AR, Coerkamp EG, de Rooy TP, de LS, Mallens WM, Coene LN, Bloem RM, van Luijt PA, van den Hout WB, van Houwelingen HC, Bloem JL. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 2007;85-93.

12. Vincken PW, ter Braak BP, van Erkell AR, de Rooy TP, Mallens WM, Post W, Bloem JL. Effectiveness of MR imaging in selection of patients for arthroscopy of the knee. Radiology 2002;739-46.

13. Noyes FR, Barber SD, Mooar LA. A rationale for assessing sports activity levels and limitations in knee disorders. Clin.Orthop.Relat Res. 1989;238-49.

14. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J.Orthop.Sports Phys.Ther. 1998;88-96.

15. Crues JV, III, Mink J, Levy TL, Lotysch M, Stoller DW. Meniscal tears of the knee: accuracy of MR imaging. Radiology 1987;445-8.

16. Lotysch M, Mink J, Crues JV, Schwartz SA. Magnetic resonance imaging in the detection of meniscal injuries. Magnetic Resonance Imaging 1986;185.

17. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis 29. Ann.Rheum.Dis. 1957;494-502.

18. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis 27. Osteoarthritis.Cartilage. 1995;3-70.

19. Huetink K, Nelissen RG, Watt I, van Erkel AR, Bloem JL. Localized development of knee osteoarthritis can be predicted from MR imaging findings a decade earlier. Radiology 2010;536-46.

20. Tegner Y, Lysholm J. Rating systems in the evaluation of knee ligament injuries. Clin.Orthop.Relat Res. 1985;43-9.

21. McDermott ID, Amis AA. The consequences of meniscectomy. J.Bone Joint Surg.Br. 2006;1549-56.

22. Herrlin S, Hallander M, Wange P, Weidenhielm L, Werner S. Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial. Knee.Surg.Sports Traumatol.Arthrosc. 2007;393-401.

23. Yim JH, Seon JK, Song EK, Choi JI, Kim MC, Lee KB, Seo HY. A comparative study of meniscectomy and nonoperative treatment for degenerative horizontal tears of the medial meniscus. Am.J.Sports Med. 2013;1565-70.

24. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. Health Qual.Life Outcomes. 2003;64.

25. DeHaven KE. Decision-making factors in the treatment of meniscus lesions. Clin.Orthop.Relat Res. 1990;49-54.

Chapter 6

Genetic contribution to development of radiographic knee osteoarthritis in a population presenting with non-acute knee symptoms a decade earlier

Kasper Huétink

Paul van der Voort

Johan L. Bloem

Rob G.H.H. Nelissen

Ingrid Meulenbelt

Conditionally accepted; Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders

Abstract

In this study the contribution of the OA susceptibility genes *ASPN*, *GDF5*, *DIO2* and the *7q22* region to radiographic development of knee osteoarthritis (OA) in patients with a mean age of 40.6 years ± 7.9 (SD) who suffered from non-acute knee complaints a decade earlier was examined. Dose response associations of 4 SNP's on the susceptibility genes were determined by comparing 36 patients who showed development of OA on radiographs (Kellgren&Lawrence score ≥1) with 88 patients who had no development of OA on radiographs and normal cartilage. Multivariate logistic regression analysis including the variables age, gender, body mass index (BMI) and reported knee trauma was performed. A dose response association of *DIO2* SNP rs225014: odds ratio (OR) 2.3, 95% CI 1.1-4.5 (P=0.019) and *GDF5* SNP rs143383: (OR) 2.0, 95% CI 1.1-3.8 (P=0.031) was observed with knee OA development. The *ASPN* and *7q22* SNPs were not associated with OA development.

Introduction

Osteoarthritis (OA) of the knee is a common cause of musculoskeletal disability and is characterized by late-onset degeneration of articular cartilage, which is marked by the recapitulation of OA articular chondrocytes to a growth plate morphology and signalling and breakdown of matrix proteins[1]. This leads to the development of fibrillations, fissures and ulcerations at the articular cartilage surface most sensitively detected by magnetic resonance (MR) imaging [2]. To detect common underlying pathways that affect susceptibility, large scale genetic studies have been performed and have revealed a considerable number of robust OA susceptibility gene products which appear to be active in a shared pathway involving the developmental process of endochondral ossification [3,4]. The susceptibility genes *ASPN* [5], *GDF5* [6], *DIO2* [3] and the *7q22 locus* [7] are considered consistent early OA susceptibility signals that have shown replication in several distinct studies for OA development [8] and additionally showed functional follow up data that provided insight into underlying disease mechanisms [9-11]. Progression of disease could result in reactivation of genes involved in endochondral ossification, leading to loss and mineralization of articular cartilage, a process known to contribute to OA [3,12].

The aim of this study is to examine the contribution of the risk alleles of *ASPN, GDF5, DIO2* and the top SNP of the *7q22 locus* to radiographic development of knee OA in a relatively young study population that presented with non-acute knee symptoms a decade earlier by comparing patients with radiographic OA development and patients without signs of OA in the knee on radiographs and MR images.

