Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis

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Pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis

Pathofysiologische en prognostische waarde van echografie in knie artrose

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 27 januari 2015 des middags te 2.30 uur

door

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geboren op 12 november 1970
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CONTENTS

1

GENERAL INTRODUCTION

OSTEOARTHRITIS

Epidemiology

Osteoarthritis (OA) is a very common degenerative joint disorder. In the Netherlands, reported point prevalence rates were about 660.000 for all types of OA. Prevalence rates for women are almost twice as high as those for men[1]. The incidence of OA is rising because of the ageing population and it will become a growing health issue in the coming decades[2].

Clinical features and diagnosis

Pain is a hallmark feature of OA. In general, pain is intermittent and worse after incriminating activity. Furthermore, OA leads to stiffness which is usually worse in the morning or after a period of inactivity. This stiffness is short lived (less than 30 minutes) in contrast to stiffness in inflammatory arthropathies which often lasts an hour or more. Eventually, patients experience loss of mobility and function and complaints interfere with daily activities. Commonly, multiple joints are involved, but patients' complaints might be focused on a single joint. Overall, OA can have detrimental effects on mood, sleep, fatigue and health related quality of life[3-5].

Clinical investigation (in addition to history taking) is mandatory and sufficient to diagnose OA[6]. The extent of the involved joints and limitations in mobility can be established. Also it is necessary to exclude other causes of pain like inflammatory arthritis and pain syndromes. Imaging modalities like plain radiography are not mandatory to diagnose OA, but can be used to exclude other diseases. There is only a weak correlation between radiography and pain and functional impairment, so radiography alone, is not suitable to define the severity of the disease[7].

Prognosis

OA is known to progress gradually in the course of years. Complaints might be stable over several years, but patients might also experience (inflammatory) flares[2, 4, 6]. Depending on the joints involved, progression can ultimately lead to the need for joint replacement. Because there might be a significant discrepancy between radiography and complaints, it is important to differentiate clinical from radiographic progression. Radiographic stage is usually defined by joint space narrowing and scoring of bone involvement like osteophyte formation and sclerosis [8, 9].

Pathophysiology

Pathophysiology of OA is only partly understood. Cartilage loss from the articular surface of synovial joints has long been thought to be the central pathophysiological characteristic of OA. Mechanical aspects (trauma, weight bearing activities, malalignment) are known to be important in development and progression of OA. In recent years, however, it has become clear that several other (peri)articular structures like bone and synovium also play an important role in the process. Inflammation appears to be another significant driving

force in the process of OA. In current theories about the process of OA the chondrocyte still plays an central role implying the inability to repair damaged cartilage under the influence of mechanical and biochemical changes in the joint. It appears however, that synovitis and inflammatory markers also have a crucial and contributory role [3].

Types of OA

OA appears to be a heterogeneous disease, both in disease course as in risk factors for development and progression. Classifying OA in subtypes, for example according to the site, seems to reveal more homogeneous groups which are more accessible for research. So far, knee-, hand- and hip OA have been described as separate entities. These are also the most frequently involved sites[3, 10]. Also other classifications according to different phenotypes have been suggested. This classification is based on suspected pathophysiologic processes like for example: cartilage driven, bone driven and inflammation driven.

Therapy

So far, no disease modifying therapy is available and this is mainly due to the fact that pathophysiology is not completely understood. Therefore, current guidelines for the medical management of patients with knee OA suggest multimodal treatment combining pharmacological (e.g. analgesics, local glucocorticoids) and non-pharmacological (education, life-style management and exercise) measures. Ultimately, surgical options like joint replacement are available [11, 12].

Focus of research

It is becoming clear that other (peri) articular tissues than cartilage play an important role in the process of OA. Furthermore, inflammation is considered to be one of the key processes. With several newer imaging modalities like US and MRI, many (peri) articular soft tissue structures like synovium, effusion, and tendons and ligaments can be visualised. In order to contribute to insights in the complex pathophysiologic process in a heterogeneous disease like OA, in research, it seems important to focus to a homogeneous group of OA patients. Furthermore, identifying patients with worse prognosis might help focus therapeutic trials and focus research on pathophysiology. As pain is a hallmark symptom of OA and cause of considerable disability, it is also an important focus of research. These areas of research have also been formulated by European League Against Rheumatology (EULAR) and American College of Rheumatology (ACR)[10, 13].

In conclusion, there is a need for research on soft tissue pathology that focusses on relation with pain, pathophysiology and prognosis in different subtypes of OA patients.

ULTRASONOGRAPHY

Ultrasonography (US) is an imaging technique which involves sound waves outside the audible range with frequencies of > 20 kHz. The technique makes use of the difference in density of the different tissue structures using the way that sound waves are reflected

on these transitions. Through electric signals, these reflections are transmitted into a grey scale image. Sound waves are not able to penetrate bone and are therefore only capable of visualising soft tissue structures. Sound waves with a high frequency can pick up small details but cannot penetrate deep into the tissue as opposed to low frequency waves. So, with the choice of the frequency of the sound wave there is a trade-off between depth of penetration and detail.

Musculoskeletal ultrasound is used to visualise (peri)articular soft tissue structures as well as muscles. It is able to visualise structures of the joint including synovium, effusion, articular cartilage, the extra-articular part of the menisci and the surface of the articular bone. Outside the joint US is able to form images of tendons, ligaments and bursae. Because it is a dynamic procedure, the investigator is able to compress structures and find out if they are displaceable, perform dynamic investigation and compare left and right.

US has advantages over other imaging techniques. In contrast to conventional radiography it is capable of visualising soft tissue structures and it is very safe. Compared to CT and MRI, it requires no contrast agents and allows creation of static, as well as dynamic images. Also it is relatively inexpensive, feasible and can be performed under a wide range of circumstances. Unfortunately, it has some drawbacks, the most important one being that US is an operator dependant tool, which hampers standardisation and makes the results dependant on the skills of the investigator.

In order to use US in as a measuring instrument in OA, validity and reliability have to be satisfying. Although this has not been subject of extensive research, both issues have previously been addressed: US in OA has shown to have moderate to good criterion and construct [14, 15] validity. Criterion validity has been tested mainly in cadaver/orthopaedic studies in which US results were compared to anatomical preparations or biopsies from arthroscopic procedures. Construct validity has been tested more extensively and relied mostly on comparing US to MRI or conventional radiography[15]. As for reliability, some work has been done in a limited set of soft tissue structures and has shown satisfying results on intra- as well as inter observer reproducibility[14-16].

AIM AND OUTLINE OF THIS THESIS

The first step was to develop and test a knee OA US protocol. In **chapter two**, this process is described. First, as at the time of selection of the US items, no widely accepted protocol to systematically investigate knee OA was available, we developed our US protocol based on pathophysiologic concepts, previous research on this topic and recommendations of experts and working groups (i.e. OMERACT (Outcome Measures in Rheumatology in Clinical Trials) task force)[15, 17-23]. Six items were selected: To evaluate inflammation joint effusion and synovial hypertrophy were included[14, 24, 25]. To visualise more localized and focal stress related inflammation, infrapatellar bursitis was selected[15, 26]. Baker's cyst was included because of it's common nature in knee OA, the fact that it might reflect inflammation as well as mechanical stress and the fact that it is easy to assess with US[15, 27-29]. Two features were selected because of their more mechanical and permanent nature. Meniscal protrusion as a sign of meniscal pathology is quite

common in knee OA and known for it's gradual progression. The same is true for cartilage thickness. Gradual decrease in amount and quality of the cartilage layer on the surface of the bony parts of the joint is thought to be a hallmark feature of OA. Power Doppler mode to demonstrate increased blood flow and probably inflammation of the synovium, was not included in the protocol. Because this is a very machine dependent feature and difficulties of standardization of this feature with deeper located structures, it was decided that it might hamper reproducibility to include it.

Two rheumatologists, trained and certified in US were involved. To guarantee independency of observations, the US investigators were blinded for the results of US-, X-ray- or physical examinations. Consensus was reached performing calibration sessions in which 15 patients were investigated. Thereafter, US was performed independently by the two rheumatologists in 60 outpatients fulfilling the American College of Rheumatology (ACR) clinical criteria for knee OA[30]. Cartilage thickness and meniscal protrusion (if >3 mm) were measured on a continuous scale, all other variables were scored dichotomously.

The second step in this study was to estimate the prevalence of the different abnormalities for the dichotomous variables and the point estimates and variance for the continuous measures. Also, we assessed inter observer reliability.

Our studies were conducted in the framework of a specialized knee- and hip OA outpatient clinic. All patients were treated according to a multimodal treatment protocol comprising education, physical therapy, step up analgesics (acetaminophen, non steroidal anti-inflammatory drugs, tramadol) and intra-articular injection with triamcinolonacetate and advice on weight reduction if indicated[31].

Chapter three and four are dedicated to gathering knowledge on pathophysiology of pain in knee OA, which is one of the disease's hallmark features.

The cause of pain in knee OA is not well understood. The level of pain is at most moderately associated with the level of radiographic knee OA [32]. Previous research has also shown that knee pain in OA is multifactorial. Mechanical, structural, inflammatory, bone related (e.g. bone marrow lesions), neurological and psychosocial factors play a role in the complex process that results in painful knee OA[32, 33]. As cartilage is aneural and avascular, despite it being a central feature in the disease process, it is unlikely that pain originates here. The periost is the only part of the bone, capable of producing pain signals. So, it is likely that pathology in other surrounding structures like for example soft tissue structures (synovium, tendons and bursae) but also nerves or vascular structures contributes to pain.

Limited previous US and magnetic resonance imaging (MRI) research suggests a possible association between inflammatory features like effusion and synovial hypertrophy and Baker's cyst on one hand and pain on the other hand[15, 24, 26, 28, 34-38]. In **chapter three**, therefore, we investigated the cross sectional association between US findings and pain in 180 knee OA patients. In **chapter four** we further focus on pathophysiology of pain in knee OA by assessing effect of intra-articular glucocorticoids. The effect on pain of intra-articular glucocorticoids in knee OA on the short term is well established (3-4 weeks)[39]. In current multimodal treatment guidelines administration of intra-articular glucocorticoids is not advised as standard treatment, but can be considered in patients with a flare of knee pain, especially in those with local signs of inflammation[11,

12, 40]. This is based on the anti-inflammatory properties of glucocorticoids. So far however, solid evidence for inflammation being a solid predictor for response to intra-articular glucocorticoids in knee OA is lacking. Studies using ultrasonography (US) show inconsistent results concerning the predictive value of inflammation (effusion, synovial hypertrophy) for response[41, 42]. In this study the aim was to investigate the predictive value of US characteristics at inclusion for the effect of intra-articular glucocorticoids in knee OA in 62 patients with symptomatic knee OA at four weeks.

The longitudinal course in US abnormalities is the subject of **chapter five**. We aimed for insight in the behaviour of soft tissue pathology in the course of time, which also might be of help for long term outcome prediction. For any US feature to be able to predict long term clinical outcome this feature should be stable in time, as more fluctuating features will inevitably have lower associations with an outcome measure. The goal of this study was thus to identify the prevalence of distinct patterns (stable vs fluctuating) in a set of US features in a cohort of patients receiving standard multimodal treatment for knee OA at T=0, T=3 months and T=12 months. For this purpose, a prospective, explorative study was conducted including 55 patients with knee OA. All six US features were investigated at 3 time points during one year. In addition, a composite inflammatory score was composed.

The arguably most promising aspect of US in knee OA is the ability to predict more long term clinical outcome.

In **chapter six** therefore, the longitudinal association between US pathology at baseline and radiographic and clinical progression of knee OA after two years of follow up was investigated. For this purpose the association between a set of US features and radiographic and clinical progression of knee OA after two years of follow up was investigated in 125 patients. Clinical progression – by lack of validated worsening criteria - was defined using the inverse Osteoarthritis Research Society International (OARSI)[43] responder criteria or progression to total knee replacement. A 2-point or more increase in Altman score[9] or progression to total knee replacement was considered radiologic progression. Associations between more inflammatory US features (synovial hypertrophy, effusion and Baker's cyst) and mechanical features US (e.g. meniscal protrusion, cartilage thickness) on one hand, and clinical and radiological progression in knee OA on the other hand, was investigated in this study.

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2

ULTRASONOGRAPHIC ANALYSIS IN KNEE OSTEOARTHRITIS: EVALUATION OF INTEROBSERVER RELIABILITY

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Bevers K, Zweers MC, van den Ende CHM, Martens HA, Mahler EAM, Bijlsma JWJ, Wakefield RJ, van den Hoogen FHJ and den Broeder AA

ABSTRACT

Objective Evidence for the validity of US in detecting structural joint pathology in OA is increasing. However, despite the rapidly emerging field of US in OA, few studies have reported on the inter-observer reliability of US to date. The objective of this study was to assess inter-observer reliability of ultrasonography (US) in the evaluation of specifically defined features in osteoarthritis (OA) of the knee.

Methods US was performed independently by two rheumatologists in 60 outpatients fulfilling the American College of Rheumatology clinical criteria for knee OA. The acquisition protocol comprised medial meniscus protrusion, synovial hypertrophy, effusion, infrapatellar bursitis and cartilage thickness. Cartilage thickness and meniscal protrusion (if >3 mm) were measured on a continuous scale, all other variables were scored dichotomously.

Results Inter-observer agreement (κ value) was moderate for protrusion of the medial meniscus (0.54), good for infrapatellar bursitis (0.66) and effusion (0.74), excellent for Bakers' cyst (0.85) and poor for the detection of synovial hypertrophy (-0.08).

Inter-observer reliability was good for the measurement of medial meniscus protrusion (correlation coefficient 0.80, 95% limits of agreement -1.93 to 1.94 mm) and cartilage thickness (correlation coefficient 0.62 and 0.68, 95% limits of agreement -0.87 to 0.84 mm and -0.77 to 0.96 mm at the medial and lateral condyle respectively).

Conclusion This study demonstrated good reproducibility of US in the assessment of the majority of the investigated mechanical, inflammatory and degenerative features of knee OA, and contributes to exploring the use of US in knee OA as a useful tool in research as well as in clinical practice.

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder, with the knee being one of the most frequently involved sites. Knee OA has traditionally been imaged with conventional radiography, providing little information about soft tissue structures (1). As OA is a disease of the entire joint, characterized by cartilage breakdown, subchondral bone alterations, formation of osteophytes, meniscal degeneration and synovial inflammation, information about these pathologic findings will likely give insight into the complex process of development and progression of knee OA(2). Ultrasonography (US), a non-invasive, safe and relatively inexpensive imaging tool, allows visualisation of these structures(3;4). For US to be implemented structurally, guidelines on the use of US in OA are being developed(5-9).

Evidence for the validity of US in detecting structural pathology in OA is increasing(10). Cartilage degeneration, a a hallmark feature of, can be accurately imaged with US as good correlations between US and histology have been found(10-12). Furthermore, good agreement between US and magnetic resonance imaging (MRI) in visualising effusion and synovial hypertrophy in patients with symptomatic knee OA has been shown(13).