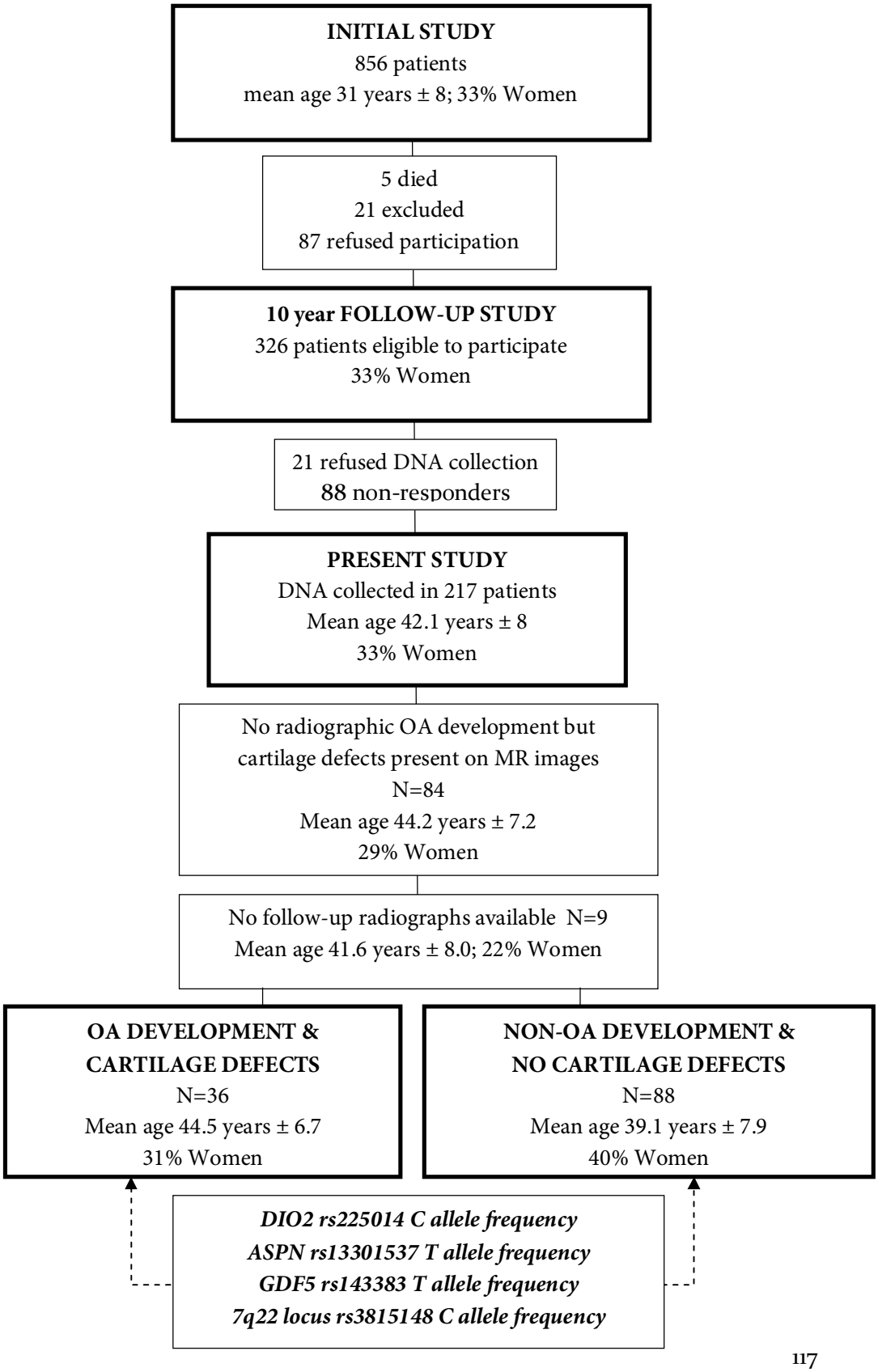
Methods

Study population

Study design: Case-control, Level of Evidence: 3. The current study was approved by the Medical Ethics Review Boards and written informed consent of each participant was obtained. The current study is a follow-up of a trial performed 10 years ago. The initial study consisted of 856 patients (mean age 31 years ± 8.0 standard deviation (SD)) with non-acute knee complaints, defined as persistent knee complaints i.e. pain, swelling and instability, lasting more than four weeks [13]. After 10 years ± 0.90 (SD), all 856 patients of the initial study were contacted and invited for follow-up

[14]. To obtain DNA, all initial eligible 326 follow-up participants were contacted and sent a saliva collection container for DNA extraction. Eventually, 217 patients (67%) could be included. Of the 109 lost subjects, 21 patients refused participation and 88 did not respond to the contact letter sent by mail, a second letter sent after 1 month and three contact attempts by telephone. MR images and radiographs of the initial symptomatic knee were taken at inclusion and after 10 years. The presence of on radiographs detectable OA features was compared between the baseline and follow-up images. None of the patients showed radiographic knee OA at baseline. Due to different scanning techniques and other scoring methods used at baseline and after 10 year follow-up, the MR outcomes from baseline and follow-up outcomes could not be compared accurately to assess OA development. Therefore, a certain degree of OA development in those patients without radiographic OA development but with cartilage defects visible on MR images could not be ruled out. In order to compare patients with radiographic OA development to a control group without any signs of OA development, only patients without cartilage defects visible on MR images were used as controls. Ultimately, a total of 124 (15%) patients were included in the current study (Figure 1).

Figure 1 Flowchart response to follow-up



Radiographic knee examination and assessment

Standardized weight bearing posterior-anterior knee radiographs next to supine lateral radiographs of the knee were made at baseline and at 10 year follow-up. At baseline one of six musculoskeletal radiologists with at least four years of experience scored the radiographs for overall severity of OA using the K&L system [15]. The follow-up radiographs were scored by an experienced musculoskeletal radiologist and a research fellow using the same K&L scoring method [14]. Individual development of OA was obtained by comparing the baseline K&L score to the follow-up K&L scores. Development of OA was considered to be present at a K&L score of 1 point or more.

Knee MRI

MRI examinations after 10 years of the initial affected knee were performed on a 3 T system (Achieva 3T, Philips Medical Systems, Best, the Netherlands). Due to different MRI scanning techniques used at baseline and at 10 year follow-up, only the follow-up scans were used to assess cartilage defects. Focal cartilage defects were defined as an abrupt transition between the defect and surrounding cartilage, a diffuse cartilage defect was defined as a gradual transition between normal and thinned cartilage [16]. Cartilage defects outcome scores were used in a binary (absent vs. present) fashion

DNA

DNA from patients was obtained using saliva collecting containers (Oragene OG-250, DNA Genotek, Ontario, Canada). Recent studies have shown that the use of saliva samples is a good alternative to blood samples to obtain genomic DNA of high quality [17].

The containers were sent to all 326 eligible patients including instructions for use. All patients were asked to wash their mouth once with water and to wait at least 30 seconds. Then, the patients were asked to spit in the white container, to cap the container with the blue lid, and finally to gently shake the sample. The Oragene saliva samples were stored according to manufacturer at room temperature until DNA extraction. On average saliva sampes were stored for 1.5 month.

DNA was extracted from saliva samples using the Oragene kit (DNA Genotek) as described by the manufacturer. The Oragene saliva samples were incubated at 50°C for 2 hours. The 0.5 ml samples were transferred to a 1.5 mL Eppendorf tubes ; 20 µ L of Oragene purifier was added, and the sample was mixed by inversion and incubated on ice for 10 minutes. The samples were then centrifuged in a small, bench top microfuge for 3 minutes at 18,000 g at room temperature and the supernatant was transferred to a new tube. 0.5 mL of 95% ethanol was added; the samples were mixed by inversion at least five times and incubated for 10 minutes at room temperature. The samples were then centrifuged in a small, bench top microfuge for 1 minute at 18,000g at room temperature, the supernatants were discarded, and the DNA was dissolved in 100 µ L TE buffer (10 mmol/L Tris-HCl, 0.1 mmol/L EDTA (pH 8.0)) and quantified. The DNA samples were stored at 4°C until PCR analysis.

For the candidate gene association study we selected 4 SNPs on 4 candidate genes *ASPN, GDF5*, *DIO2* and the *7q22 locus*. These susceptibility genes have been shown to replicate in several distinct studies for primary OA [8]. In the current study we hypothesize that these susceptibility genes already contribute to development of radiographic knee OA in relatively young patients suffering from knee complaints. The P-values of Hardy-Weinberg test were for *DIO2*: 0.385, for *GDF5*: 0.916, for *ASPN*: 0.033 and for the *7q22 locus*: 0.242. All genotypes were included in the equation. Following is a description of the 4 candidate genes selected for the current study.

DIO2

Iodothyronine deiodinase enzyme type 2 (*DIO2*) is a regulator of thyroid hormone metabolism in the growth plate, where thyroid hormone triggers terminal maturation of growth plate chondrocytes [8]. *DIO2* has recently been shown to be a susceptibility gene for primary OA [3,18]. In a genome-wide linkage scan and association analysis an association was found between OA and the minor *C* allele of SNP rs225014.[3]. We hypothesize that the *DIO2* gene also contributes to development of radiographic knee OA in the current study population.

ASPN

Asporin (*ASPN*) inhibits transforming growth factor-β (TGF-β), which has a crucial role in the development and homeostasis of cartilage [19]. *ASPN* is expressed at low levels in normal cartilage but is expressed abundantly in OA articular cartilage. Due to polymorphisms in the *ASPN* gene, variant *ASPN* proteins arise with a variable number of aspartic acid (*D*) repeats in the amino-terminal end of the protein [20]. The *T* allele of SNP (rs13301537) is associated with variants of the *ASPN* gene encoding 13 (*D13*) and 14 (*D14*) aspartic acid repeats [21]. In a Japanese and Han Chinese population, but not in a Caucasian population, *D14* was associated with knee OA and in a Caucasian population *D13* was associated with a decreased risk of knee OA [21,22].

GDF5

Growth differentiation factor 5 (*GDF5*) is a bone morphogenetic protein (BMP) involved in early development of joints in embryonic tissues and is expressed throughout the synovial joint tissues during life [23]. The SNP (rs143383) is the most widely replicated genetic association with knee OA, with the risk-associated *T* allele showing reduced expression relative to the *C* allele in OA [6]. The *GDF5* rs143383 polymorphism is associated with knee OA in both Asians and Caucasians [6,24].

7q22 locus

Conserved oligomeric Golgi complex subunit 5 (*COG5*) was recently discovered in a genome-wide association study as a novel gene involved in OA. The *C* allele of SNP (rs3815148) was associated with an increased risk of knee OA [7] .

SNP genotyping

Genotyping was carried out in 217 samples at OA susceptibility SNPs from 4 genes: *ASPN, GDF5, DIO2* and the 7q22 locus. Selected SNPs were fit in a Sequenom multiplex assay designed by the Assay Designer software version 3.1 (Sequenom, San Diego, CA). SNPs were genotyped by mass spectrometry (the homogeneous MassARRAY system; Sequenom, San Diego, CA) using standard conditions. PCR reactions were carried out in a final volume of 5 µl and contained 2.5 ng of genomic DNA. Genotypes were assigned using Genotyper version 3.0 software (Sequenom, San Diego, CA). The genotyping success rate was 98,02% ± 0.75 (SD). Internal genotyping controls

were included, with a concordance rate of 100%. Genotype frequencies for the tested SNPs were all in Hardy-Weinberg equilibrium (Table 1).

Statistical methods

A case-control approach was also used to assess the association between the susceptible risk allele frequencies of the of the 7 selected SNP's in patients with knee OA development and in patients without radiographic development of knee OA. Radiographic development of OA was defined a K&L score of ≥1. Patients who did not show radiographic OA development, but who did have cartilage defects detected on the follow-up MR images were excluded from further analysis (Figure 1). A logistic regression model was fitted to measure the strength of the association with the different genotypes (dose response), which is expressed as odds ratios (OR) with 95% confidence intervals (95% CI). In these analyses we adjusted for age, gender, body mass index (BMI) and reported knee trauma. P-values < 0.05 were considered to indicate statistical significance. In order to assess the discriminating power of the different genotypes studied, we generated receiving operator curves (ROC) using knee development as outcomes and age, sex, BMI and trauma as conventional risk factors.

Results

Population characteristics

Of the 124 patients included in the current study, 5 patients (4 %) were of non-Caucasian descent. At follow-up, the mean age of the 124 patients included for the association study was 40.6 years ± 7.9 (SD), 46 (37.1%) of the patients were female and the average body mass index (BMI) was 25.6 ± 3.5 (SD).

OA development

Of the 36 patients who developed radiographic knee OA after 10 years follow-up 27 had a K&L score of 1, and 9 had a K&L score of 2. Of the 172 patients without radiographic development of OA, 84 (48.8%) showed cartilage defects detected on MR images, and 88 (51.2%) did not. The latter patients were used as controls. Patients with radiographic development of knee OA were

significant older and had significantly higher BMI's than the controls without OA development and without cartilage lesions (Table 1).

As shown in Table 1, the minor *C* allele frequency of the rs225014 SNP in the control group without OA development and without cartilage lesions was 0.341 whereas, in the study group with OA development the minor *C* allele frequency was 0.471. There was a significant association for the presence of the minor *C* allele of SNP rs225014 of the *DIO2* gene and radiographic knee OA development (OR 1.8, 95% CI 1.00-3.18; *P* value 0.049). This effect increased when corrected for Age, BMI and Trauma (OR 2.3, 95% CI 1.14-4.49; *P* value 0.019). The *GDF5* T-allele frequency of the rs143383 SNP was 0.366 in the control group without OA development and cartilage lesions and 0.444 in the OA development group. Corrected for Age, BMI and Trauma, there was a significant association for the presence of the *T* allele of SNP rs143383 of the *GDF5* gene and OA development (OR 2.0, 95% CI 1.07-3.78, *P* value 0.031). The OA susceptibility SNP in *ASPN* and at the *7q22 locus* did not show association (Table 1).

Finally, we investigated whether the genes associated to increasing aspects of joint destruction as measured by radiographs and/or MRI characteristics after 10 years as defined by subjects without radiographic OA nor cartilage lesions visible on MR images (N=88), no radiographic signs of OA but with cartilage defects visible on MR images (N=84), and radiographic OA with cartilage defects visible on MR images (N=36). *DIO2* showed significant association (*P* Value 0.020) with increasing signs of cartilage destruction visible on both radiographs and MR images (Table 2).

Table 1

Multivariate regression analysis outcomes of OA development

Variables	No OA development & No Cartilage defects N = 88	OA development N = 36	Uncorrected OR	95% CI	Uncorrected P-Value	Corrected OR	95% CI	Corrected P-Value
Gender	35 (39.8%)	11 (30.6%)	0.67	0.29-1.53	0.336	0.75	0.28-2.01	0.561
Age	39.1 ± 7.9 (SD)	44.5 ± 6.7 (SD)	1.10	1.04-1.17	0.001*	2.00	1.03-1.17	0.004*
BMI	25.2 ± 3.6 (SD)	26.7 ± 2.7 (SD)	1.14	1.02-1.28	0.019*	1.10	0.96-1.27	0.162
Trauma	54 (64.3%)	20 (60.6%)	0.86	0.37-1.96	0.710	1.18	0.46-3.05	0.733
DIO2 rs225014 *C* allele frequency	0.341	0.471	1.79	1.00-3.18	0.049*	2.27	1.15-4.49	0.019*
ASPN rs13301537 *T* allele frequency	0.244	0.300	1.19	0.65-2.18	0.575	1.20	0.53-2.7	0.659
GDF5 rs143383 *T* allele frequency	0.366	0.444	1.40	0.81-2.39	0.225	2.01	1.07-3.78	0.031*
7q22 locus rs3815148 *C* allele frequency	0.241	0.264	1.15	0.60-2.20	0.684	1.13	0.51-2.52	0.760

*Statistically significant difference. OA = osteoarthritis, OR = Odds ratio, CI = Confidence Interval, SD = Standard Deviation

Table 2

Multivariate regression analysis outcomes of OA development and cartilage lesions visible on MR imaging

Variables	No OA development & No Cartilage defects on MRI N = 88	No OA development but Cartilage defects on MRI N = 88	Radiographic OA development & Cartilage defects N = 36	P-Value
DIO2 rs225014 *C* allele frequency	0.341	0.409	0.471	0.020*
ASPN rs13301537 *T* allele frequency	0.244	0.244	0.300	0.411
GDF5 rs143383 *T* allele frequency	0.366	0.378	0.444	0.206
7q22 locus rs3815148 *C* allele frequency	0.241	0.244	0.264	0.586

OA = osteoarthritis, OR = Odds ratio, CI = Confidence Interval. Outcomes were corrected for Age, Sex, BMI and Trauma

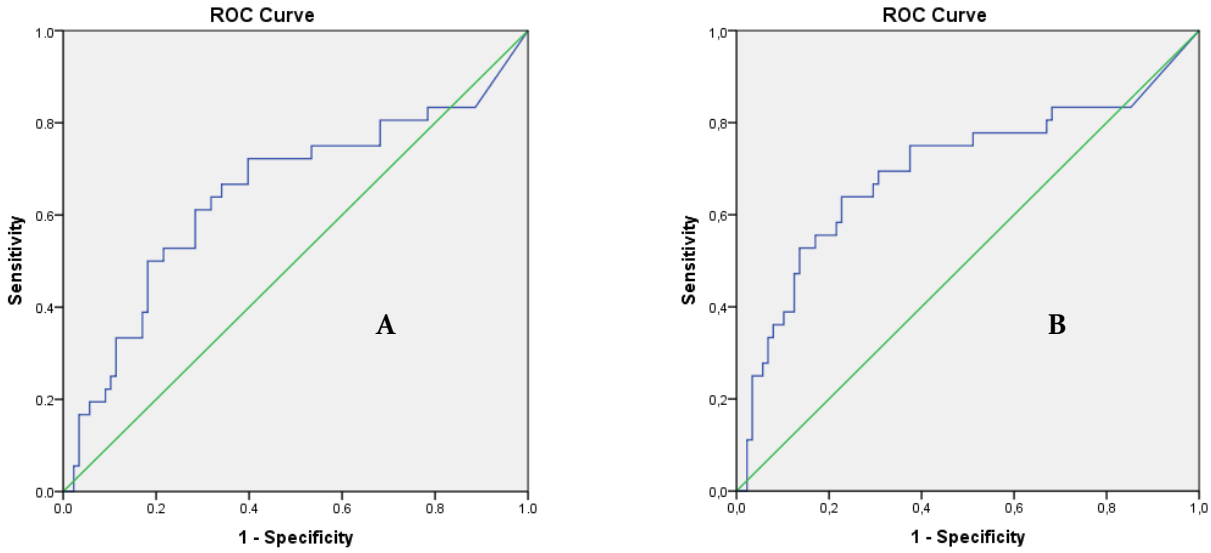
*Statistically significant difference.