However, despite the rapidly emerging field of US in OA, few studies have reported on the inter-observer reliability of US to date. As US is known to be an operator-dependant modality, lack of inter-reader agreement could restrict its use, especially in clinical practice. So far, few studies have reported reproducibility data on US in knee OA and no standardised and reproducible US protocol for knee OA has been developed. Although various studies report US detection of synovial inflammation(14), there is a lack of reliability data on synovial hypertrophy and effusion in knee OA. In studies on patients with knee arthritis inter-observer agreement for synovial hypertrophy varied from 0.4 to 0.7 and reported agreement on the presence or absence of effusion in the knee varied between 0.65 and 0.77(10). Data on inter-observer agreement for cartilage thickness included only a few patients and inter-rater reliability ranged from 0.6 to 0.9 (15;16) Furthermore, only a limited number of studies addressed inter-observer reliability of US in the detection of meniscus lesions, Baker's cyst and infrapatellar bursa(17;18). Therefore, the aim of this study was to investigate the inter-observer variability of a set of specifically defined US features comprising inflammatory, degenerative and mechanical aspects in knee OA.

PATIENTS AND METHODS

Patients

A total of 60 consecutive patients attending our outpatient clinic and fulfilling the American College of Rheumatology (ACR)(19) clinical criteria for knee OA were included in our study. The criteria used were: knee pain (>15 days of the last month) plus at least three of the following: age >50 years, morning stiffness <30 minutes, crepitus, bony enlargement, bony tenderness, no palpable warmth. Exclusion criteria were: inflammatory rheumatic diseases or deposition diseases possibly leading to secondary OA, severe co-morbidity exceeding the complaints of knee OA and planned orthopaedic surgery within

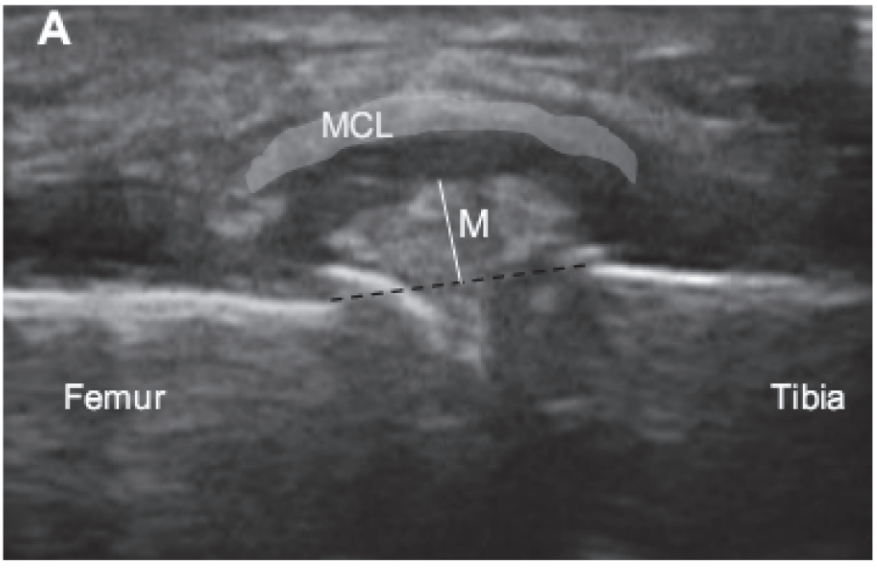
the next 3 months. Patients underwent weight bearing antero-posterior radiographs of the knee, and had ultrasound assessment of the most symptomatic knee by two trained ultrasonographers. We studied the most symptomatic knee because this study was carried out in the framework of an osteoarthritis cohort which focuses on an index knee.The local Medical Research Ethics Committee, region Arnhem-Nijmegen (The Netherlands) approved the study design (study number 2009/095).

US investigation

All patients were assessed independently on the same day by two rheumatologists trained and certified in US (HM and KB). They had 4 and 2 years respectively professional experience in US and had performed >500 US investigations each. To guarantee independency of observations, the US investigators were blinded to the results of prior US-, X-ray- or physical examinations. The two involved rheumatologists reached consensus on the US acquisition prior to the study by investigating 15 patients together. Based on previous US studies, EULAR guidelines(5) and pathophysiologic concepts of OA, we decided to investigate 6 different US features:

1. Effusion: a ≥ 4mm anechoic area in the suprapatellar recess, evaluated using a longitudinal scan in line with the patellar tendon with the leg in passive full extension. Structures are labelled as effusion if they are fully compressible to discriminate effusion from synovial hypertrophy. The site of maximal effusion is measured.
2. Synovial hypertrophy: a hypoechoic area (which is poorly compressible and nondisplaceable) of ≥2mm in the suprapatellar recess in line with the patellar tendon, measured with the leg in full extension with a longitudinal scan. The site of maximal hypertrophy is measured.
3. Meniscal protrusion: protrusion of meniscal tissue out of the joint space >3 mm from the joint line, evaluated at the medial joint space with the knee in full extension with a longitudinal scan (fig 1A). The maximal protrusion is measured from the joint line to the menical-synovial fluid interface. It is measured with the medial collateral ligament in sight, perpendicular to the joint line.
4. Deep infrapatellar bursitis: an enlarged infrapatellar bursa (>2 mm) on both longitudinal and transverse scans with the knee in 45° flexion.
5. Baker's cyst: a hypo-anechoic area between the medial gastrocnemius and the semimembranosus tendon examined with the patient in prone position on the posterior/medial side of the fully extended knee applying a transverse and longitudinal scan. The maximum diameter is measured (mm) in a transverse plane.
6. Femoral cartilage thickness: an anechoic band with sharp hyperechoic margins, measured perpendicular to the surface at the intercondylar notch and at the medial and lateral condyle (5 mm just medial or lateral from the top of the condyle), with the transducer immediately above the patella in a transverse plane and with the knee in maximum flexion (fig 1B). The outer hyperechoic margin is included in the measurement

The ultrasound machine used in this study was a MyLab 25 gold (Esaote Biomedica, Genoa, Italy), with a 35 mm linear transducer (frequency 8-15 mHz). The complete US investigation took about five minutes per patient.



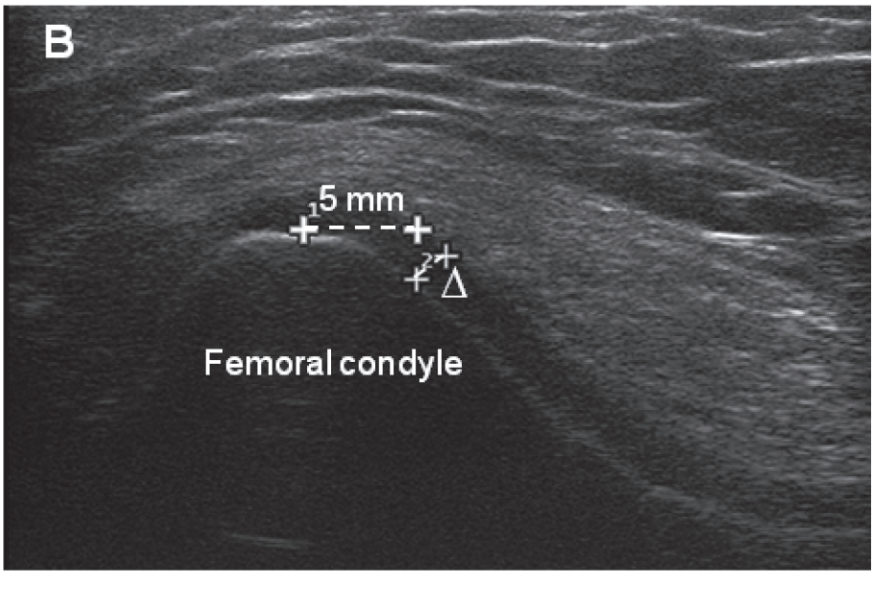


Figure 1

A. Ultrasound image of medial meniscus with measurement of protrusion. Protrusion of the meniscus (M) was measured between the medial collateral ligament (MCL) and the joint space (dashed line).

B. Femoral condyle cartilage with measurement of cartilage thickness of lateral condyle. Cartilage thickness was measured perpendicular to the surface 5 mm from the top of the condyle (Δ).

Statistical analysis

Based on kappa statistics, sixty patients were required in this study to reach an agreement of 0.7 (95%-confidence interval (CI) of 0.2), assuming a prevalence of 15-50% of different US features. Inter-observer agreement for dichotomous variables was evaluated using unweighted kappa statistics and percentage of exact agreement. Kappa values <0.20 were considered poor, between 0.20 and 0.40 fair, between 0.41 and 0.60 moderate, between 0.61 and 0.80 good and >0.80 excellent(20).

Inter-observer agreement for continuous or ordinal variables was assessed by calculating the concordance correlation coefficient and respective 95% CI(21). Bland Altman analysis was performed to determine 95% levels of agreement and modified Bland Altman plots using regression analyses to account for trend were depicted(22). Statistical analysis was performed using the statistical software package Stata10 (StataCorp, Texas, USA).

RESULTS

A total of sixty patients were included in our study. Patient characteristics are shown in table 1. The prevalence of the various pathophysiological features differed notably; infrapatellar bursitis and synovial hypertrophy were observed infrequently, whereas meniscal protrusion was found in over half of the patients (Table 2). Inter-observer agreement was poor for the presence or absence of synovial thickening, moderate for protrusion of the medial meniscus and good for infrapatellar bursitis and joint effusion and excellent for Bakers' cyst (Table 2).

Table 1 Patient characteristics (n = 60)

Women, %	72
Age (years), mean (SD)	53.6 (10.3)
BMI, mean (SD)	29.1 (6.3)
Disease duration (years), median (range)	3 (0.1 - 22)
Duration of complaints (years), median (range)	8 (0.2 – 40)
K&L score (%)	
1	28
2	43
3	17
4	12
Most symptomatic knee (n)	
Right	29
Left	31

Table 2 Prevalence and inter-observer reliability of ultrasonography-detected pathology in knee osteoarthritis.

Observation	Prevalence KB (%)	Prevalence HM (%)	Agreement (%)	Kappa (95% CI)
Meniscus protrusion	68	68	80	0.54 (0.31 - 0.77)
Baker's cyst	22	29	95	0.85 (0.68 - 1.00)
Infrapatellar bursitis	2	3	98	0.66 (0.04 - 1.00)
Effusion	8	15	95	0.74 (0.47 - 1.00)
Synovial hypertrophy	10	5	83	-0.08 (-0.16 - 0.01)

Cartilage thickness (mean ± SD) was 1.93 (0.54) mm (range 0.0 – 3.8) at the medial condyle, 1.99 (0.59) mm (range 0.0 – 3.6) at the lateral condyle and 2.47 (0.68) mm (range 1.6 – 5.0) at the intercondylar notch. Inter-observer agreements for femoral articular cartilage thickness measurements were moderate to good (Table 3). Figure 2A-C shows the difference between the 2 observers' measurements of cartilage thickness and mean measurements. The 95% limits of agreement as determined by Bland Altman analysis were as follows: medial condyle -0.87 to 0.84 mm; lateral condyle -0.77 to 0.96 mm; intercondylar notch -1.53 to 0.99 mm.

When protrusion of the medial meniscus was present, inter-observer agreement for the degree of bulging was excellent (Table 3, 95% limits of agreement -1.93 to 1.94 mm). However, with increasing size of meniscal protrusion, the measurement became less precise (figure 2D).

Table 3 Inter-observer reliability for measurement of femoral articular cartilage thickness and meniscal protrusion

Observation	Correlation coefficient (95% CI)	Difference; limits of agreement (95% CI)	
Medial femoral cartilage thickness	0.62 (0.46 – 0.79)	-0.11	-0.98 - 0.77
Lateral femoral cartilage thickness	0.68 (0.54 – 0.82)	0.30	-1.31 - 1.92
Intercondylar notch cartilage thickness	0.50 (0.33 – 0.66)	-0.05	-0.85 - 0.75
Medial meniscus protrusion	0.80 (0.68 – 0.92)	0.19	-3.48 - 3.78

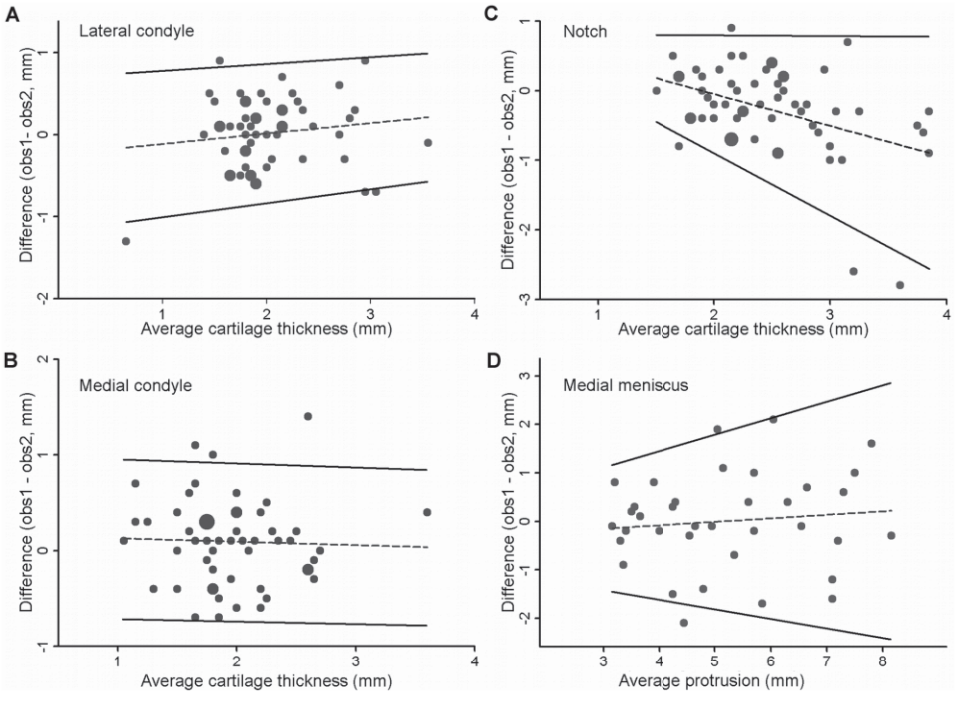


Figure 2 Adapted Bland-Altman plots illustrating inter-observer agreement for US measurement of femoral cartilage thickness (A-C) and medial meniscus protrusion (D). Dashed line: mean, solid line: 95% limit of agreement.

DISCUSSION

Although US is a highly operator-dependant technique, few studies have addressed the inter-observer variability of US in the assessment of knee pathology in OA. Knowledge of US reliability is pivotal before US can be implicated in research or clinical practice. In this study, we assessed the inter-observer reliability of multiple concurrently studied US features in the evaluation of OA. We chose six different US features, covering inflammatory, mechanical and degenerative aspects of knee OA. Our results show moderate to excellent inter-observer reliability for detection of infrapatellar bursitis, effusion, meniscal protrusion and Baker's cysts and for the measurement of cartilage thickness.

Despite standardised measurements and the use of bony/anatomic landmarks, we found lower inter-observer reliability for cartilage thickness than previously demonstrated for healthy subjects (11;16;23;24). This is most likely due to the difficulty of defining the boundaries of cartilage-bone and cartilage-soft tissue at sites of cartilage damage(12;16;25). In addition, maximal flexion of the knee (as opposed to fixed flexion), required to visualise the weight-bearing parts of the femoral condyles, potentially differs between measurements due to pain during knee bending. Furthermore, the standardisation of our

measurement resulted in suboptimal isonisation of the ultrasound beam, which can result in underestimation of the cartilage thickness.