Increased risk prediction of DIO2 and GDF5 genotypes

To investigate the possibility to use the *DIO2* and *GDF5* genotypes as a predictive tool, we next performed a receiver operating characteristics (ROC) analysis. Two models were fitted with knee OA development after a non-acute knee symptoms as the outcome. Model one consisted only of age, gender, BMI and trauma, model two included age, gender, BMI, trauma and *DIO2* and *GDF5* genotypes. The predictive value of the anthropometric traits alone as reflected by the area under the curve (AUC) was 0.647 (95%CI 0.530-0.764), however, when genotypes of the *DIO2* and *GFD5* gene were added the AUC improved to 0.697 (95%CI 0.582-0.812) (Figure 2).

Figure 2

Receiver operating characteristics (ROC) analysis diagrams. The outcome is osteoarthritis (OA) development a decade after knee complaints. In Figure 2A the model included age, gender, trauma and BMI. In Figure 2B the model included age, gender, BMI, trauma, DIO2 and GDF5 genotypes.



*In Figure **2A** the area under the curve (AUC) is 0.647 (95%CI 0.530-0.764). In Figure **2B** the AUC is 0.697 (95%CI 0.582-0.812).*

Discussion

In the current study we showed that the *DIO2* OA susceptibility SNP rs225014 and the *GDF5* susceptibility rs143383 SNP are significantly associated with development of knee OA (OR 2.3; 95% CI 1.14-4.49 and OR 2.0; 95% CI 1.07-3.78, respectively) in a relatively young patient group with a mean age of 44 years with a history of knee complaints a decade ago. This effect appeared independent of other factors related to knee OA development such as knee trauma, age and BMI. Prediction of knee OA development improved from an average AUC of 0.647 for age, sex, BMI and trauma alone to an AUC of 0.697 when including *DIO2* and *GDF5* genotypes in the risk prediction model, almost reaching clinical relevant AUC value (≥ 0.7). Furthermore, an increased minor allele frequency of *DIO2* is related to signs of OA development visible on both radiographs and MR images (P Value 0.020) and a similar trend is visible for *GDF5*, however, not significant (P Value 0.206).

These data are in line with recently published data showing that articular cartilage expression of *DIO2* is epigenetically regulated and that particularly *DIO2* rs225014 risk allele carriers are less able to maintain cartilage homeostasis due to the fact that subtle changes in methylation, generally occurring upon environmental changes such as micro traumas, resulted in detrimental up-regulation of *DIO2* [9]. Type II deiodinase (D2), expressed by the DIO2 gene regulates the bioavailability of intracellular T3 in specific tissues such as the growth plate and facilitates terminal maturation of hypertrophic chondrocytes. Functional genomic studies showed high expression of *DIO2* mRNA and D2 protein levels in osteoarthritic as compared to healthy cartilage [18]. Furthermore, *DIO2* allelic imbalance was assessed and showed that the OA risk allele 'C' was more abundantly present in articular joint tissues than the wild-type allele 'T' [18]. Up regulation of *DIO2* expression in a human in vitro model resulted in a marked reduction of the capacity of chondrocytes to deposit ECM components, including type II and type X collagen, while inducing OA-specific markers of cartilage matrix degeneration and mineralization [9]. In mice undergoing a forced running regime it has been shown that *DIO2* deficiency has a protective effect on the homeostasis of articular cartilage in the knee joints [25].

It may be that trauma at relatively early age affects the the propensity of the highly specialized, maturational arrested articular chondrocytes to loose their maturational arrested state loss of epigenic control, among others, of the *DIO2* gene.

Our results show that the T allele of the *GDF5* SNP rs143383 is significantly associated with development of knee OA with an OR of 2.0 (95% CI 1.07-3.78). This is in line with earlier findings that *GDF5* rs143383 polymorphism is associated with knee OA in both Asians and Caucasians [6,24,26]. Recent research showed that *GDF5* stimulation of human chondrocytes inhibits expression of cartilage ECM degrading enzymes MMP13 and ADAMTS4 and stimulates the expression of cartilage anabolic genes *ACAN* and *SOX*9 [27]. *GDF5* stimulation also inhibits the canonical Wnt signaling pathway through expression of the DKK1 and FRZB inhibitors. The Wnt signaling pathway plays an important role during cartilage development, and activation of the pathway in the adult cartilage tissue leads to hypertrophy, initiation of calcification and tissue degradation via increased expression of ECM degrading components [27]. Therefore altered expression of the *GDF5* gene may result in ECM degradation and decrease of cartilage quality which may induce OA development.

It is commonly accepted that a clinically useful diagnostic markers should have an AUC of 0.7 or higher [28]. Adding *DIO2* and *GDF5* genotypes in the model resulted in a significant increase of the AUC from 0.647 to 0.697. The latter underscores, that although patient characteristics and environmental factors are important, genetic factors play a substantial role in knee OA development.

Non of the investigated SNP's of the *ASPN*, and the *7q22 locus* genes were significantly associated with OA development in the current study population. These findings are in line with outcomes of recent studies which report conflicting evidence about these genes in OA development [29,30]

In total five patients patients of non-Caucasian descent were included in this study, however, upon discarding these patients, *DIO2* and *GDF5* outcomes remained the same, indicating that these patients did not drive our associations and possibly that these genes confer risk to OA development in both Caucasian and non-Caucasian populations as previously shown.[3,6,10,11,18,31,32] .

Several limitations of the study should be mentioned. Due to different scanning techniques and other scoring methods used at baseline and after 10 year follow-up, the MR outcomes from baseline and follow-up outcomes could not be compared accurately to assess OA development. There-

fore, a certain degree of development in those patients without radiographic OA but with cartilage defects visible on MR images could not be ruled out. In order to compare patients with radiographic OA development to a control group without any signs of OA development, only patients without cartilage defects visible on MR images were used as controls. This restriction resulted in exclusion of 43% of the initial study group, leading to a significant smaller study population. Being aware of the tendency of association studies to produce false-positive results, additional replication is necessary. In the current study gender differences were not related to OA development. This may be explained by the fact that the female participants in the relatively young study population were mostly pre-menopausal.

In conclusion, the presence of the minor C-allele of the *DIO2* SNP rs225014 and the T allele of the *GDF5* SNP rs143383 are associated with OA development in a relatively young study population 10 years after knee complaints. Subsequent ROC analyses showed that determining *DIO2* and *GDF5* genotypes significantly improves risk prediction towards clinical relevant values.

Reference List

1 Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. Arthritis Rheum 1998; 41(8):1343-1355.

2 Hunter DJ. Advanced imaging in osteoarthritis. Bull NYU Hosp Jt Dis 2008; 66(3):251-260.

3 Meulenbelt I, Min JL, Bos S et al. Identification of DIO2 as a new susceptibility locus for symptomatic osteoarthritis. Hum Mol Genet 2008; 17(12):1867-1875.

4 Evangelou E, Kerkhof HJ, Styrkarsdottir U et al. A meta-analysis of genome-wide association studies identifies novel variants associated with osteoarthritis of the hip. Ann Rheum Dis 2014; 73(12):2130-2136.

5 Ikegawa S, Kawamura S, Takahashi A et al. Replication of association of the D-repeat polymorphism in asporin with osteoarthritis. Arthritis Res Ther 2006; 8(4):403.

6 Miyamoto Y, Mabuchi A, Shi D et al. A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis. Nat Genet 2007; 39(4):529-533.

7 Kerkhof HJ, Lories RJ, Meulenbelt I, Jonsdottir I et al. A genome-wide association study identifies an osteoarthritis susceptibility locus on chromosome 7q22. Arthritis Rheum 2010; 62(2):499-510.

8 Bos SD, Slagboom PE, Meulenbelt I. New insights into osteoarthritis: early developmental features of an ageing-related disease. Curr Opin Rheumatol 2008; 20(5):553-559.

9 Bomer N, den Hollander W, Ramos YF, et al. Underlying molecular mechanisms of DIO2 susceptibility in symptomatic osteoarthritis. Ann Rheum Dis 2014.

10 Nakajima M, Kizawa H, Saitoh M, Kou I et al. Mechanisms for asporin function and regulation in articular cartilage. J Biol Chem 2007; 282(44):32185-32192.

11 Reynard LN, Bui C, Syddall CM, Loughlin J. CpG methylation regulates allelic expression of GDF5 by modulating binding of SP1 and SP3 repressor proteins to the osteoarthritis susceptibility SNP rs143383. Hum Genet 2014; 133(8):1059-1073.

12 Young DA, Bui C, Barter MJ. Understanding CpG methylation in the context of osteoarthritis. Epigenomics 2012; 4(6):593-595.

13 Vincken PW, ter Braak AP, van Erkel AR et al. MR imaging: effectiveness and costs at triage of patients with nonacute knee symptoms. Radiology 2007; 242(1):85-93.

14 Huetink K, Nelissen RG, Watt I et al. Localized development of knee osteoarthritis can be predicted from MR imaging findings a decade earlier. Radiology 2010; 256(2):536-546.

15 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16(4):494-502.

16 Kornaat PR, Ceulemans RY, Kroon HM et al. MRI assessment of knee osteoarthritis: Knee Osteoarthritis Scoring System (KOSS)--inter-observer and intra-observer reproducibility of a compartment-based scoring system. Skeletal Radiol 2005; 34(2):95-102.

17 Hansen TV, Simonsen MK, Nielsen FC, Hundrup YA. Collection of blood, saliva, and buccal cell samples in a pilot study on the Danish nurse cohort: comparison of the response rate and quality of genomic DNA. Cancer Epidemiol Biomarkers Prev 2007; 16(10):2072-2076.

18 Bos SD, Bovee JV, Duijnisveld BJ et al. Increased type II deiodinase protein in OA-affected cartilage and allelic imbalance of OA risk polymorphism rs225014 at DIO2 in human OA joint tissues. Ann Rheum Dis 2012; 71(7):1254-1258.

19 Sakao K, Takahashi KA, Arai Y et al. Asporin and transforming growth factor-beta gene expression in osteoblasts from subchondral bone and osteophytes in osteoarthritis. J Orthop Sci 2009; 14(6):738-747.

20 Kizawa H, Kou I, Iida A et al. An aspartic acid repeat polymorphism in asporin inhibits chondrogenesis and increases susceptibility to osteoarthritis. Nat Genet 2005; 37(2):138-144.

21 Valdes AM, Loughlin J, Oene MV et al. Sex and ethnic differences in the association of ASPN, CALM1, COL2A1, COMP, and FRZB with genetic susceptibility to osteoarthritis of the knee. Arthritis Rheum 2007; 56(1):137-146.

22 Xu L, Li Z, Liu SY, Xu SY, Ni GX. Asporin and osteoarthritis. Osteoarthritis Cartilage 2015.

23 Luyten FP. Cartilage-derived morphogenetic protein-1. Int J Biochem Cell Biol 1997; 29(11):1241-1244.

24 Valdes AM, Evangelou E, Kerkhof HJ et al. The GDF5 rs143383 polymorphism is associated with osteoarthritis of the knee with genome-wide statistical significance. Ann Rheum Dis 2011; 70(5):873-875.

25 Bomer N, Cornelis FM, Ramos YF et al. The effect of forced exercise on knee joints in Dio2-/- mice: type II iodothyronine deiodinase-deficient mice are less prone to develop OA-like cartilage damage upon excessive mechanical stress. Ann Rheum Dis 2014. Published Online First: 30 December 2014.

26 Valdes AM, Doherty S, Muir KR et al. Genetic contribution to radiographic severity in osteoarthritis of the knee. Ann Rheum Dis 2012; 71(9):1537-1540.

27 Enochson L, Stenberg J, Brittberg M, Lindahl A. GDF5 reduces MMP13 expression in human chondrocytes via DKK1 mediated canonical Wnt signaling inhibition. Osteoarthritis Cartilage 2014; 22(4):566-577.

28 Wians FH. Clinical Laboratory Tests: Which, Why, and What Do The Results Mean? Lab Medicine 2009;105-13.

29 Kerkhof HJ, Bierma-Zeinstra SM, Castano-Betancourt MC et al. Serum C reactive protein levels and genetic variation in the CRP gene are not associated with the prevalence, incidence or progression of osteoarthritis independent of body mass index. Ann Rheum Dis 2010; 69(11):1976-1982.

30 Song GG, Kim JH, Lee YH. A meta-analysis of the relationship between aspartic acid (D)-repeat polymorphisms in asporin and osteoarthritis susceptibility. Rheumatol Int 2014; 34(6):785-792.

31 Gruber HE, Ingram JA, Hoelscher GLet al. Asporin, a susceptibility gene in osteoarthritis, is expressed at higher levels in the more degenerate human intervertebral disc. Arthritis Res Ther. 2009;11(2):R47.

32 Evangelou E1, Chapman K, Meulenbelt I, et al. Large-scale analysis of association between GDF5 and FRZB variants and osteoarthritis of the hip, knee, and hand. Arthritis Rheum. 2009; 60(6):1710-21.

Chapter 7

Summary and General Discussion

Chapter 1 provides a general introduction. The main aim of this thesis is to determine which prognostic factors for knee OA development can be identified in a relatively young population with a history of knee complaints. Identifying these specific prognostic factors may help to distinguish high-risk knee patients for the development of knee osteoarthritis (OA) early in life. Additionally, we investigated the short-term and long-term clinical effects of surgical management of traumatic meniscal tears.

In **Chapter 2** we defined localized development of knee osteoarthritis OA that arises from anterior cruciate ligament (ACL) and meniscal injuries identified on 0.5T MR images performed a decade ago in patients with sub-acute knee symptoms. Also the effect of surgical management of these lesions on OA development was investigated. A follow-up study was performed in 326 patients (mean age 42 years, 33% female) who were all part of a cohort of 855 knee patients who participated in a study on the cost-effectiveness of 0.5T magnetic resonance (MR) imaging relative to diagnostic arthroscopy. The mean follow-up was 10 years. Initial findings and differences in treatment were compared with follow-up radiographs and 3.0T MR scans. Odds ratios (OR) with 95%CI confidence intervals were used to identify effects between variables.
Patients with ACL ruptures had an increased risk of developing joint space narrowing (JSN), cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts medially or laterally (OR, 2.4–9.8). Patients with medial meniscal tears had an increased risk of developing JSN, cartilaginous defects, osteophytes, and bone marrow lesions medially (OR, 2.0–15.3). Patients with lateral meniscal tears had an increased risk of developing JSN, cartilaginous defects, osteophytes, bone marrow lesions, and subchondral cysts laterally (OR, 2.1–10.5). Meniscectomy and ACL reconstruction had no effect on the risk of developing OA.
We conclude that localized development of knee OA arises from ACL and meniscal lesions identified on MR images a decade earlier in patients with sub-acute knee symptoms and that surgical treatment of ACL and meniscal lesions have no effect on the development of OA.