In contrast to studies of inflammatory arthropathies(14), inter-observer reliability was poor for the detection of synovial hypertrophy in osteoarthritic knees. This is probably due to the low occurrence of synovial hypertrophy in our population and hence limited US training and consensus on acquisition between the observers. In a large cohort of painful knee osteoarthritis, prevalence of synovial hypertrophy and effusion on US was 16.9% and 43.7%, respectively(7). In this study, inflammation correlated strongly with advanced radiographic disease. Therefore, this higher incidence of inflammatory characteristics might reflect more advanced disease, (67% of patients with K&L score of ≥3)(7) as compared to our cohort (29% of patients with K&L score ≥3). In addition to this, we might have missed a number of patients with effusion, as we measured fluid only at the suprapatellar recess with the leg relaxed. Tension on the quadriceps muscles might reveal more fluid from the suprapatellar pouch.

The main limitation of our study was the relatively small study population, owing to which different US features were observed in a small number of patients and precision was sometimes lower than aimed for. Furthermore, we did not study intra-observer reproducibility because of practical difficulties (particularly blinding for previous measurements) and because intra-observer reliability is generally higher than inter-observer reliability. Some previous studies have determined inter-observer reliability of reading acquired ultrasound images, however, as ultrasound is a dynamic investigation, it is more important to study differences in the acquisition of images. This study contributes to exploring the use of US in knee OA, by addressing the visualisation of a set of soft tissue structures in the knee. In conclusion, the present study demonstrates moderate to excellent inter-observer reliability of US in the inspection of different inflammatory, mechanical and degenerative characteristics of knee OA. Therefore, US potentially might prove to become a useful tool in research as well as in clinical practice.

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ULTRASONOGRAPHIC FEATURES IN SYMPTOMATIC OSTEOARTHRITIS OF THE KNEE AND RELATION WITH PAIN

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ABSTRACT

Objective Radiographic knee osteoarthritis (OA) is moderately associated with pain. As OA is a disease of the entire joint, ultrasonography (US), visualising cartilage and of soft tissue structures, might provide more insight in the complex process of pain in knee OA. The objective of this study was to investigate the cross sectional association between US findings and pain in knee OA.

Methods In this observational study 180 patients fulfilling the American College of Rheumatology clinical criteria for knee OA underwent US examination of the most symptomatic knee. The US protocol comprised assessment of synovial hypertrophy, joint effusion, infrapatellar bursitis, Baker's cyst, medial meniscus protrusion and cartilage thickness. To evaluate the association between US features and pain (Numerated Rating Scale (NRS) from 0-10 and the Knee injury and Osteoarthritis Outcome Score (KOOS) subscale pain), regression analysis was performed.

Results In regression analysis, no association between US or clinical or demographic features and the level of knee pain was found.

Conclusion In this cohort no association between US features and the degree of knee pain was found. Despite the attractive profile of US (easy accessible, inexpensive and no radiation involvement) and the fact that previous research suggested otherwise, it remains uncertain which part of pain in knee OA is explained by pathology in soft tissue structures and whether US of the knee is the imaging tool of choice to visualise some of this pathology.

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder, with the knee being one of the most frequently involved sites. Knee OA causes pain and stiffness and can lead to considerable disability and consequently to a reduced of quality of life. As the incidence of OA increases with age, this will become a major health issue and socio-economic problem in the coming decades [1].

The cause of pain in knee OA is not well understood. The level of radiographic knee OA is at most moderately associated with the level of pain[2]. Therefore it is unlikely that pain is predominantly caused by only bone and cartilage pathology. Previous research has shown knee pain in OA to be multifactorial [3]. Mechanical, structural, inflammatory, bone related, neurological and psychological factors play a role in the process that results in painful knee OA [4]. As OA is a disease of the entire joint that is characterized by cartilage breakdown, subchondral bone alterations and formation of osteophytes as well as soft tissue abnormalities including meniscal degeneration, bursitis, tendinitis, bakers cyst and synovial inflammation, information about these soft tissue structures might provide more insight in their potential role the complex process of pain in knee OA [5].

Musculoskeletal ultrasonography (US) is a relatively new imaging tool which is non-invasive, safe and relatively inexpensive and is able to create static as well as dynamic images. In addition, it has shown to be more sensitive than clinical examination to pick up peri- and intra-articular soft tissue lesions [6]. This creates the possibility to visualise structural/mechanical (eg cartilage and meniscal tissue), as well as inflammatory properties (eg synovial proliferation and effusion) with the same instrument. US in knee OA has proven to be feasible and showed moderate to good validity [7, 8] and interobserver reliability [9, 10]. So far, few studies have addressed the relationship between US features and pain. Associations between sonographic signs of inflammation like synovial effusion, synovial hypertrophy and Baker's cyst and pain have been found [11-16], but findings are not consistent across studies [7, 8]. Furthermore the generalizability of the results of these studies is hampered by the relatively low number of enrolled patients and the limited set of examined sonographic features. Of note, a recent systematic review on MRI findings and pain in knee OA concluded that associations between bone marrow lesions and effusion/synovitis on one hand and pain on the other hand suggest that presence of this pathology might play a role in the origin of pain in symptomatic knee OA [17].

In an attempt to contribute to the body of knowledge about the pathophysiology of pain in knee OA, we decided to investigate a more extensive set of previously defined US features in a large, well defined set of patients with symptomatic knee OA. The aim of this study is to cross-sectionally investigate the association between ultrasonographic findings and pain in knee OA.

PATIENTS AND METHODS

Patients

The design of this study is a cross sectional, single centre, observational study.

A total of 180 consecutive consenting patients attending our specialized knee- and hip OA outpatient clinic and fulfilling the American College of Rheumatology clinical criteria for knee OA were included in our study. The symptomatic knee was appointed as index joint. If patients had bilateral knee OA, the most symptomatic knee was selected. The local Medical Research Ethics Committee, region Arnhem-Nijmegen (The Netherlands) approved the study design (study number 2009/095). Exclusion criteria were: other rheumatic or orthopaedic diseases leading to inflammatory arthritis or secondary OA, severe co-morbidity exceeding the complaints or limitations of the knee OA, orthopaedic procedures planned within the next three months, or cognitive or sensorimotor problems interfering with filling in questionnaires.

Data acquisition

On inclusion, demographic (age, gender) and clinical data (BMI, duration of complaints), data on pain, use of analgesics and knee X-rays were collected. Pain was assessed using two measures, a Numerical Rating Scale (NRS) from 0-10 and the Knee injury and Osteoarthritis Outcome Score (KOOS) subscale pain. [18] (Likert scale version) The KOOS includes the questions of the original Western Ontario and McMaster University Arthritis Index (WOMAC), and to optimize generalizability we used a KOOS pain score that is fully WOMAC compatible. Because it is yet unclear whether US features are likely to be momentary or more chronic, we decided to include two pain measures; one reflecting severity of pain at the day of the ultrasound assessment (NRS pain) and the other reflecting severity of pain in the past two weeks (KOOS pain). No threshold of pain was required to be included in the study. Weight bearing fixed flexion posterior-anterior radiographs were collected and graded according to Kellgren and Lawrence systematics [19]. Scoring was performed by an experienced rheumatologist. Intra-observer agreement revealed a kappa score of 0.84.

Ultrasonography

Ultrasonography was performed by two rheumatologists and a post doc physician, who were trained in musculoskeletal US and previously involved in inter reader reliability research of the applied US protocol. This protocol showed moderate to good inter observer reliability [9]. Because we introduced a new investigator, and because interobserver agreement of synovial hypertrophy was previously dissatisfying, we slightly adjusted the protocol and performed renewed calibration sessions. Renewed interobserver agreement tests showed good results with kappa values varying from 0.59 to 1.00 for all items including synovial hypertrophy (supplementary reproducibility data of separate US features available). The protocol is based on results of previous US studies (especially the OMERACT definitions) [20, 21] and pathophysiologic concepts of knee OA. In selecting US candidates for our protocol, we first focused on to what extent these features were linked to osteoarthritis in previous literature. Secondly, we looked for US data on content validity and reproducibility.

This protocol focuses on two domains, comprising inflammatory (synovial hypertrophy and effusion and bursitis), and mechanical aspects (medial meniscus protrusion, Baker's cyst and cartilage thickness). Clinical evaluation and US examination were obtained on the same day. The investigator performing US was unaware of clinical and radiographic results. The ultrasound machine used in this study was a MyLab 25 gold (Esaote Biomedica, Genoa, Italy) with a 35 mm linear transducer (frequency 8-15 mHz). The complete US investigation took about ten minutes per patient. The US protocol comprised the following items:

1. Effusion: a ≥ 4mm hypoechoic or anechoic intra-articularmaterial that is displaceable and compressible in the suprapatellar recess, evaluated using a longitudinal scan with the leg in passive full extension.
2. Synovial hypertrophy: an abnormal hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible of ≥2mm in the suprapatellar recess, measured with the leg in full extension with a longitudinal scan.
3. Meniscal protrusion: protrusion of meniscal tissue out of the joint space >3 mm from the joint line, evaluated at the medial joint space with the knee in full extension with a longitudinal scan
4. Infrapatellar bursitis: an enlarged infrapatellar bursa (>2 mm) on both longitudinal and transverse scans with the knee in 45° flexion.
5. Baker's cyst: a hypo-anechoic area between the semimembranosus and medial gastrocnemius tendon examined with the patient in prone position on the dorsal/ medial side of the fully extended knee applying a transverse and longitudinal scan. The maximum diameter was measured (mm) in a transverse plane.
6. Cartilage thickness: an anechoic band with sharp hyperechoic margins, measured perpendicular to the surface at the intercondylar notch and at the medial and lateral condyle (5 mm just medial or lateral from the top of the condyle), with the transducer immediately above the patella in a transverse plane and with the knee in maximum flexion.

Statistical analysis

Checks for assumption of normality were performed for all continuous baseline data including primary outcome measurements like NRS and KOOS pain.

To examine the interrelationship between different ultrasound features, we calculated Pearson's correlation coefficient (r) for interval/ratio – and Cramer's V (V) for nominal variables.

To examine the associations between each US feature and pain we performed univariate regression analyses with US features as independent variables and knee pain as dependent variable. This was done for both NRS pain and KOOS pain as dependent variable. In post hoc analyses, we explored the association between a composite inflammatory US score and pain, as evidence suggests that inflammatory features seem to have the most consistent association with pain. A composite US inflammatory score was calculated by allocating one point for each of the inflammatory components (effusion, synovial hypertrophy and infrapatellar bursitis) which resulted in a score ranging from 0-3. Regression analyses were performed with NRS and KOOS pain as dependent and composite US inflammation score as independent variable. Although less supported by evidence, the same analysis was performed with a composite mechanical/structural score (combined Baker's cyst, meniscal protrusion score).

Because the US features were chosen bearing the concept of inflammatory and mechanical aspects in mind, we wanted to discriminate between inflammatory and mechanical complaints as well. In post hoc analysis, two sets of items, derived from the KOOS subscale pain and subscale stiffness were conjuncted based on clinical appraisal of the content of the questions being mechanical or inflammatory of nature, and verified by factor analysis (5). Univariate regression analyses were performed to explore associations between these two sets as dependent variables (KOOS mechanical and KOOS inflammatory) and the individual ultrasound features as independent variables. Statistical analysis was performed using the statistical software package Stata10 (StataCorp, Texas, USA).

RESULTS

Study population

In table 1 patient characteristics are shown. A total of 180 patients were included in this study, of which 120 (67%) were female. The mean age was 57 years. The majority of the patients was overweight and Kellgren and Lawrence score II was the predominant radiographic classification of the knee OA. The mean NRS was 6.1 ± 1.7 indicating moderate to high pain levels.

Table 1 Baseline data; clinical and radiographic data of study participants

Population (n)	**180**
Age (years) (mean, SD)	57 ± 9.2
Gender male (n,%)	60 (33%)
Body Mass Index (mean, SD)	28.8 (7.4)
Duration of complaints (years) (mean, SD)	8.6 ± 9.5
Use of analgesics	
Yes (n,%)	99 (55%)
No (n,%)	81 (45%)
Kellgren & Lawrence grade	
0 (n,%)	19 (10.6%)
I (n,%)	43 (23.9%)
II (n,%)	70 (38.9%)
III (n,%)	23 (17.8%)
IV (n,%)	15 (8.3%)
*KOOS pain score (Mean,SD) (range)	57.0 ± 16.5 (10-100)
°NRS pain (mean, SD) (range)	6.1 ± 1.7 (0-10)

*KOOS pain score: normalized data (0-100) in which 0 indicates no complaints and 100 indicates maximal complaints
°NRS: numerical rating scale (0-10) in which 0 indicates no complaints and 10 indicates maximal complaints

Prevalence of ultrasound features

Ultrasonographic findings are listed in table 2. In this cohort of patients with painful knee OA, meniscal protrusion was the most prevalent ultrasonographic feature (111, 61.7%), whereas infrapatellar bursitis was quite rare (10, 5.6%). Statistically significant associations between different US features were found for the three measures of cartilage thickness (*r*:0.45-0.50) and between synovial hypertrophy and joint effusion (V: 0.18).

Table 2 Ultrasonographic findings in symptomatic knee OA

n	**180**
Effusion (≥ 4 mm) (n,%)	30 (16.7%)
Synovial hypertrophy (≥ 2mm) (n,%)	37 (20.6%)
Meniscal protrusion (> 3 mm) (n,%)	111 (61.7%)
Infrapatellar bursitis (> 2mm) (n,%)	10 (5.6%)
Baker's cyst (n,%)	47 (26.1%)
Cartilage thickness	
Medial epicondyl mm(mean, SD)	1.75 (0.56)
Interconylar notch mm(mean, SD)	2.26 (0.67)
Lateral epicondyl mm(mean, SD)	1.86 (0.50)

Associations between ultrasonographic features and pain

Univariate regression analyses showed no association between separate ultrasonographic features and NRS pain or KOOS pain scores. We did repeat the regression analysis in the seperate K&L groups, but again, no significant associations between US and pain were found. The subsequent post hoc sensitivity analysis using the composite inflammatory and composite mechanical/structural score as independent variable yielded the same result. No associations between clinical or radiographic aspects (BMI, age, sex, Kellgren and Lawrence score) and pain scores were found. Univariate analyses using the KOOS-derived mechanical and inflammatory complaints as dependent variable and ultrasonographic features as independent variables showed no statistically significant associations.

DISCUSSION

In this cohort of 180 patient with painful knee OA we were unable to demonstrate any explanation based on ultrasonographic findings for the level of knee pain. Our findings, although perhaps somewhat unexpected, suggest that the level of knee pain in knee OA

is not strongly determined by soft tissue abnormalities in the majority of patients, and that other mechanisms play a role in this process.

Our findings are in line with the limited previous data from smaller studies on the relation between levels of knee OA pain and US features. De Miguel and co-workers found an association between Baker's cyst and suprapatellar effusion and VAS pain in motion, when comparing patients with pain and without pain but they found no association with severity of pain[12]. D'Agostino and colleagues found an association between joint effusion and sudden aggravation of knee pain, but again no association between US inflammatory signs and pain during activity [11].