In **Chapter 3** we validated a newly developed quantification method that automatically detects and quantifies the joint space width (JSW) in hand radiographs. Decrease of JSW is considered to be an important marker of cartilage damage, one of the main characteristics of OA. Repeatability, accuracy

and sensitivity to changes in JSW were determined and the influence of joint location and joint shape on the measurements was tested.
A mechanical micrometer set-up was developed to define and adjust the true JSW in an acrylic phantom joint and in human cadaver-derived phalangeal joints. Radiographic measurements of the JSW were compared to the true JSW. Repeatability, systematic error (accuracy) and sensitivity (defined as the smallest detectable difference (SDD)) were determined. The influence of joint position on the JSW measurement was assessed by varying the location of the acrylic phantom on the X-ray detector with respect to the X-ray beam and the influence of joint shape was determined by using morphologically different human cadaver joints.
The mean systematic error was 0.052 mm in the phantom joint and 0.210 mm in the cadaver experiment. In the phantom experiments, the repeatability was high (SDD = 0.028 mm), but differed slightly between joint locations ($p = 0.046$), and a change in JSW of 0.037 mm could be detected. Dependent of the joint shape in the cadaver hand, a change in JSW between 0.018 and 0.047 mm could be detected.

The automatic quantification method is sensitive to small changes in JSW. Considering the published data of JSW decline in the normal and osteoarthritic population, the first signs of hand OA progression with this method can be detected within one or two years.

In **Chapter 4** we identified risk factors for knee osteoarthritis (OA) development in a young to middle-aged population with sub-acute knee complaints in order to define high risk patients who may benefit from early preventive or future disease modifying therapies. The relationship between known OA risk factors from literature described in older study populations and OA development and knee function (Knee injury and Osteoarthritis Outcome Score (KOOS)) in 319 relatively young knee patients (mean age 41.5 years) was investigated. OA development visible on radiographs and MR images and KOOS knee function outcome scores 10 years after sub-acute knee complaints were assessed. Associations between OA development and age, gender, activity level (Tegner Scale), Body Mass Index (BMI), meniscal or ACL lesions, OA in first-degree relatives and radiographic hand OA were determined using multivariable logistic regression analysis. KOOS knee function outcomes were compared to normal population reference values and associations with age, gender, activity level, BMI, and ACL or meniscal lesions were determined using MANCOVA analysis.

OA on radiographs and MR in the tibiofemoral compartment (TFC) is associated with increased age (OR: 1.10, 95%CI 1.04-1.16 and OR: 1.07, 95%CI 1.02-1.13). TFC OA on radiographs only is associated with ACL and/or meniscal lesions (OR: 5.01, 95%CI 2.14-11.73), presence of hand OA (OR: 4.69, 95%CI 1.35-16.32) and higher Tegner activity scores at baseline before the complaints (OR: 1.20, 95%CI 1.01-1.43). The presence of OA in the TFC diagnosed only on MRI is associated with a family history of OA (OR: 2.44, 95%CI 1.18-5.06) and a higher BMI (OR: 1.13, 95%CI 1.04-1.23). OA in the patellofemoral compartment (PFC) diagnosed on both radiographs and MR is associated with an increased age (OR: 1.06, 95%CI 1.02-1.12 and OR: 1.05, 95%CI 1.00-1.09). PFC OA diagnosed on radiographs only is associated with a higher BMI (OR: 1.12, 95%CI 1.02-1.22). The presence of OA in the PFC diagnosed on MR only is associated with the presence of hand OA (OR: 3.39, 95%CI 1.10-10.50). Compared to normal reference values, the study population had significantly lower KOOS scores in all different subscales. Lower KOOS scores in all subscales were associated with an increased BMI (Effect size reaching from 0.024- 0.064). TFC OA according to the Delphi criteria was associated with lower outcomes in the subscales Sports and Recreation and Quality of life (Effect size 0.027 and 0.021). The presence of JSN and osteophytes in the PFC was associated with lower Quality of life scores (Effect size 0.017). Higher Tegner Activity scores at baseline were associated with higher scores in the subscales Pain and Sports and recreation (Effect size 0.018 and 0.019). A higher age was associated with lower scores in the subscales ADL and Pain (Effect size 0.018 and 0.048). The presence of ACL and/or meniscal lesions was associated with lower Symptoms scores (Effect size 0.019).
These results show that knee OA development in young to middle aged patients with a history of sub-acute knee complaints is associated with the presence of known risk factors for knee OA. OA is already visible on radiographs and MRI after 10 years. These high risk patients may benefit from adequate OA management early in life.

In **Chapter 5** we investigated the short-term and long-term clinical effects of surgical management of traumatic meniscal tears in knee patients without knee locking symptoms. A 10 year follow-up in 118 patients with sub-acute knee complaints (mean age 32 years SD 7.8) was performed. Clinical outcome measures of surgically and conservatively treated patients were compared using the Noyes and KOOS knee questionnaires.
There were no differences in short- and long-term Noyes scores and long-term cross-sectional KOOS *Pain*, *Symptoms*, *ADL* and *Quality of life* outcomes. KOOS *Sports and Recreation* outcomes were

significantly better in surgically treated patients (19.2 points, 95% CI 1.5; 36.8, p=0.033). Higher activity levels before the start of the complaints improved this effect.
Therfore, partial meniscectomy of traumatic meniscal tears may result in better Sports and Recreation related long-term clinical outcomes. This effect is positively associated with higher activity levels before injury. Future randomized controlled trials may elucidate the effect of surgical treatment of traumatic meniscal tears.

In **Chapter 6** we examined the contribution of the OA susceptibility genes *ASPN, GDF5, DIO2* and the 7q22 region to radiographic development of knee osteoarthritis (OA) after 10 years in patients with knee complaints a decade earlier.
A dose response association of 4 SNP's on the susceptibility genes *ASPN, GDF5, DIO2* and the *7q22 locus* were determined by comparing 36 patients who showed development of OA on radiographs with 88 patients who had no development of OA on radiographs and normal cartilage on MRI. OA development was defined as a Kellgren and Lawrence (K&L) score ≥1. Multivariate logistic regression analysis including the variables age, gender, body mass index (BMI) and reported knee trauma was performed to determine associations between OA development and the presence of the risk alleles.
A dose response association of *DIO2* SNP rs225014: odds ratio (OR) 2.3, 95% CI 1.1-4.5 (P=0.019) and *GDF5* SNP rs143383: (OR) 2.0, 95% CI 1.1-3.8 (P=0.031) was observed with knee OA development. The *ASPN* and 7q22 SNPs were not associated with OA development..
We conclude that the presence of the risk alleles of the *DIO2* SNP rs225014 and the the *GDF5* SNP rs143383 are associated with OA development in a relatively young study population 10 years after knee complaints. Determining *DIO2* and *GDF5* genotypes significantly improves risk prediction towards clinical relevant values.

General Conclusion

In this thesis we demonstrated that several known risk factors for knee OA development i.e. ACL ruptures, meniscal tears, the presence of hand OA and increased BMI, are already associated with knee OA development as demonstrated on radiographs and MR images early in life. Identifying these factors in young to middle aged patients suffering from knee complaints helps to define high risk patients who may benefit from early preventive exercise therapy or maybe disease modifying drugs which might be developed in the future.

Meniscectomy and ACL reconstruction have no effect on knee OA development after 10 years in patients with sub-acute knee complaints.

The in this thesis validated automatic JSW quantification method is sensitive to small changes in JSW of the finger joints. The first signs of hand OA development with this method can be detected within one or two years.

In patients with traumatic meniscal tears but without knee locking symptoms, there may be some benefits from treatment with meniscectomy in long-term Sports and Recreation knee function outcomes compared to conservative treatment. Future randomized controlled trials may elucidate the effect of surgical treatment of traumatic meniscal tears.

Chapter 8

Nederlandse Samenvatting

Hoofdstuk 1 is een algemene introductie van dit proefschrift. Het belangrijkste doel van het promotieonderzoek is om te bepalen welke prognostische factoren voor de ontwikkeling van knieartrose kunnen worden geïdentificeerd in een relatief jonge groep kniepatiënten. Het vaststellen van deze specifieke prognostische factoren zou kunnen bijdragen aan het vroegtijdig identificeren van hoogrisico patiënten met betrekking tot de ontwikkeling van knieartrose. Daarnaast onderzochten we de effecten van chirurgische behandeling van traumatische meniscusletsels op de kniefunctie op korte termijn en lange termijn.