Some previous ultrasonographic studies in knee OA do show associations between US features and pain, but only when comparing patients with and without pain. In these studies, 2 aspects stand out: first, they include a control group of patients without pain which enhances contrast, and second, there is a broad variety in the ultrasonographic features that show an association with pain and in the pain measure that is used, with consistent replication of the findings being absent. Variables that have been found to be associated with presence of pain include for example medial compartment synovitis [16], quadriceps tendon thickness [15], Baker's cyst and suprapatellar effusion [12]. Also the pain measures used vary from pain expressed as Visual Analog Scale (VAS) pain at rest, medial knee pain and VAS pain in motion. However, although the studied US items often overlap, associations found can often not be replicated. So, thusfar, in line with our findings, no single US finding has been consistently linked to the level of pain in knee OA.

Our study has some limitations that could have resulted in a false negative study, one of them being a possible selection bias. The majority of patients enrolled in this cohort were referred by orthopaedic surgeons (tertiary referral) because patients had complaints of knee OA, but knee replacement was not considered warranted at the moment. As a result, patients in our sample showed relatively high levels of pain, but rather moderate radiographic damage compared to other cohorts as the majority of our patients were classified as K&L score 1 and 2. It is possible that other origins of pain, which cannot be captured by ultrasonographic features (for example bone marrow lesions, or locoregional pain syndrome) might have played a relatively large role in the expression of symptoms in our sample. Furthermore, based on this selection, one might anticipate on a rather homogeneous group in terms of outcome measures (NRS and KOOS pain), which might hamper the possibility of finding associations. However, considering the adequate variation in both pain levels and radiological severity of the knee OA and prevalence of US features, we believe that our results truly demonstrate the absence of an apparent association between the US features and the level of pain.

Because there seems to be a more consistent association between synovial inflammation visualised by MRI and pain [17], one could argue that US might not be the imaging tool of choice to visualise inflammation in detail because MRI is likely be more sensitive and is able to visualise more sites of possible inflammation. The same is true for cartilage measurements. With uneven distribution of cartilage over the tibia plateau, 3D volumetric cartilage measurements a likely to be more precise. However, we tried to minimize the marge of error by performing multiple measurements in one patient and previous interreader reliability investigation for cartilage measurements revealed

satisfactory correlation coefficient values of 0.50-0.68 [9].The US beam has limited tissue, and absent bone penetration compared to MRI techniques.

The selection of the ultrasonographic features and the used US protocol might also have influenced our results. We used a previously validated US protocol, that consisted of widely used US features including both inflammatory and mechanic factors. Although many other candidate features can be considered, unfortunately, up to date, there is no international consensus on which anatomical parts or US features might play the most important role in pain in knee OA. Also, the prevalence of some of these features is rather low, thus hampering the possible predictive value for pain.

The way the features are assessed can also perhaps be optimised. Assessing effusion for example might be more sensitive when the entire area of the suprapatellar bursa is scanned and in a transverse plane as well, especially when the quadriceps is activated. Synovitis in the medial compartment could have been assessed in addition to the suprapatellar area. However, we believe that our core set is a valid and well balanced set of soft tissue US features that could have been expected to be implicated in knee OA pain.

In conclusion, in our study we were not able to demonstrate an association between US features and pain in a cohort of patients with painful knee OA. Although our study has some limitations, our results confirm the earlier findings about the lack of association between the level of pain and US features.

Despite the attractive profile of US (easy accessible, inexpensive and no radiation involvement) and the fact that previous research suggested otherwise, it remains uncertain which part of pain in knee OA, is explained by pathology in soft tissue structures and it if US of the knee is the imaging tool of choice to visualise some of this pathology.

Longitudinal extension of the study will further assess whether US features can be predictive for future signs and symptoms of knee OA, and what the course is of US abnormalities in knee OA.

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4

ARE ULTRASONOGRAPHIC SIGNS OF INFLAMMATION PREDICTORS FOR RESPONSE TO INTRA-ARTICULAR GLUCOCORTICOIDS IN KNEE OSTEOARTHRITIS?

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ABSTRACT

Objective To investigate the predictive value of Ultrasound (US) characteristics for the effect of intra-articular glucocorticoids in knee Osteoarthritis (OA).

Methods In this prospective cohort study, 62 patients with symptomatic knee OA (clinical knee OA criteria, pain>4 on a Numerical Rating Scale (NRS; 0-10)) received an intra-articular glucocorticoid injection (40 mg triamcinolone acetonide). Patients with NRS pain ≤ 4 at 4 weeks were defined as responders. On inclusion, demographics, clinical data (body mass index, local swelling) knee X-rays and Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire were collected. Six US features were assessed including: effusion, synovial hypertrophy, Baker's cyst, infrapatellar bursitis, meniscal protrusion and cartilage thickness. Stepwise multiple logistic regression analyses with forward selection were conducted to identify possible predictors

Results At 4 weeks, 42% of the study participants reached a NRS ≤4; an effect comparable to existing literature. Regression analyses showed that patients who used analgesics at baseline were less likely to have a good response. The small proportion of patients with infrapatellar bursitis was more likely to respond to the injection.

Conclusion No patient, disease or US characteristic of inflammation, turned out to be a reliable and clinically meaningful predictor for the effect of intra-articular glucocorticoids after four weeks in knee OA.

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder, with the knee being one of the most frequently involved sites. So far no disease modifying drugs for OA are available. Therefore, current guidelines for the medical management of patients with knee OA suggest multimodal treatment combining pharmacological (e.g. analgesics, local glucocorticoids) and non-pharmacological (education, life-style management and exercise) measures (1-3). In these guidelines administration of intra-articular glucocorticoids is not advised as standard treatment, but can be considered in patients with a flare of knee pain, especially in those with local signs of inflammation.

The effect on pain of intra-articular glucocorticoids in knee OA is well established. It is clear but relatively short-lived (max. 3-4 weeks), with numbers needed to treat of 3-4(4). Although few side effects of intra-articular injections are reported, it is an invasive procedure which not all patients are willing to undergo. Furthermore, because of the prevalent nature of the condition, many intra-articular injections could be prevented if a priori selection of patients with better chance of response would be possible.

So far, evidence for solid predictors for response to intra-articular glucocorticoids in knee OA is lacking as studies on this topic are sparse. Based on the anti-inflammatory properties of glucocorticoids, one might expect a higher chance of response in patients with signs of inflammation. This is supported by previous research which suggested that intra-articular glucocorticoids are more beneficial in patients with clinical joint effusion(5;6). However, studies using ultrasonography (US) show inconsistent results concerning the predictive value of inflammation (effusion, synovial hypertrophy) for response to intra-articular glucocorticoids(7;8). It has even been suggested that patients without inflammation are better responders(9).

In search of possible inflammatory and mechanical features which might predict response, it is attractive to use US as imaging modality. It is a very practical tool and has shown good construct validity (10;11) and moderate to good interobserver reliability(12;13) in knee OA. Furthermore is able to visualise (peri)articular structures (inflammatory as well as non-inflammatory) which are involved in the process of knee OA(10;14).

So, in this study, we investigated the predictive value of US characteristics for the effect of intra-articular glucocorticoids in knee OA.

PATIENTS AND METHODS

Study design

This prospective study was conducted in the framework of a specialized knee- and hip OA outpatient clinic. All patients also received multimodal treatment comprising education, physical therapy, step up analgesics (acetaminophen, non-steroidal anti-inflammatory drugs, tramadol) and advice on gradual weight reduction when indicated(15). The local Medical Research Ethics Committee, region Arnhem-Nijmegen (The Netherlands) approved the study design (study number 2009/095). All patients signed informed consent.

Patients

From November 2010 to May 2011, 62 patients fulfilling the clinical American College of Rheumatology (ACR) criteria for knee OA criteria(16) were included. Radiographic OA was not an inclusion criterion. The symptomatic knee was appointed as index joint. If patients had bilateral knee OA, the most symptomatic knee was selected. All included patients were treated with blind intra-articular injection of 40 mg triamcinolone acetonide in addition to standardized multimodal treatment. No aspiration of synovial fluid was performed and no local anesthetic was injected. Following injection, patients were recommended to rest and avoid weight-bearing activities for 24h. Use of anticoagulants was no exclusion criterion.

Exclusion criteria were: pain score on numerical rating scale (NRS, 0 -10) of ≤ 4, other rheumatic or orthopedic diseases leading to inflammatory arthritis or secondary OA, co-morbidity exceeding the complaints or limitations of the knee OA, orthopedic procedures planned within the next three months, or cognitive or sensorimotor problems interfering with filling out questionnaires.

Data acquisition

On inclusion, demographics, clinical data (body mass index, local swelling) and knee X-rays were collected. Posterior-anterior fixed flexion and lateral knee radiographs were graded using Kellgren and Lawrence (K&L) systematics(17).

Follow-up was planned at 4 weeks by telephone. The numerical rating scale (NRS; range 0 - 10) on pain was recorded on both visits. At baseline, patients were asked to fill out the Dutch version of the KOOS (Likert-scale version) questionnaire, (with permission, www.koos.nu). Pain and function subscales were calculated as normalized scores (0 – 100, where 100 signifies most severe complaints).

Ultrasonography

Ultrasonography was performed by two rheumatologists and a post-doc physician, who were trained in musculoskeletal US and previously involved in inter reader reliability research of the applied US protocol. A previously developed US protocol was used which showed moderate to good inter observer reliability (12). Because we introduced a new investigator and as interobserver agreement of synovial hypertrophy was previously dissatisfying, we performed renewed calibration sessions. Renewed interobserver agreement tests in 23 patients showed moderate to good results for all items (table 1). We did not repeat interobserver reliability tests in infrapatellar bursitis, because of the very low prevalence of this item. The protocol is based on results of previous US studies (especially the OMERACT definitions) (18;19) and pathophysiologic concepts of knee OA. It focuses on two domains, comprising inflammatory (synovial hypertrophy and effusion and bursitis), and mechanical aspects (medial meniscus protrusion, Baker's cyst and cartilage thickness). We did not include Power Doppler measurements as this seems to be a rather rare feature in knee OA(14), and Power Doppler is a very machine dependent tool, which hampers generalizability.

Clinical evaluation and US examination were obtained on the same day. The investigator performing US was unaware of clinical and radiographic results. The ultrasound machine used in this study was a MyLab 25 gold (Esaote Biomedica, Genoa, Italy) with a 35 mm linear transducer (frequency 8-15 mHz). The complete US investigation took about ten minutes per patient. The US protocol comprised the following items:

1. Effusion: a ≥ 4mm hypoechoic or anechoic intra-articularmaterial that is displaceable and compressible in the suprapatellar recess, evaluated using a longitudinal scan with the leg in passive full extension.
2. Synovial hypertrophy: an abnormal hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible of ≥2mm in the suprapatellar recess, measured with the leg in full extension with a longitudinal scan.
3. Meniscal protrusion: protrusion of meniscal tissue out of the joint space >3 mm from the joint line, evaluated at the medial joint space with the knee in full extension with a longitudinal scan
4. Infrapatellar bursitis: an enlarged infrapatellar bursa (>2 mm) on both longitudinal and transverse scans with the knee in 45° flexion.
5. Baker's cyst: a hypo-anechoic area between the semimembranosus and medial gastrocnemius tendon examined with the patient in prone position on the dorsal/ medial side of the fully extended knee applying a transverse and longitudinal scan. The maximum diameter was measured (mm) in a transverse plane.
6. Cartilage thickness: an anechoic band with sharp hyperechoic margins, measured perpendicular to the surface at the intercondylar notch and at the medial and lateral condyle, with the transducer immediately above the patella in a transverse plane and with the knee in maximum flexion. A summary score of cartilage thickness was computed.

Table 1 Interobserver agreement US features

Observation	**Kappa (n=23)**
Effusion	1.00
Synovial hypertrophy	0.65
Baker's cyst	1.00
Meniscal protrusion	0.59
	Correlation coefficient (95%CI)
Medial femoral cartilage thickness	0.77 (0.60-0.95)
Lateral femoral cartilage thickness	0.74 (0.57-0.92)
Intercondylar notch cartilage thickness	0.75 (0.57-0.94)

Statistical analysis

Descriptives were computed. Frequencies, means and Standard Deviations (SD) were calculated where appropriate.

Effect of intra-articular injection:

NRS pain ≤ 4 at four weeks after injection was the primary outcome measure. Decrease in NRS pain at T=4 weeks was a secondary outcome measure.

Patients with NRS pain ≤ 4 at 4 weeks were defined as responders.

Outcomes were checked for confounding/effect modification on the following items: age, BMI, KOOS at baseline, gender, K&L score and use of analgesics.

Prediction of response

To compare responders and non-responders on baseline characteristics, chi-square tests and T-tests were performed, where appropriate. To determine potential predictors of response to intra-articular glucocorticoids (NRS pain ≤4 at 4 weeks), stepwise multiple logistic regression analyses with forward selection ($p < 0.20$) were conducted. The following variables were included in the model: age, gender, body mass index (BMI), knee swelling at physical examination at baseline, use of analgesics at baseline, NRS pain and KOOS ADL at baseline and US features (i.e. Baker's cyst, effusion, synovial hypertrophy, infrapatellar bursitis, meniscal protrusion and cartilage thickness). As effusion, synovial hypertrophy and infrapatellar bursitis are considered to be expressions of the same pathophysiologic inflammatory process and we were especially interested in inflammation, we performed post hoc analyses with composite inflammatory determinant score (yes/no). It was considered to be positive if effusion and/or synovial hypertrophy and/or infrapatellar bursitis (Composite inflammatory score A) or effusion and/or synovial hypertrophy (Composite inflammatory score B) were present. Predictor variables with an association of $p < 0.20$ to the dependent variable were retained in the final model. Anticipating a response rate of 40%, we would need 70 patients to include 3 predictors (rule of thumb: 1 predictor for 10 responders) in our final regression model. Statistical analysis was performed using the statistical software package Stata10 (StataCorp, Texas, USA).

RESULTS

Baseline characteristics

From November 2010 until April 2011, a total of 62 knee OA patients fulfilling our in- and exclusion criteria received an intra-articular injection with glucocorticoid. Baseline characteristics are shown in tables 2 and 3. Table 2 shows a typical (20;21) knee OA cohort with predominantly overweight women with moderate type OA according to radiographic K&L score.

Response to intra-articular injection

At four weeks, 42% of the injection group reached a NRS ≤4. Mean values of NRS pain decreased from 6.6 (±1.0) at baseline to 4.9 (±1.9) at T=4 weeks. No confounding/effect modification was established.

Table 2 Baseline characteristics

Number of patients (n)	**62**
Age (years) (SD)	55.4 (8.7)
Women (%)	58
BMI (kg/m^2) (SD)	30.2 (5.6)
Pain at baseline° (NRS) (SD)	6.6 (1.0)
Kellgren & Lawrence score (%)	
0	11
1	26
2	35
3	21
4	7
KOOS adl (score)* (SD)	55.7 (18.0)
Use of analgesics (%)	53

*Knee Osteoarthritis Outcome Score; function in daily living: normalized data (0-100) in which 0 indicates no complaints and 100 indicates maximal complaints
°NRS: numerated rating scale (0-10) in which 0 indicates no complaints and 10 indicates maximal complaints

Table 3 Baseline prevalence of US features

Effusion (n, %)	**15 (24%)**
Synovial hypertrophy (n, %)	14 (23%)
Meniscal protrusion (n, %)	41 (66%)
Infrapatellar bursitis (n, %)	6 (10%)
Baker's cyst (n, %)	20 (32%)
Cartilage thickness (mean) (mm, SD)	1.9 ± 0.4
Composite inflammatory score A*	46 (44%)
Composite inflammatory score B*	35 (42%)

*Composite inflammatory score A: effusion and/or synovial hypertrophy and/or infrapatellar bursitis
*Composite inflammatory score B: effusion and/or synovial hypertrophy

Prediction of response to intra-articular glucocorticoids

Baseline characteristics for responders versus non-responders are shown in Table 4. Except for pain and condylar cartilage thickness, no significant baseline differences between the subgroups were found. Table 5 shows the results of the final logistic regression model with clinical and US variables ($P < 0.20$) predicting response of intra-articular glucocorticoids at four weeks.

Table 4 Characteristics of patients injection group (responders vs non-responders)

	Responders (n=26)	Non-responders (n=36)
Age (years) (SD)	55 (7.8)	56 (9.4)
Women (%)	46	67
BMI (kg/m^2) (SD)	29.2 (5.0)	31.0 (6.1)
Pain at baseline (NRS 0 - 10)(SD)	6.3 (1.2)	6.8 (1.0)
Pain at 4 weeks (NRS 0 - 10)(SD)	3.0 (1.0)	6.2 (1.0)
Analgesics users (%)[†]	46	78
KOOS adl (mean, SD)	51 (20)	59(16)
Ultrasonography features		
Baker's cyst (%)	35	31
Effusion (%)	19	28
Synovial hypertrophy (%)	23	22
Infrapatellar bursitis (%)	15	6
Meniscal protrusion (%)	69	64
Cartilage thickness (mm)(SD)	2.0 (0.4)	1.8 (0.4)

[†] Statistical significant (p value<0.05)

Table 5 Results of the final logistic regression model predicting response of intra-articulair corticosteroids at four weeks

Predictor	OR (95 % CI)	P-value
Analgesic use at baseline	0.19 (0.05-0.70)	0.01
Infrapatellar bursitis	11.46 (1.21-108.20)	0.03
KOOS-adl	0.96 (0.92-1.00)	0.04
Gender (female)	0.41 (0.12-1.41)	0.16

DISCUSSION

In this pragmatic clinical trial we found that, besides perhaps infrapatellar bursitis, no other patient, disease or US characteristic of inflammation turned out to be a reliable and clinically meaningful predictor for the effect of intra-articular glucocorticoids in knee OA.

Our study confirms the somewhat controversial earlier finding that inflammation is no predictor for response to intra-articular triamcinolone acetate in knee OA. As glucocorticoids have strong anti-inflammatory properties, one would expect a better effect of intra-articular injection in patients with clinical or US signs of inflammation.

So far, results from previous studies on this subject are conflicting. Some studies suggested a beneficial effect of intra-articular glucocorticoid injection in patients with signs of inflammation(5;6). Others do not find any difference in effect or even higher response rates in patients without inflammatory signs(7-9). In our study, none of the beforehand suspected inflammatory candidates for prediction of response (eg knee swelling and effusion and synovial hypertrophy detected with US) proved to be an actual predictor. Thus, so far, the rationale for reserving intra-articular injection for patients with signs of local inflammation, is not supported by evidence.

Surprisingly, we did demonstrate that, infrapatellar bursitis – although not very prevalent - seemed to be associated with higher response rates in our cohort. This is not easy to understand. Firstly, infrapatellar bursitis is a localised problem and not necessarily a sign of integral inflammation of the knee. Furthermore this bursa does not communicate with the joint. So the mechanism of effect of an intra-articular injection is not completely clear. Although diffusion of part of the intra-articular glucocorticoid or systemic effects could play a role. As the prevalence of this bursitis is very low with resulting wide confidence intervals, it might well be a spurious finding. In this cohort of 6 patient with infrapatellar bursitis two were non-responders and 4 were responders.

We recognize that there are several limitations to this study. First, we chose to administer blind instead of US guided injections. As US guided injections in the knee have higher accuracy of needle placement, higher response rate would have been possible. On the other hand, our response rates are comparable with other cohorts and blind injections are much more common in daily practice. We realise that this study comprises of a limited number of study participants. Based on our sample size calculation, we were allowed to include 3 instead of 4 predictors in the final model. However this rule does not take the effect size into account. Because we were interested in clinically meaningful predictors, the current amount of patients would have enabled us to detect the ones with a major contribution to prediction.

In conclusion – despite the use of ultrasound – it was not possible to predict efficacy of intra-articular glucocorticoids based on the presence of inflammation.

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5

THE COURSE OF ULTRASONOGRAPHIC ABNORMALITIES IN KNEE OSTEOARTHRITIS: ONE YEAR FOLLOW UP

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ABSTRACT

Objective Imaging of (peri)articular structures and inflammation with ultrasound (US) during the course of Osteoarthritis (OA) might contribute to knowledge about early diagnosis of OA, prognosis and possibly the effect of disease modifying drugs. Our goal was to identify the prevalence of distinct patterns (stable vs fluctuating) in a set of US features in a cohort of patients receiving standard multimodal treatment for knee OA at T=0, T=3 months and T=12 months.

Design This was a prospective, explorative study including 55 patients fulfilling the American College of Rheumatology clinical criteria for knee OA. 6 US features were investigated including: effusion, synovial proliferation, infrapatellar bursitis, meniscal protrusion, Baker's cyst and cartilage thickness at 3 time points during one year. A composite inflammatory score was composed. Overall prevalence was assessed as well as individual patterns which were appointed as stable or unstable.

Results Inflammation like effusion and synovial hypertrophy does occur in over 40% of patients at some time in the year of follow up and shows a fluctuating pattern. Meniscal protrusion and Baker's cyst however are more stable features.

Conclusions Our study gives insight in the prevalence and course of US abnormalities in patients with knee OA and contributes to the knowledge on the possible role of this imaging modality in research.

INTRODUCTION

Osteoarthritis (OA) is a common joint disorder, with the knee being one of the most frequently involved sites. It is characterized by degradation of cartilage and other (peri) articular structures and causes pain and stiffness, which can lead to considerable disability and in turn to decrease of quality of life and work impairment. [1;2].

So far no disease modifying drugs for OA are available, mainly due to the fact that pathophysiology and relation with subsequent signs and symptoms are not completely understood. OA is not merely a disease of bone and cartilage but it affects the entire joint including soft tissue structures like menisci and synovium [3]. Visualising these (peri) articular structures during the course of OA might contribute to knowledge about early diagnosis of OA and prognosis. Besides, knowledge about the natural course of the disease through imaging might contribute to evaluating the effect of possible disease modifying drugs[4].

Among the available imaging tools in OA, Ultrasonography (US) has a very attractive profile. It is, in contrast to conventional radiography, able to visualise (peri)articular soft tissue structures. In addition, US in knee OA has shown good construct validity [5;6] and moderate to good interobserver reliability[7;8]. Compared to Magnetic Resonance Imaging (MRI) which also produces images of soft tissue structures, it is relatively safe, inexpensive and less time consuming.

Prior research focussed mainly on cross sectional associations of US abnormalities with knee pain or progression to knee replacement[9-14]. Little is known however, about the course of soft tissue pathology visualised by US in time and thus about the course and behaviour of soft tissue structures in the osteoarthritic knee[5]. In theory, inflammatory aspects like effusion and synovial proliferation are likely to fluctuate in time. Mechanical features (eg meniscal protrusion), however, are expected to be more permanent and progress over time. This is of importance, because heavily fluctuating features are less likely to be useful for long-term prediction. The limited number of previous US follow up studies suggest that Baker's cyst is a relatively stable feature which tends to persist up till 3 years whereas synovial effusion is more momentary and tends to diminish 6 months after hyaluronic acid injection[15-17]. Evidence from MRI studies shows a very gradual decrease in cartilage thickness and increase in meniscal pathology over time with follow up data up till 36 months[18;19]. Little is known about the follow up of inflammatory changes on MRI in knee OA[20].

Therefore, in this explorative study we assessed a set of US features in the course of time in order to identify the ones which might be more eligible candidates for long term prediction. Our goal was to identify the prevalence of distinct patterns (stable vs fluctuating) in a set of US features in a cohort of patients receiving standard multimodal treatment for knee OA at T=0, T=3 months and T=12 months.

PATIENTS AND METHODS

Study design

This prospective, study was carried out in the framework of a specialized knee- and hip OA outpatient clinic. All patients were treated according to a multimodal treatment protocol comprising education, physical therapy, step up analgesics (acetaminophen, non steroidal anti-inflammatory drugs, tramadol) and intra-articular injection with triamcinolonacetate and advice on weight reduction if indicated [21]. In this protocol, patients were followed up every 4 weeks in the first 3 months, after that, out-patient visits were planned yearly. The local Medical Research Ethics Committee, region Arnhem-Nijmegen (The Netherlands) approved the study design (study number 2009/095).

Patients

A total of 55 consecutive consenting patients fulfilling the American College of Rheumatology clinical criteria for knee OA[1] were included in our study. The symptomatic knee was appointed as index joint. If patients had bilateral knee OA the most symptomatic knee was selected. Exclusion criteria were: other rheumatic or severe orthopaedic diseases leading to inflammatory arthritis or secondary OA, co-morbidity exceeding the complaints or limitations of the knee OA, orthopaedic procedures planned within the next three months and cognitive or sensorimotor problems interfering with filling out questionnaires.

Data acquisition

On inclusion knee X-rays were collected. Weight bearing fixed flexion posterior-anterior radiographs were graded using Kellgren and Lawrence systematics (K&L) [1]. The patient was in standing position, knee flexed in 20-30 degrees, and feet internal rotated 10 degrees. At three time points (T0=inclusion, T1=three months,T2= twelve months), the US investigation was performed. At baseline clinical, demographic data and data on pain and analgesics were collected. Pain was assessed using a Numerated Rating Scale (NRS) from 0-10. The Knee injury and Osteoarthritis Outcome Score (KOOS) (Likert scale version)[22] was used as an instrument to assess the patients' opinion about their knee associated problems. KOOS scores were transformed in a way that 0 indicates no complaints and 100 indicates maximum complaints.

Ultrasonography

Ultrasonography was performed by a rheumatologist (KB) and a post-doc physician, who were trained in musculoskeletal US and previously involved in inter reader reliability research of the applied US protocol. Both investigators performed US on T0 and T1 (evenly distributed). For practical reasons (acceptance job offer elsewhere second investigator) KB performed all investigations on T2. The protocol is based on results of previous US studies (especially the OMERACT definitions) and pathophysiologic concepts of knee OA[5;6;10;23]. It focuses on two domains, comprising inflammatory (synovial hypertrophy, effusion and bursitis), and mechanical aspects (medial meniscus

protrusion, Baker's cyst and cartilage thickness). In a previous study, the protocol showed moderate to good inter observer reliability for all items except synovial hypertrophy[7]. To improve our results on synovial hypertrophy, we performed renewed calibration sessions in 5 patients with both investigators. Thereafter, 23 patients were blindly investigated by both assessors and interobserver agreement was calculated, yielding a new kappa value for synovial hypertrophy of 0.65. Overall, we managed to improve our interobserver agreement as new kappa values ranged from 0.59 for meniscal protrusion to 1.00 for Baker's cyst and effusion. For cartilage thickness, the minimal correlation coefficient was 0.74 (95% CI: 0.57-0.92) with difference of 0.12 (95 %CI limits of agreement :-0.67-0.91 mm). Clinical evaluation and US examination were obtained on the same day. The investigator performing US was unaware of clinical and radiographic results. The ultrasound machine used in this study was a MyLab 25 gold (Esaote Biomedica, Genoa, Italy) with a 35 mm linear transducer (frequency 8-15 mHz). The complete US investigation took about ten minutes per patient. The US protocol comprised the following items:

1. Effusion: a ≥ 4mm hypoechoic or anechoic intra-articular material that is displaceable and compressible in the suprapatellar recess, evaluated using a longitudinal scan with the leg in passive full extension[9].
2. Synovial hypertrophy: an abnormal hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible of ≥2mm in the suprapatellar recess, measured with the leg in full extension with a longitudinal scan[9].
3. Meniscal protrusion: protrusion of meniscal tissue out of the joint space >3 mm from the joint line, evaluated at the medial joint space with the knee in full extension with a longitudinal scan[10] (fig A).
4. Infrapatellar bursitis: an enlarged infrapatellar bursa (>2 mm) on both longitudinal and transverse scans with the knee in 45° flexion[10].

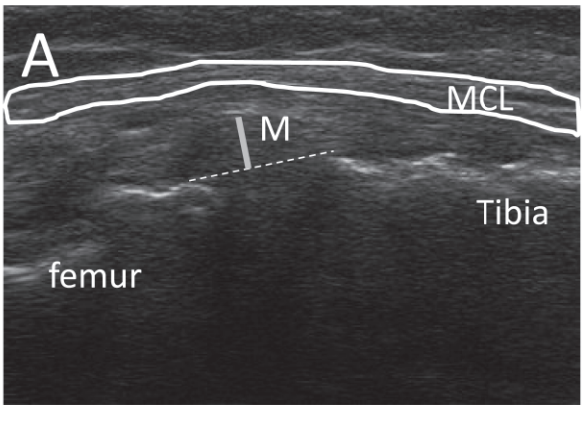

Figure A Meniscal protrusion (M)
Measured between the medial collateral ligament (MCL) and the joint space (dashed line).

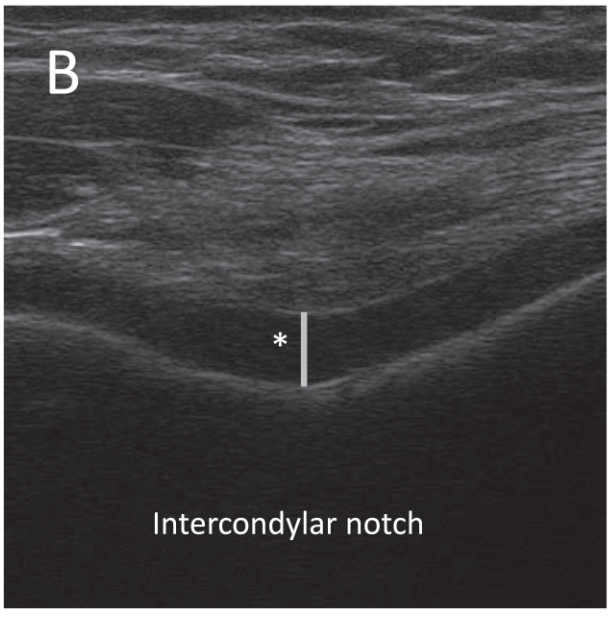

Figure B Cartilage thickness intercondylar notch
*=cartilage thickness

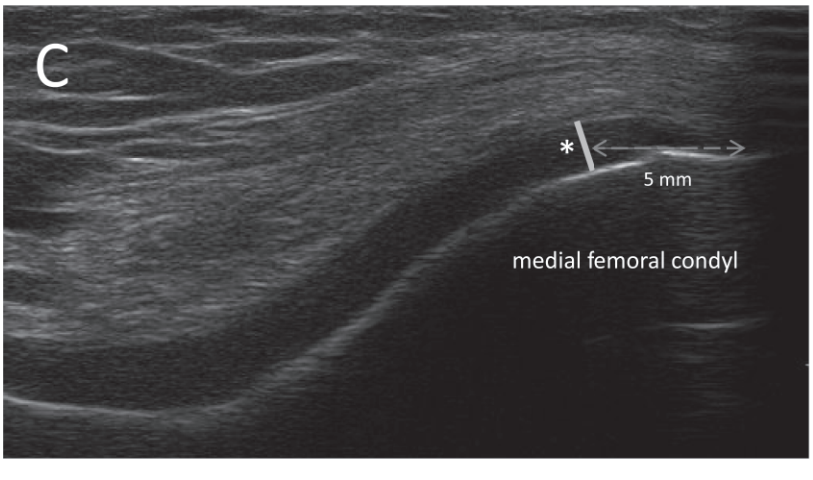

Figure C Cartilage thickness medial femur condyl
*=cartilage thickness

5. Baker's cyst: a hypo-anechoic area between the semimembranosus and medial gastrocnemius tendon examined with the patient in prone position on the dorsal/medial side of the fully extended knee applying a transverse and longitudinal scan. The maximum diameter was measured (mm) in a transverse plane.
6. Cartilage thickness: an anechoic band with sharp hyperechoic margins, measured perpendicular to the surface at the intercondylar notch (fig B) and at the medial (fig C) and lateral condyle (5 mm just medial or lateral from the top of the condyle), with the transducer immediately above the patella in a transverse plane and with the knee in maximum flexion. Because of the uneven distribution of cartilage over the femoral head we performed 3 measurements and calculated a mean value. Measurements were standardised in calibration sessions and interobserver reliability of these measurements was acceptable, with correlation-coefficients of 0.74-0.77.