In **Hoofdstuk 2** wordt beschreven hoe knieartrose zich volgens specifieke patronen ontwikkelt bij patiënten met subacute knie klachten en voorste kruisband (VKB) en/of meniscusletsel, zichtbaar op 0.5T magnetische resonantie (MR) beelden 10 jaar eerder. Ook het effect van chirurgische behandeling van dit letsel op artrose ontwikkeling werd onderzocht. Er werd een follow-up studie uitgevoerd bij 326 patiënten (gemiddelde leeftijd 42 jaar, 33% vrouwen) die deel uit maakten van een cohort van 855 kniepatiënten welke participeerden in een studie naar de kosteneffectiviteit van 0.5T MR ten opzichte van diagnostische artroscopie, uitgevoerd 10 jaar geleden. De gemiddelde follow-up tijd was 10 jaar. Uitkomsten van letsel op bij aanvang van de studie en de verschillende behandelingmethoden werden vergeleken middels follow-up röntgenfoto's en 3.0T MRI-scans. Odds ratio's (OR) met 95%CI betrouwbaarheidsintervallen werden gebruikt om de effecten tussen de variabelen te bepalen.
Patiënten met VKB letsel hadden een verhoogd risico op het ontwikkelen van gewrichtspleet vernauwing, kraakbeen defecten, osteofyten, beenmerglaesies, en subchondrale cysten mediaal of lateraal (OR, 2,4-9,8). Patiënten met mediale meniscus scheuren hadden een verhoogd risico op het ontwikkelen gewrichtspleet vernauwing, kraakbeen defecten, osteofyten en beenmerglaesies mediaal (OR, 2,0-15,3). Patiënten met laterale meniscus scheuren hadden een verhoogd risico op het ontwikkelen van gewrichtspleet vernauwing, kraakbeen defecten, osteofyten, beenmerglaesies en subchondrale cysten lateraal (OR, 2,1-10,5). Meniscectomie en VKB reconstructie hadden geen effect op het risico van het ontwikkelen van knieartrose.
Wij concluderen dat knieartrose zich volgens specifieke patronen ontwikkeld gerelateerd aan VKB en meniscus laesies geïdentificeerd op MR beelden tien jaar geleden bij patiënten met subacute knie symptomen. Chirurgische behandeling van VKB en meniscus laesies hebben geen effect op de ontwikkeling van artrose.
In **Hoofdstuk 3** wordt de validatie van een nieuw ontwikkelde kwantificatie methode die automatisch de grootte van de gewrichtsspleet van vingergewrichten detecteert en kwantificeert in röntgenfoto's

van de hand bepaald. Afname van de grootte van de gewrichtsspleet wordt gezien als een belangrijke maat voor de afname van kraakbeen, één van de belangrijkste kenmerken van artrose. Reproduceerbaarheid, nauwkeurigheid en gevoeligheid voor veranderingen van de grootte van de gewrichtsspleet werden bepaald en de invloed van plaatsing van het gewricht ten opzichte van de röntgenbuis en de vorm van het gewricht op de metingen werd getest.
Een mechanische micrometer set-up werd ontwikkeld om de werkelijke grootte van de gewrichtsspleet te definiëren en aan te passen in een plexiglas fantoomgewricht en in humane vingergewrichten verkregen middels dissectie. Automatische röntgenmetingen van de grootte van de gewrichtsspleet werden vergeleken met de werkelijke grootte van de gewrichtsspleet. Reproduceerbaarheid, systematische fout (nauwkeurigheid) en gevoeligheid voor veranderingen (gedefinieerd als de kleinste detecteerbare verschil (Smallest Detectable Difference = SDD)) werden bepaald. De invloed van de positie ten opzichte van de röntgenbuis op de grootte van de gewrichtsspleet meting werd bepaald door het variëren van de locatie van het plexiglas fantoomgewricht op de detectorplaat ten opzichte van de röntgenbundel. De invloed van de verschillende gewrichtsvormen werd bepaald door de uitkomsten van de morfologisch verschillende humane kadaver gewrichten te vergelijken.
De gemiddelde systematische fout was 0,052 mm in het fantoomgewricht en 0,210 mm in het kadaver experiment. In de fantoom experimenten was de reproduceerbaarheid hoog (SDD = 0,028 mm), maar deze was enigszins verschillend afhankelijk van de lokalisatie ten opzichte van de röntgenbundel (p = 0,046). Een verandering van de grootte van de gewrichtsspleet van 0.037 mm kon betrouwbaar worden bepaalld. Afhankelijk van de vorm van de humane kadaver gewrichten kon een verandering van de grootte van de gewrichtsspleet tussen de 0,018 en 0,047 mm betrouwbaar worden bepaald.
De automatische kwantificatie methode is gevoelig is voor kleine veranderingen in de grootte van de gewrichtsspleet. Gezien de gegevens verkregen uit de literatuur met betrekking tot de gewrichtsspleet afname in de normale populatie en in patiënten met handartrose, kunnen de eerste tekenen van handartrose progressie met deze methode worden gedetecteerd binnen één of twee jaar.

In **Hoofdstuk 4** worden risicofactoren voor knieartrose ontwikkeling in een relatief jonge groep patienten met subacute knieklachten bepaald om hoogrisico patiënten te kunnen identificeren welke zouden kunnen profiteren van de vroege preventieve of in de toekomst te ontwikkelen medicamenteuze therapieën. De relatie tussen artrose risicofactoren bekend uit onderzoek bij oudere onderzoekspopulaties en artrose ontwikkeling en kniefunctie werd onderzocht in 319 relatief jonge kniepatiënten (ge-

middelde leeftijd 41,5 jaar). Artrose ontwikkeling na 10 jaar werd vastgesteld op röntgenfoto's en MR-beelden. Tevens werden subjectieve kniefunctie uitkomstscores (KOOS vragenlijst) 10 jaar na de subacute knieklachten bepaald. Associaties tussen artrose ontwikkeling en leeftijd, geslacht, activiteitenniveau (Tegner vragenlijst), Body Mass index (BMI), meniscus of ACL-laesies, artrose in de eerstegraads familieleden en handartrose zichtbaar op röntgenfoto's werden bepaald met behulp van multivariabele logistische regressie-analyse. KOOS kniefunctie uitkomsten werden vergeleken met de normale referentiepopulatie waarden en associaties met artrose ontwikkeling, leeftijd, geslacht, activiteitenniveau, BMI, en ACL of meniscus letsels werden bepaald met een MANCOVA analyse.
Artrose zichtbaar op röntgenfoto's en MR beelden in het tibiofemorale compartiment (TFC) is geassocieerd met hogere leeftijd (OR: 1.10, 95%CI 1,04-1,16 en OR: 1.07, 95%CI 1,02-1,13). TFC artrose zichtbaar op röntgenfoto's is geassocieerd met VKB en / of meniscus letsel (OR: 5,01, 95%CI 2,14-11,73), de aanwezigheid van handartrose (OR: 4,69, 95%CI 1,35-16,32) en hogere Tegner activiteit scores voordat het klachten begonnen (OR: 1,20, 95%CI 1,01-1,43). De aanwezigheid van artrose in het TFC zichtbaar op MR beelden is geassocieerd met het voorkomen van artrose in eerstegraads familieleden (OR: 2.44, 95%CI 1,18-5,06) en een hogere BMI (OR: 1.13, 95%CI 1,04-1,23). ARTROSE in het patellofemorale compartiment (PFC) zowel zichtbaar op röntgenopnamen en MR beelden is geassocieerd met een hogere leeftijd (OR: 1,06, 95%CI 1,02-1,12 en OR: 1.05, 95%CI 1,00-1,09). PFC artrose zichtbaar op alleen röntgenopnamen is geassocieerd met een hoger BMI (OR: 1.12, 95%CI 1,02-1,22). De aanwezigheid van artrose in het PFC gediagnosticeerd op MR beelden is geassocieerd met de aanwezigheid van handartrose (OR: 3.39, 95%CI 1,10-10,50). In vergelijking met de normale referentiewaarden, hadden de onderzoekspopulatie significant lagere KOOS scores in alle verschillende subschalen. Lagere KOOS scores in alle subschalen was geassocieerd met een verhoogd BMI (Effectgrootte 0.024- 0.064). TFC artrose zichtbaar op MR beelden was geassocieerd met een lagere scores in de KOOS subschalen Sport en Recreatie en Kwaliteit van leven (Effectgrootte 0,027 en 0,021). De aanwezigheid van gewrichtspleet vernauwing en osteofyten in het PFC was geassocieerd met een lagere kwaliteit van leven score (Effectgrootte 0,017). Hogere Tegner activiteiten scores voordat de knieklachten begonnen waren geassocieerd met hogere scores in de subschalen Pijn en Sport en Recreatie (Effectgrootte 0,018 en 0,019). Een hogere leeftijd werd geassocieerd met lagere scores in de subschalen ADL en Pijn (Effect grootte 0,018 en 0,048). De aanwezigheid van ACL en / of meniscus letsels werd geassocieerd met een lagere Symptomen scores (Effect grootte 0,019).