Statistical analysis

In generating descriptive statistics, means, standard deviations and 95% confidence intervals were computed for continuous variables. Continuous baseline data were checked for skewness. For dichotomous variables frequencies and 95% confidence intervals according to the adjusted Wald method[24] were computed.

To examine the change of prevalence rates of US features in time we used Mc Nemar test for categorical variables and paired t-test for continuous variables, where appropriate. As effusion and synovial proliferation are considered to be expressions of the same pathophysiologic process, a composite inflammatory score was created which was considered to be positive if effusion and/or synovial proliferation were present at one time point. The course of US pathology with dichotomous outcome measures was described using distinct patterns. Because there are three dichotomous measurements in time, there are eight possible US patterns conceivable. Since we were interested in the stability of these features in time, we divided these patterns into stable and unstable (e.g. fluctuating or not). We appointed 2 patterns as stable (present(1,1,1) or absent (0,0,0) on all time-points). The 6 other patterns were appointed unstable in which 2 are arising/increasing (0,0,1/0,1,1), 2 are diminishing/disappearing (1,1,0/1,0,0) and 2 are random (0,1,0/1,0,1). To describe the individualized course of cartilage thickness, we calculated the proportion of patients which showed decrease or increase in two time frames (T0-T1 and T0-T2). Statistical analysis was performed using the statistical software package Stata10 (StataCorp, Texas, USA).

RESULTS

Study population

Baseline characteristics are displayed in table 1, revealing a typical knee OA cohort with predominantly women with moderate type OA according to radiographic K&L score.

Table 1 Baseline characteristics study population at inclusion

Patients (n)	55
Female (n,%)	35 (64)
Age (years) (mean,SD)	57 ± 8
BMI (kg/m^2) (mean,SD)	29 ± 7
Kellgren&Lawrence score	
0 (n,%)	7 (13)
I (n,%)	16 (29)
II (n,%)	17 (30)
III (n,%)	12 (22)
IV (n,%)	3 (6)
°NRS pain (mean, SD)(range)	5.9 ± 1.6 (2-9)
*KOOS (mean, SD)(range)	
ADL	48 ± 20 (2-100)
Pain	54 ± 17 (14-100)
NSAID users (n, %)	20 (36)
40 mg of intra-articular triamcinolonacetate (n,%)	29 (53)

°NRS: numerated rating scale (0-10) in which 0 indicates no complaints and 10 indicates maximal complaints
*Knee Osteoarthritis Outcome Score; function in daily living/pain: normalized data (0-100) in which 0 indicates no complaints and 100 indicates maximal complaints

Prevalence of US pathology / US patterns

The overall prevalence of US abnormalities in time is shown in table 2. Meniscal protrusion and Baker's cyst were common, whereas infrapatellar bursitis was rather rare. Most of the variation in prevalence of US features on a group level appeared in the inflammatory components (i.e. synovial hypertrophy and effusion). Synovial hypertrophy and the composite inflammatory score decreased significantly from T0-T2 (p-value 0.02 and <0.01 respectively). For presence of Baker's cyst, meniscal protrusion and infrapatellar bursitis, there is no significant change in the course of the year of follow up. Cartilage thickness increased significantly from baseline to 12 months; differences are 0.35mm, 0.29mm and 0.28mm ($p<0.05$) for the three locations, respectively.

In table 3 the course of prevalence of US pathology in time is shown in more detail for each US feature. 0 denotes absent, 1 denotes present. Of the eight conceived patterns, a and b are stable (marked in grey). The other patterns are unstable.

Nearly half of the patients (43%) shows any sign of inflammation (i.e. synovial hypertrophy and/or effusion) during the year of follow up. In the proportion of patients which do show inflammation at any time point, it turns out that both effusion and synovial hypertrophy are fluctuating features (effusion: e, g and h predominant patterns; synovial hypertrophy: e, f and h predominant patterns).

Table 2 Overall prevalence of US abnormalities at three time-points: T0: inclusion, T2: 3 months, T2: 12 months

	T0 (n=55)	T1 (n=49)	T2 (n=55)
Effusion			
n (%, 95% CI)	8 (15, 7-26)	7 (14, 6-24)	5 (9, 4-20)
Synovial hypertrophy			
n (%, 95% CI)	9 (16, 9-28)	3 (6, 1-15)	1 (2, 0-11)
*Composite inflammation			
n (%, 95% CI)	17 (31, 20-44)	9 (18, 9-28)	6 (11, 5-22)
Meniscal protrusion			
n (%, 95% CI)	36 (65, 52-77)	34 (69, 50-75)	38 (69, 56-80)
Infrapatellar bursitis			
n (%, 95% CI)	5 (9, 4-20)	2 (4, 3-13)	4 (7, 2-18)
Baker's cyst			
n (%, 95% CI)	19 (35, 23-48)	21 (43, 26-51)	22 (40, 28-53)
Cartilage thickness (mm)			
mean,SD (95% CI)			
Medial epicondyl	1.6 ± 0.5 (1.4-1.7)	1.7 ± 0.5 (1.6-1.9)	1.9 ± 0.5 (1.7-2.0)
Intercondylar notch	2.0 ± 0.5 (1.9-2.1)	2.1 ± 0.6 (2.0-2.3)	2.3 ± 0.7 (2.1-2.5)
Lateral epicondyl	1.7 ± 0.4 (1.6-1.8)	1.8 ± 0.4 (1.7-2.0)	2.0 ± 0.5 (1.9-2.1)

* Effusion and/or synovial proliferation
95% CI = 95% Confidence Interval

Infrapatellar bursitis does not occur in 84% of the patients at any time during follow up. All patients that do develop bursitis show instable prevalence patterns and bursitis was never consistently present at all time points.

Meniscal protrusion occurs at any time point in over 80% of the patients. Intermittent patterns are infrequent. Baker's cyst is a stable feature, displaying a stable pattern in 80% of the patients. In the remaining patients the majority of the patient develops a Baker's cyst during follow up.

Cartilage thickness measured by US increases in one year of follow up (table 2). Post hoc, individualized analyses of the proportion of patients with an increase in cartilage thickness showed a steady increase in both time frames (data not shown).

DISCUSSION

To our knowledge, this is the first study to systematically investigate US soft tissue abnormalities in the course of time in a cohort of patients receiving standardized multimodal treatment for knee OA.

Table 3 Number of patients with distinct US patterns in the course of one year (T0,T1,T2)

US patterns T0-T1-T2	Effusion (n,%, 95%CI)	Synovial hypertrophy (n,%,95%CI)	*Composite inflammation (n,%,95%CI)	Meniscal protrusion (n,%,95%CI)	Infrapatellar bursitis (n,%,95%CI)	Baker's cyst (n,%,95%CI)
a.0 - 0 - 0 stable	42 (76, 64-68)	43 (78, 65-87)	28 (57, 43-70)	9 (16, 9-28)	46 (84, 72-91)	29 (53, 40-65)
b.1 - 1 - 1 stable	3 (6, 1-15)	0 (0, 0-8)	3 (6, 1-17)	27 (49, 36-62)	0 (0, 0-8)	15 (27, 17-40)
c.0 - 0 - 1 increasing	1 (2, 0-10)	1 (1.8, 0-11)	2 (4, 0-14)	4 (7, 2-18)	3 (5, 1-15)	2 (4, 3-13)
d.0 - 1 – 1 increasing	0 (0, 0-8)	0 (0, 0-8)	0 (0, 0-8)	4 (7, 2-18)	1 (2, 0-11)	2 (4, 3-13)
e.1 - 0 – 0 decreasing	4 (7, 2-18)	8 (15, 7-26)	9 (18, 10-32)	4 (7, 2-18)	4 (7, 2-18)	0 (0, 0-8)
f.1 - 1 – 0 decreasing	0 (0, 0-8)	1 (2, 0-11)	3 (6, 1-17)	2 (4, 3-13)	1 (2, 0-11)	1 (2, 0-11)
g.1 - 0 - 1 random	1 (1.8)	0 (0, 0-8)	1 (2, 0-12)	3 (5, 1-15)	0 (0, 0-8)	3 (5, 1-15)
h.0 - 1 – 0 random	4 (7, 2-18)	2 (4, 0-13)	3 (6, 1-17)	2 (4, 3-13)	0 (0, 0-8)	3 (5, 1-15)

Total number of patients n = 55
: stable patterns
0 = absent
1 = present
* Effusion and/or synovial proliferation
95% CI = 95 % Confidence Interval

Although supportive pharmacologic treatment was given to this cohort, this is typical for OA patients and the cohort is comparable with other active Knee OA cohort with respect to treatment.

We showed that the prevalence of inflammatory features like effusion and synovial hypertrophy show a fluctuating pattern in time in contrast to meniscal protrusion and Baker's cyst, which are more stable. Of all assessed US pathology, inflammation seems to be the only feature that declined consistently in the year of follow up after treatment. Because information about soft tissue structures is likely to contribute to the body of knowledge on OA and because of the attractive profile of US (harmless, inexpensive and non time-consuming), this study contributes to knowledge about the positioning of this tool in research on OA. Based on our results, meniscal protrusion and Baker's cyst might be useful in studies for long term prediction of clinical or radiological outcome, whereas effusion and synovial hypertrophy and infrapatellar bursitis seem more momentary phenomenon.

Comparing our results to the limited previous research available in this field, our study shows comparable prevalence figures on Baker's cyst[15;17]. These studies also show persistent presence on US, even after intra-articular injection/arthroscopic surgery. Our data show comparable results to former US studies which showed decrease of inflammation after intra-articular hyaluronic acid injection. In a study on follow up of inflammation detected with US in hand OA, a similar decline was observed after 3 months of conservative treatment [25]. The decrease in our study could very well be a result of the natural course of the disease. It might also be a treatment effect as all patients received standardized multimodal treatment which included non steroidal anti-inflammatory drugs (NSAID) and intra-articular glucocorticoid injection in half of the patients.

Meniscal protrusion seemed to fluctuate somewhat more than expected based on pathophysiologic concept of the nature of meniscal protrusion and previous research which suggests gradual increase of meniscal pathology over time[18;19]. Although the majority of patients show a stable pattern, a third of our patients showed fluctuation in time. One might hypothesize that it is possible for a medial meniscus to be slightly changed in position depending on weight, effusion etc. Furthermore, comparison with previous research is hampered by the difference in follow up time (3 years follow up vs one year in our study) and difference in imaging modality (MRI vs US).

Much to our surprise, cartilage thickness seemed to increase in this cohort in the course of one year. This is contradictive with current views that expect cartilage thickness to decrease in time, as cartilage thickness increase has only been reported thus far after treatment with joint distraction [26], and has not been observed after conservative OA treatment. However, we have no other satisfying explanation for our findings. A chance finding seems unlikely because the same significant magnitude of change is consistently seen in all three measured domains and between the different time points. In recent years it has become clear that visualising femoral cartilage with US is known to have various difficulties: 1. Uneven distribution over the femoral head 2. Positioning of the probe with repeated measurements 3. Loss of the sharpness of the cartilage border in the process of degeneration, which hampers precise measurement 4. The alteration of aspect of the cartilage (increase of hyperechogenity) in the process of degeneration which should be taken into account. Unfortunately, a lot of the detailed information about the pitfalls (and

possible solutions) on US measurement of cartilage [27;28] was not available at the time of the development of the protocol. It is possible that our measurements do not represent absolute cartilage thickness, but they still tell us something about the course in time, which is what we aimed for.

We considered the possibility that a systematic error was introduced by having all measurements on T2 performed by one investigator and all measurement before that by two randomly assigned investigators. The fact that results of the first and second time frame do not differ substantially, makes this an unlikely explanation. In this study, cartilage thickness was not our main focus as inflammation and structural changes like Baker's cyst might be even more important features in knee OA. Cartilage thickness, however will be subject of future US research in an attempt to verify or falsify our current findings.

Our study has some limitations, including the limited number of patients, length of follow up, number of US time points and the choice of US features. A larger number of patients would have enabled us to give more precise estimates. More frequent US investigation could have provided more insight in how long some abnormalities are present and if they might disappear and reappear in a certain time frame. Furthermore, assessment of long term degenerative characteristics (i.e. cartilage thickness, meniscal protrusion) would have benefitted from more prolonged follow-up. Concerning our US protocol, it would possibly have been of value to include osteophytes, because US has proven to pick up small osteophytes, which can be a very early sign of OA, more sensitively than plain radiography. However, at the time of the selection of the US items, no widely accepted protocol to systematically investigate knee osteoarthritis with US was available. We chose to include mechanical features: meniscal protrusion, Baker's cyst and cartilage and excluded osteophytes because these can be visualised using plain radiography. We aimed for features that are not visualised by plain radiography and focused on soft tissue instead of bony parts.

We were aware of the fact that correlation with MRI would have strengthened the construct validity of our results. On the other hand, correlation between US and MRI for the items studied in our cohort has been investigated before and has shown satisfying results[5]. Secondly, we were interested in practical, feasible protocol, with limited costs and patient burden and felt that previously demonstrated validity of US features was sufficient to address the course in time.

In conclusion, our study gives insight in the prevalence and typical course of US abnormalities in patients with knee OA. It shows that inflammation is a momentary phenomenon and can decrease in the course of follow up and that Baker's cyst and meniscal protrusion are stable features which possibly are more eligible candidates for long term prediction.

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6

ULTRASONOGRAPHIC PREDICTORS FOR CLINICAL AND RADIOLOGICAL PROGRESSION IN KNEE OSTEOARTHRITIS AFTER 2 YEARS FOLLOW UP

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ABSTRACT

Objectives The aim of this study was to investigate the association between a set of Ultrasound (US) features and radiographic and clinical progression of knee Osteoarthritis (OA) after two years of follow up.

Methods A total of 125 patients fulfilling American College of Rheumatology clinical criteria for knee OA underwent US examination of the most symptomatic knee. The US protocol included assessment of synovial hypertrophy, joint effusion, infrapatellar bursitis, Baker's cyst, medial meniscus protrusion and cartilage thickness. Clinical progression was defined using the inverse OARSI responder criteria or progression to total knee replacement. Radiologic progression was defined as a 2-point or more increase in Altman score or progression to total knee replacement. Regression analyses were performed with baseline US features as independent variables and progression (two separate models for clinical progression and radiographic progression) as dependent variable.

Results A total of 31 (25%) patients fulfilled the criteria of clinical progression and 60 (48%) patients fulfilled the criteria of radiologic progression. Presence of Baker's cyst showed a statistically significant association with clinical (OR: 3.07; 95% CI: 1.21 – 7.78) as well as radiological (OR: 2.84; 95% CI: 1.17 – 6.90) progression. Synovial hypertrophy showed a weaker but consistent association with clinical- as well as radiologic progression (OR: 2.11; 95% CI: 0.80 - 5.57).

Conclusion We demonstrated a longitudinal association between Baker's cyst (and to a lesser extent synovial hypertrophy) at baseline and radiological and clinical progression after two years.

INTRODUCTION

Pathophysiology of osteoarthritis (OA) is not completely understood and so far, no disease modifying drugs are available[1, 2]. In general, the disease is known to show a gradual progression[1], although large differences exist between patients. Because of the heterogeneous nature of OA progression, recent research has focused on factors predicting progression. Identifying patients with progression might help identify patients at risk for rapid worsening and direct future research on therapeutic interventions

Several factors have shown to be associated with progression of knee OA including age, presence of OA in multiple joints, Body Mass Index (BMI) and the degree of radiographic OA [3]. However, radiography only visualizes structural damage in bone and cartilage. As OA is known to affect the entire joint including soft tissue structures, structural changes in these tissues might theoretically predict progression as well.

Ultrasonography (US) is, in contrast to conventional radiography, able to visualise these (peri)articular soft tissue structures and it has shown to be more sensitive than clinical examination[4]. Compared to Magnetic Resonance Imaging (MRI), which is also capable of sensitively imaging soft tissue structures, it is very practical, inexpensive and less time consuming.

US in knee OA has shown good construct validity[5, 6] and moderate to good interobserver reliability[7, 8]. Therefore, US might be an attractive prediction tool both in research and clinical practice.

So far, data on the predictive value of US features for progression in knee OA are sparse. One study found an association between effusion detected by US and subsequent knee replacement after three years[9], suggesting that inflammation might be associated with disease progression. The aim of the current study was to investigate the association between a set of US (inflammatory and mechanical) features and radiological and clinical progression of knee OA after two years of follow up.

PATIENTS AND METHODS

Study design/patients

This prospective, observational study was carried out in the framework of a specialized knee- and hip OA outpatient clinic where patients are treated according to a multimodal treatment protocol [10]. Consecutive patients visiting the outpatient clinic between May 2010 and May 2011 with complete US investigation at baseline and available data on knee replacement or radiologic outcome at 2 years were eligible for inclusion in this study. All patients fulfilled the American College of Rheumatology clinical criteria for knee OA[11]. At inclusion, demographic and clinical data were collected.The local Medical Research Ethics Committee, region Arnhem-Nijmegen (The Netherlands) approved the study design (study number 2009/095).All patients signed for informed consent.

OUTCOMES

Radiological progression

On inclusion and after 2 years, weight bearing fixed flexion posterior-anterior radiographs were collected. On X-rays, joint space narrowing (JSN) and osteophytes in the index knee were graded using the Osteoarthritis Research Society International (OARSI) atlas in both tibiofemoral and patellofemoral joints (both graded 0–3; total scores JSN: 0-6 osteophytes: 0-12)[12]. Also knee radiographs were graded using Kellgren and Lawrence (K&L) systematics[13]. Radiological progression was defined by at least a 2-point score increase in sum JSN score or osteophyte score or at least 1-point score increase in both domains over 2 years or progression to total knee replacement.

Clinical progression

Western Ontario and McMaster University Arthritis Index (WOMAC)[14] was used as the primary patient reported outcome measure. Pain and function scores were transformed in a way that 0 indicates no complaints and 100 indicates maximum complaints. Also Patient Global Assessment (PGA) on a numerical rating scale from 0 – 10 was recorded.

Clinical progression was defined, by lack of validated worsening criteria in knee OA, using inverse OARSI responder criteria[15]: a minimum of 50 % and 20 points (absolute) increase in pain; **or** a minimum of 50 % and 20 points (absolute) decrease in function ; **or** worsening in 2 out of 3 domains (Pain, function, PGA) of 20% and 10 points (absolute). Patients who underwent total knee replacement during follow-up were also classified as clinical progressor.

Ultrasonography

Ultrasonography was performed by a rheumatologist (KB) and a post-doc physician, who were trained in musculoskeletal US and previously involved in inter reader reliability research of the applied US protocol[7, 16]. The investigator performing US was unaware of clinical and radiographic results. The ultrasound machine used in this study was a MyLab 25 gold (Esaote Biomedica, Genoa, Italy) with a 35 mm linear transducer (frequency 6-18 mHz). The US protocol comprised the following items: Effusion (≥4mm), synovial hypertrophy (≥2mm), meniscal protrusion (>3mm), infrapatellar bursitis, Baker's cyst and cartilage thickness (mm). Besides cartilage thickness, all items were scored dichotomously.

Statistical analysis

Data were checked for missings and assumptions of normality. Descriptive statistics were computed; means and standard deviations or median and interquartile range for continuous variables if appropriate.

To examine the associations between US features and progression we performed a series of logistic regression analyses with US features as independent variables and progression as dependent variable (2 separate models for radiographic an clinical progression).

Infrapatellar bursitis was not included in the regression analyses because of the very low prevalence (6%) of this US feature that renders an unstable regression model.

For the regression analyses the following steps were taken. First, unadjusted logistic regression analyses were performed to examine the association between US features (i.e., effusion, synovial hypertrophy, meniscal protrusion, Baker's cyst and cartilage thickness) and progression. Second, for the US features that showed an univariate association with progression possible confounding was examined. Potential confounders were age, gender, BMI, duration of complaints, analgesics, WOMAC function, and KL- score. WOMAC pain as potential confounder was dropped because of collinearity (r = .82 between WOMAC pain and WOMAC function). Third, potential confounders were retained in the final adjusted model if the regression coefficient of the main effect (US feature) in the regression model changed by at least 10% when adding the potential confounder to the model using forward selection approach. All steps were performed for clinical as well as radiologic progression.Statistical analyses were performed using the statistical software package Stata10 (StataCorp, Texas, USA).

RESULTS

A total of 125 patients fulfilling the in- and exclusion criteria were included in our study. Clinical data were missing in 10 patients (8%). Baseline characteristics are shown in table 1.

Clinical and radiological progression

A total of 31 (25%) patients fulfilled the criteria for clinical progression, 60 (48%) patients fulfilled the criteria for radiological progression and 26 patients (21%) fulfilled both criteria. 60 patients (48%) did not fulfill any progression criterion

Regression analyses

The results of the final regression analyses are shown in table 2.

US presence of Baker's cyst at baseline shows a statistically significant association with clinical, as well as radiological progression. For synovial hypertrophy a large but non-significant association with clinical and radiological progression was found.

Table 1 Baseline data; clinical, US and radiographic data of study participants

Population (n)	**125**
Age (years) (mean, SD)	57 ± 9.4
Gender female (n, %)	68 (54%)
Body Mass Index (kg/m^2) (mean, SD)	27.8 ± 7.8
Duration of complaints	
(years) (mean, SD)	8.7 ± 10.0
*WOMAC	
pain (mean, SD)	52.6 ± 16.8
function (mean, SD)	51.5 ± 18.4
#Altmann score	
Joint space narrowing (mean, SD)	1.6 ± 1.3
Osteophyte score (mean, SD)	4.1 ± 2.9
Kellgren & Lawrence score	
(0-4) (mean, SD)	1.9 ± 1.1
US pathology	
Effusion (n, %)	21 (17%)
Synovial hypertrophy (n, %)	27 (22%)
Meniscal protrusion (n, %)	79 (63%)
Infrapatellar bursitis (n, %)	8 (6%)
Baker's cyst (n, %)	33 (26%)
Cartilage thickness (mm) (mean, SD)	2.0 ± 0.4

*WOMAC score: normalized data (0-100) in which 0 indicates no complaints and 100 indicates maximal complaints
Altmann score: total scores Joint Space Narrowing: 0-6 Osteophyte score: 0-12

Table 2 Multivariate associations (adjusted for confounders) US features and radiologic/ clinical progression

	Radiologic progression			**Clinical progression**		
Variable	**Odds ratio**	**P-value**	**95% CI**	**Odds ratio**	**P-value**	**95% CI**
Effusion	2.39	0.11	0.82 - 6.97	#	#	#
Synovial hypertrophy	2.11	0.13	0.80 - 5.57	2.11	0.13	0.80 – 5.57
Baker's cyst	2.84	0.02*	1.17 – 6.90	3.07	0.02*	1.21 – 7.78

*Statistical significant ($p<0.05$)
#not retained in the final model

DISCUSSION

In this study we demonstrated an association between Baker's cyst on US investigation at baseline and clinical and radiological progression in knee OA after 2 years of follow up.

To our knowledge we are the first to establish this particular association. Previous research has shown inflammatory aspects detected with US to be associated with disease progression[9]. One could hypothesize that synovial proliferation and Baker's cyst are both expressions of the same inflammatory process. Effusion and synovial proliferation are more fluctuating in time as opposed to Baker's cyst which is a very stable feature[16]. Perhaps Baker's cysts emerge during inflammatory episodes but do not disappear after inflammation diminishes and are therefore a marker for past inflammation as well. Because of its stability, Bakers's cyst seems to be a more feasible predictor for long term follow up than other inflammatory features. Also, visualizing Baker's cyst with US is a very practical, non-time-consuming, non-invasive procedure which shows excellent interobserver reliability[7, 8] and construct validity[17, 18].

Our study has some limitations. Mylab 25 is technically not a high end US machine. One could argue that more technically developed machines with larger screens might provide more detailed and clearer images, which might contribute to the sensitivity of the imaging. However, for the purpose of this study, we think that the current machine is very well capable of reliably visualising the presence of the pathology of interest in this study.

The US protocol could be questioned with respect to measurement of effusion. Effusion occurs in multiple compartments of the joint. By measuring these features only in the suprapatellar recess with the leg in passive full extension might not have enabled us to visualize this to its full extent. So far no validated protocol exists to measure effusion with US. We aimed for a very practical, easily reproducible protocol which in retrospect, might have led to somewhat underestimation of the total amount of effusion and theoretically to a (false) absent association between effusion and progression.

As patients in this cohort received multimodal treatment protocol comprising non-steroidal anti-inflammatory drugs and intra-articular injection with triamcinolonacetate if indicated, one could argue that the effects that are observed are treatment effect and not merely the natural course of OA. However, no disease modifying therapy for OA is available, and current therapy recommendations consist of multimodal treatment for pain relief and maintenance of function only. Moreover, a definite relationship between anti-inflammatory therapy and decrease in inflammation on US/MRI and a subsequent decrease in inflammation and clinical improvement in OA has not been demonstrated yet. Also, intra-articular glucocorticoids are known to have a rather short lived effect and are unlikely to affect clinical outcome at two years. On top of that, the fact that analgesic use did not turn out to be a confounder of the association between US pathology and progression, militates against the idea that medication use could be associated with improvement of inflammatory features. Also, the arguments mentioned above only apply to clinical progression and not to radiological progression which is not influenced by medication. So overall, we think that the observed associations are valid for the more or less natural course of knee OA and that the cohort is comparable with other active Knee OA cohort with respect to treatment.

In conclusion, we demonstrated a clear, large and consistent association between Baker's cyst on US and radiological and clinical progression after two years in established knee OA, and to a lesser extent for synovial hypertrophy. This finding needs confirmation, but US aassessment of these features might be a candidate to help define knee OA patients with worse prognosis which can be useful in research as well as daily clinical practice.

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7

SUMMARY AND DISCUSSION

Summary

In this thesis, some aspects of the value of the imaging modality ultrasonography(US) to study knee osteoarthritis(OA) are investigated. The knee is one of the most frequently involved sites in OA [1]. As pathophysiology of OA is known to be rather complex and so far, only partly understood, there is a need for improvement of imaging modalities to help understanding pathophysiology of complaints, finding markers for progression and target possible treatment options[2, 3]. As OA is not merely a disease of cartilage but of the entire joint including bone and soft tissue structures[4] and because US is a feasible tool to visualise these soft tissue structures[5-7], the aim of this thesis is to examine to what extent US can contribute to the knowledge on pathophysiology of pain, the course of multiple tissue pathologies and prediction of short term effect after treatment, and long term progression in knee OA.

In **chapter two**, we assessed inter-observer reliability of ultrasonography features following a self-developed standardized protocol. Meniscus protrusion and Baker's cyst were the most prevalent features (68% and 26% respectively). Inflammation was less common, yielding prevalence rates of 12% for effusion and 8% for synovial proliferation. Infrapatellar bursitis was however rare (3%). Cartilage thickness (mean ± SD) was 1.93 (0.54) mm (range 0.0 – 3.8) at the medial condyle, 1.99 (0.59) mm (range 0.0 – 3.6) at the lateral condyle and 2.47 (0.68) mm (range 1.6 – 5.0) at the intercondylar notch. Inter-observer agreement (kappa value) was moderate for protrusion of the medial meniscus (0.54), good for infrapatellar bursitis (0.66) and effusion (0.74), excellent for Bakers' cyst (0.85) and initially poor for the detection of synovial hypertrophy (-0.08). Inter-observer reliability was good for the measurement of medial meniscus protrusion (correlation coefficient 0.80, 95% limits of agreement -1.93 to 1.94 mm) and cartilage thickness (correlation coefficient 0.62 and 0.68, 95% limits of agreement -0.87 to 0.84 mm and -0.77 to 0.96 mm at the medial and lateral condyle respectively). So, this study demonstrated overall good reproducibility of US in the assessment of the majority of the investigated soft tissue pathology in knee OA.

To improve our initially disappointing results on synovial hypertrophy, we performed renewed calibration sessions in 5 patients with both investigators. Thereafter, 23 patients were investigated by both assessors, leading to an improved inter observer agreement of synovial hypertrophy of 0.65. Overall, we managed to improve our inter observer agreement as new kappa values ranged from 0.59 for meniscal protrusion to 1.00 for Baker's cyst and effusion. This made the protocol suitable to be used in following knee OA studies.

In **chapter three,** the results of the analyses of cross-sectional association between soft tissue pathology (US features) and pain are described. In this observational study 180 patients were included. To evaluate the association between US features and pain (Numerated Rating Scale (NRS) from 0-10 and the Knee injury and Osteoarthritis Outcome Score (KOOS) subscale pain)[8], regression analyses were performed. No association between US features and the level of knee pain was found.

In **chapter four** the focus is on the possible predictive value of US for the short term effect on pain of intra articular injection with triamcinolonacetate. At 4 weeks, 42% of

the 62 study participants responded to the injection (NRS ≤4), an effect comparable to the effects described in the existing literature[9]. Regression analyses revealed however no predictive value for any of the evaluated US features, including those reflecting inflammation.

In **chapter five** we demonstrated that the percentage of patients showing inflammatory features like effusion and synovial hypertrophy at one or more of three time points during one year of observation is over 40%. However, the course of US features show fluctuating patterns. Furthermore, of assessed US pathology, inflammation seemed to decline consistently in the year of follow up and, unexpectedly, cartilage thickness increased in all time frames. Meniscal protrusion and Baker's cyst are relatively stable features, which makes them more suitable in studies for long term prediction of clinical or radiological outcome.