Deze resultaten laten zien dat knieartrose bij jonge tot middelbare patiënten met een voorgeschiedenis van subacute knieklachten geassocieerd is met de aanwezigheid van bekende risicofactoren voor het ontwikkelen van knieartrose. Knieartrose ontwikkeling is in deze relatief jonge groep kniepatiënten reeds na 10 jaar zichtbaar zijn op röntgenfoto's en MR beelden. Het lijkt waarschijnlijk dat deze hoog-risico patiënten baat hebben bij een vroege, adequate artrose behandeling.

In **hoofdstuk 5** onderzochten we de klinische korte termijn en lange termijn effecten van chirurgische behandeling van traumatisch meniscusletsels in de kniepatiënten zonder slotklachten. Een 10 jaar follow-up studie bij 118 patiënten met subacute knieklachten (gemiddelde leeftijd 32 jaar, SD 7.8) werd uitgevoerd. Klinische uitkomstmaten van operatief en conservatief behandelde patiënten werden vergeleken met behulp van de Noyes en KOOS knie vragenlijsten.
Er waren geen verschillen in korte en lange termijn Noyes Score uitkomsten en langdurige cross-sectionele KOOS Pijn, Symptomen, ADL en Kwaliteit van Leven resultaten . De KOOS Sport en Recreatie resultaten waren significant beter in de chirurgisch behandelde patiënten (19,2 punten , 95 % CI 1,5 ; 36,8 p = 0,033) . Een hoger activiteitenniveau voor aanvang van de klachten was positief geassocieerd met dit effect. Uit deze resultaten blijkt dat partiële meniscectomie van traumatische meniscus scheuren lijkt te leiden tot een betere Sport en Recreatie gerelateerde functionele lange termijn resultaten . Dit effect is positief geassocieerd met een hoger activiteitenniveau voor het letsel. Toekomstige gerandomiseerde gecontroleerde studies zouden het effect van chirurgische behandeling van traumatische meniscusletsels verder kunnen ophelderen.

In **hoofdstuk 6** onderzochten we de invloed van de aanwezigheid van de risico allelen van *ASPN, GDF5, DIO2* and de 7q22 regio op ontwikkeling van knieartrose zichtbaar op röntgenfoto's bij patiënten met knieklachten 10 jaar eerder.
Een dosis respons associatie van de verschillende genotypen werd bepaald bij 36 patiënten met radiologische knieartrose en 88 patiënten zonder knieartrose en zonder kraakbeenletsels zichtbaar op MR beelden. Artrose werd gedefinieerd als een Kellgren en Lawrence (K & L) score ≥ 1. Multivariate logistische regressie-analyse met de variabelen leeftijd, geslacht, BMI en gerapporteerd knie trauma werd verricht om de associatie tussen artrose ontwikkeling bij dragers van de risico allelen van *ASPN, GDF5, DIO2* and de 7q22 regio te bepalen.

De uitkomsten van de logistische regressie-analyse laten zien dat er een dosis respons associatie van het risico C-allel van de *DIO*2 SNP rs225014: odds ratio (OR) 2.3, 95% CI 1.1-4.5 (P=0.019) en *GDF5* SNP rs143383: (OR) 2.0, 95% CI 1.1-3.8 (P=0.031) met knieartrose ontwikkeling bestaat (OR) 2.3, 95%CI CI 1,14-4,49 en (p = 0,019). Receiver operating characteristics (ROC) analyse toonde een verbetering van de voorspelling van knieartrose ontwikkeling met een gemiddelde 'area under the curve' (AUC) van 0,647 bij in achtneming van leeftijd, geslacht, BMI en trauma tot een AUC van 0,697 wanneer tevens *DIO*2 en *GDF5* genotypen als variabelen werden meegenomen in de analyse.
Wij concluderen dat *DIO*2 en *GDF5* artrose risico genotypen zijn geassocieerd met knieartrose ontwikkeling bij patiënten met knieklachten 10 jaar eerder. Het bepalen van *DIO*2 en *GDF5* genotypen verbetert de risicovoorspelling van knieartrose ontwikkeling tot klinische relevante waarden.

Algemene conclusies

Verschillende risicofactoren voor het ontwikkelen van knieartrose zichtbaar op röntgenfoto's en MR beelden kunnen relatief vroeg in het leven worden bepaald. Belangrijke risicofactoren zijn o.a. de aanwezigheid van VKB rupturen, meniscus scheuren, handartrose en een verhoogd BMI. Daarnaast speelt genetische aanleg een rol bij ontwikkeling van knieartrose. Het bepalen van deze risicofactoren helpt bij het identificeren van hoogrisico patiënten die kunnen profiteren van vroege preventieve of toekomstige, nog te ontwikkelen medicamenteuze therapieën.
De in dit proefschrift besproken gevalideerde automatische kwantificatie methode van gewrichtsspleten in vingergewrichten is in staat om betrouwbaar kleine veranderingen in de grootte van de gewrichtsspleet te bepalen. De eerste tekenen van handartrose progressie kunnen met deze methode worden waargenomen binnen één of twee jaar.
Behandeling van VKB en meniscusletsel door middel van VKB reconstructie en meniscectomie hebben geen effect op knieartrose ontwikkeling na 10 jaar in patiënten met subacute knieklachten en VKB rupturen of meniscusscheuren.
Bij patiënten met traumatisch meniscusletsel maar zonder slotklachten lijkt er, naast mogelijk enigszins beter functioneren op sportniveau, geen duidelijk positief klinisch effect te bestaan van de behandeling met meniscectomie ten opzichte van conservatieve behandeling. Gerandomiseerd onderzoek met een controlegroep zou meer duidelijkheid kunnen geven over de effecten van meniscectomie bij traumatische meniscusscheuren.

Curriculum Vitae

Kasper Huétink werd geboren 27 maart 1975 te Borne. Na het behalen van het VWO diploma in 1994 aan de Bataafse Kamp te Hengelo (O) begon hij aan de studie Fysiotherapie aan de Hogeschool van Utrecht, waar hij in mei 1998 zijn diploma behaalde. Aansluitend startte hij de studie Geneeskunde aan de Universiteit Utrecht waar hij in februari 2004 zijn artsdiploma behaalde. Na te hebben gewerkt als ANIOS Plastische Chirurgie in het Martini Ziekenhuis te Groningen en als docent Anatomie aan de Faculteit Geneeskunde van de Universiteit Utrecht startte hij in mei 2006 als artsonderzoeker bij de afdeling Radiologie en Orthopaedie in het Leids Universitair Medisch Centrum. Na tussen juni 2009 en februari 2011 te hebben gewerkt als AIOS Radiologie en tussen februari 2011 en december 2012 te hebben gewerkt als AIOS Revalidatiegeneeskunde, is hij thans werkzaam als arts in het Spine & Joint Centre te Rotterdam. Daarnaast werkt hij in deeltijd als onderzoeker bij de afdeling Orthopaedie in het Leids Universitair Medisch Centrum.