Finally, prediction of clinical and/or radiological progression by means of US in knee OA was the objective of the study in **chapter six**. A total of 31 (25%) patients fulfilled the criteria of clinical progression and 60 (48%) patients fulfilled the criteria of radiologic progression. Presence of Baker's cyst showed statistically significant associations with both clinical (OR: 3.07; 95% CI: 1.21 – 7.78) as well as radiological (OR: 2.84; 95% CI: 1.17 – 6.90) progression. Synovial hypertrophy showed a weaker but consistent association with clinical as well as radiologic progression (OR: 2.11; 95% CI: 0.80 - 5.57). These inflammatory variables might be candidate features to help identify knee OA patients with worse prognosis and could contribute to phenotyping patients on basis of structural pathology.

DISCUSSION

In this section, the following 5 important aspects of our research on US in knee OA are discussed:

1. Possibilities and limitations of US
2. Methodological considerations
3. US protocol item selection
4. Pathophysiology and pain
5. Prediction of progression

1. The possibilities and limitations of US

US holds promise as an attractive imaging tool. Because of its favorable safety profile and feasibility in performance, its use is established and/or emerging in many fields of medicine. With development of new and technically high end machines it is possible to identify small detailed features inside the body. It provides the physician with an extra sense, a way to take a look inside the body as an extension of physical examination, which can easily be incorporated in daily clinical practice. There are some issue however we will discuss here.

Agreement

Although promising at first sight, the Achilles heel of US, hampering its use in some parts of medicine remains the operator dependency and subsequently, difficulties with standardization. This is unfortunately also true for musculoskeletal US. With MRI and conventional radiography for example it is easier to produce and reproduce exact standardized settings than in grey scale US. This is also demonstrated in studies in which observer agreement is usually far better when looking at a frozen frame than with active dynamic scanning [10].

Testing intra observer agreement of US in knee OA might therefore also be of importance, but is not without difficulties. An approach would be performing the US and produce static images, which can be interpreted multiple times by the same reader. However, this would not allow to assess the reproducibility of the actual dynamic scanning which is the essential part of US investigation, and would thus lead to inflated agreement scores [10]. Alternatively, the same patient should be scanned twice by the same investigator. Precautions have to be taken then to ensure that the investigator remains blinded, as he/she is likely to remember the patient and the scanned pathology, again resulting in spurious high agreement. Because of the reasons mentioned above, and as inter observer agreement incorporates both the intra- and inter components of variation, we decided to refrain from intra observer agreement tests.

Inter observer agreement in our protocol showed satisfying results for the purpose of the studies, but was only moderate for some items (initially even insufficient for synovial hypertrophy), confirming previous findings in the literature [11-13]. Although more standardized conditions and more intensive calibration and training can enhance reproducibility of those items [13], this would at the same time reduce compatibility with daily clinical practice and hamper generalizability. So, for research purposes it might be useful to put extra effort in agreement improvement for those items with moderate agreement so far. For daily practice one could also choose to focus on those items with already good agreement.

Volume effects and quantification

As US produces two dimensional images, to visualize a structure to its full extent, several cross cuts have to be made. Differences between these cuts can result in low agreement due to volume effects, and standardization is not easy to obtain. For example, US is capable of demonstrating synovial hypertrophy and effusion in the knee and shows proper criterion validity[6]. However, it appears in multiple compartments of the joint, and therefore several attempts have been made to standardize the exact method to perform the measurement, with varying results [5, 14-16].

Measurement of cartilage thickness with US is known to have several difficulties as well: 1. Uneven distribution over the femoral head 2. Different positioning of the probe with repeated measurements. 3. Loss of the sharpness of the cartilage border in the process of degeneration, which hampers precise measurement. 4. The alteration of aspect of the cartilage (increase of hyperechogenity) in the process of degeneration [17, 18]. To be informed about the articular cartilage as a whole, volumetric measurements are probably more accurate, but are impossible to perform with conventional US. New US

machines have possibilities for 3D probes, but could offer only a partial solution for this particular problem, because in vivo it is not always possible to position the patient in a way that all cartilage is within the reach of the US beam.

In this thesis, the matter of possible incomplete measurements of synovial hypertrophy and effusion might have contributed to a (false) negative association with pain and possibly between effusion and progression. Also, the increase- instead of decrease of cartilage thickness mentioned before might be caused by some of the problems with repeated cartilage measurement

Based on these findings, we would recommend to focus on those US items that are prevalent, show high inter observer agreement after limited education and calibration, and can be classified as either present or absent without need for quantification, like for example Baker's cyst.

2. Methodological considerations

Number of patients, assessments and follow up time

For the majority of our studies the number of patients was sufficient to render results with adequate precision. However, our study on prediction of effect of intra-articular glucocorticoids could have benefitted from a somewhat larger sample size to be able to give more precise estimates of the covariate for especially infrapatellar bursitis.

Regarding the number of assessments, one could argue that the study on follow up of US features could have been improved on by using more frequent measurements, particularly from pathophysiologic viewpoint. More frequent sampling would have allowed to answer questions like: does inflammation fluctuate on monthly or perhaps even weekly basis? However, fluctuation could be demonstrated for some variables using our limited number of observations. Also, the most important US variable, Bakers cyst, was found to be stable and was indeed correlated with outcome, and it is therefore unlikely that Bakers cyst change from present to absent in between observations. Follow up of soft tissue pathology during one year shows inflammation to gradually decrease and, surprisingly, cartilage thickness to increase. As for inflammation, this might be caused by regression to the mean as patients were included when they experienced complaints, or may be due to an effect of medication. The increase in cartilage thickness is unexpected and difficult to explain. Although the most common causes of bias seem unlikely in this case, this finding is still contradictive with current views that expect cartilage thickness to decrease in time. Of note, some technical issues regarding US cartilage measurement will be discussed later. For both items, prolongation of US follow up might answer some of the questions that arise. Especially for cartilage thickness, adding possibilities for testing criterion/construct validity (eg histology from samples after knee replacement or MRI) would be desirable.

Patient selection

For generalizability of the study results, selecting the right patients is of paramount importance. The majority of patients enrolled in this cohort was referred by orthopaedic surgeons (tertiary referral) because patients had complaints of knee OA, but knee replacement was not considered warranted at the moment. This led to a selection of patients with rather high pain levels and moderate radiographic damage which might not

be representative for the general OA population. However, by comparing this cohort to other large OA cohorts, we found very similar radiographic scores at inclusion[19]. Also, they are representative for referrals to secondary care as all patients were referred by their primary physicians in the first place. All patients did fulfil ACR criteria for clinical knee OA. Therefore, we feel that a relevant sample of patients was included in our studies in general, thus resulting in generalizable results.

However, our somewhat selected patient group could present a problem when interpreting the results of our study assessing cross sectional association of US features with pain, as our patients have similar pain levels, but less radiographic damage compared to those in other studies on US and pain [7, 20-22]. This could be a reason for false negative results in two ways.

First, this selection might have led to overrepresentation of patients with other origins of pain, which cannot be captured by US (for example bone marrow lesions, locoregional pain syndrome due to central sensitisation), which in turn could lead to underestimation of a possible association between soft tissue pathology and pain.

Secondly, this selection led to a very homogeneous patient group with lack of contrast in the outcome measure pain, which again can lead to underestimation of the association between US features and pain (a variant of Neyman incidence prevalence bias). This could have been corrected when also OA patients were included with low/no pain. But when selecting patients in secondary care, this will usually be patients with pain, as OA patients without pain are not likely to seek medical help.

However, although the found absence of a relation between US features and pain can be a false negative finding, the conclusion that it does not seems of value to investigate the cause of Knee OA pain with US in patients in secondary care remains valid.

Validity of US

Validity is an essential aspect of any good measuring instrument. Although, criterion- as well as construct validity has been investigated for musculoskeletal US and has shown satisfying results, these studies are not numerous and not all items in our protocol have been studied extensively. Therefore, corroboration of our US data with MRI findings could have strengthened the construct validity of our results, as MRI is less assessor dependent and is able to visualize small details more systematically. Other modalities that could render more validity to the US findings would for example be analyses on synovial tissue (needle biopsy), or even full joint pathology analyses including bone and cartilage (obtained after total knee replacement). These approaches might be pursued in the future, especially with regard to cartilage thickness.

3. Ultrasound protocol item selection

An important issue when developing an US protocol is item selection. As mentioned, and now more formally. we aimed to include items with the following characteristics: 1/ can be visualized using US with good inter reader agreement after limited training, 2/ are prevalent in relevant knee OA population, 3/represent all domains of pathophysiology and anatomy in Knee OA 4/ that cannot be easily assessed by physical examination or plain radiography.

Of all bursae and tendons in the knee, infrapatellar bursitis was included in the protocol to visualise more localized and focal stress related inflammation, because it cannot be detected with clinical examination and it seemed a clinically relevant problem associated with knee OA based on literature available at the time. However, considering the very low prevalence of this item in our studies, it seems unlikely that it plays an important role in pathophysiology or pain in knee OA. Therefore, it seems logical to exclude this item from a new US protocol to investigate knee OA.

After deliberation, we decided not to include bony structures in our protocol because we were mainly interested in soft tissue pathology, which could not be visualised by conventional radiography. However, it is becoming more and more clear that US is able to visualise even very small osteophytes[23], and these might be promising parameters to study the course and prognosis of OA, as they are likely to be a stable feature. Furthermore, bone seems to play an important role in the process of OA in at least a subset of patients [24]. Therefore, it could be worthwhile to expand our studies with US assessment of osteophytes.

4. Pathophysiology and pain

Because pain is a hallmark feature of OA and responsible for a substantial part of disability and working impairment, focus of research on this topic is justified. Pathophysiology of pain in OA is known to be very complex. Mechanical, structural, inflammatory, bone related, neurological and psychological factors play a role in the process that results in painful knee OA[25]. US visualisation of soft tissue pathology, could theoretically shed some light on the role these factors play in the process of pain. However, the evidence for their role is sparse. So far, signs of inflammation (effusion, synovial hypertrophy and Baker's cyst) seem to be the most promising candidates [20, 21, 26]. This has, however, been more consistently demonstrated in MRI studies than US studies [27]. In this thesis, no association between US features and pain was found, and inflammation on US did not predict analgesic effect of intra-articular glucocorticoids. Considering the possibly small contribution of soft tissue pathology to pain and the difficulty with standardizing and quantifying US features reflecting inflammation, our results do not warrant future research on the association of US features with pain in established knee OA patients. If we would regard our results on absence of association between US inflammation and pain to be legitimate and a not false negative finding, this would leave us with a difficult issue. As aspects of inflammation (synovial hypertrophy and Baker's cyst) were found to be predictors for clinical deterioration, these variables should also be expected to be associated with pain, as pain is an essential aspect of clinical worsening. A possible explanation could be that inflammation does not cause pain directly, but in the course of time possibly via intermediate processes like for example central sensitization, or due to cartilage and bone destruction due to inflammation. Unraveling the relationships between pain, inflammatory signs and progression of OA, either clinical or radiological should be subject of further research.

5. Prediction of progression

Because of the heterogeneous nature of the disease with regard to clinical and radiological progression, recent research has focused on factors predicting progression. Identifying patients with high risk for progression might help to direct future research on therapeutic interventions and identify patients at risk for rapid worsening of complaints and functional capacity.

As presence of Baker's cyst (and to a lesser extent synovial proliferation) were associated with worse radiological and clinical prognosis after two years, visualising these two items with US to select patients with worse prognosis might be a promising application of US in knee OA. Interestingly, the only previous research on the predictive value of US in knee OA has shown that effusion is a predictor for subsequent knee replacement (as a proxy for disease progression). Baker's cyst was not assessed in this study. One could argue that both studies are in favor of the idea that inflammation predicts progression. Synovial proliferation, effusion and Baker's cyst might be interrelated, and both expressions of the same inflammatory process. Effusion and synovial proliferation are more fluctuating in time as opposed to Baker's cyst which is a very stable feature[28]. One could speculate that a Baker's cysts emerge during inflammatory episodes (like in inflammatory arthritis) but do not disappear after inflammation diminishes and are therefore a marker for past inflammation as well Unfortunately, we could not reproduce the association with effusion. This might be explained by our possibly incomplete measurements on effusion or differences in outcome variable and patient selection.

As this has not been demonstrated before we feel it would be desirable to reproduce our findings, preferably making use of more validated worsening criteria. This because in our study, due to lack of validated criteria, we defined our own OA worsening criteria based on sparse literature on this topic [19, 29-31]. Although our criteria seem to have adequate face and content validity, we feel that our results would be even more compelling with validated outcome measures.

In conclusion: as US is more sensitive to pick up Baker's cyst than clinical investigation, shows excellent inter observer [13, 32]agreement, proper criterion/construct validity, is a prevalent and very stable feature in knee OA [28], US assessment of this feature might be a candidate feature to help define knee OA patients with worse prognosis.

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8

NEDERLANDSE SAMENVATTING

PATHOFYSIOLOGISCHE EN PROGNOSTISCHE WAARDE VAN ECHOGRAFIE IN KNIE ARTROSE

ARTROSE

Artrose is een veel voorkomende gewrichtsaandoening. In 2011 waren in Nederland meer dan 1.2 miljoen mensen bij de huisarts geregistreerd met artrose. Artrose is deels een verouderingsproces en door de vergrijzing zal het aantal Nederlanders dat lijdt aan artrose in de komende jaren nog aanzienlijk stijgen. De ziekte komt vaker voor bij vrouwen dan bij mannen.

De aandoening wordt ook wel gewrichtsslijtage genoemd en wordt gekenmerkt door afname van de hoeveelheid en de kwaliteit van het gewrichtskraakbeen, dat beide botoppervlakten van het gewricht bekleedt. Het gevolg is dat een patiënt pijn, stijfheid en functiebeperking van het aangetaste gewricht ervaart. Vrijwel alle gewrichten kunnen aangedaan zijn, maar de knieën en heupen zijn het meest frequent betrokken.

Is een gewricht eenmaal aangetast, dan schrijdt het proces in de loop van jaren geleidelijk voort en kan het uiteindelijk, in sommige gevallen, noodzakelijk zijn om een gewrichtsvervangende operatie uit te voeren. Er bestaat geen therapie die het beloop daadwerkelijk beïnvloedt. Dat heeft voornamelijk te maken met het feit, dat het ziekteproces tot op heden nog niet doorgrond is. Het onderzoek naar artrose heeft zich met name gericht op het kraakbeen, hetgeen een centrale rol in het ziekteproces leek te spelen. Inmiddels is duidelijk geworden dat artrose niet eenvoudigweg slijtage is, maar dat ontstekingsprocessen ook een rol spelen en dat diverse andere onderdelen van het gewricht, zoals bijvoorbeeld het gewrichtskapsel en botstructuren, een belangrijke rol spelen in het ziekteproces. Traditioneel werd een gewricht afgebeeld door middel van een röntgenfoto, waarop alleen botten zichtbaar gemaakt kunnen worden en een indruk verkregen wordt van de hoeveelheid kraakbeen in het gewricht. Met nieuwere beeldvormende technieken zoals echografie zijn we inmiddels ook in staat 'zachte weefsels' van het gewricht zoals kapsels, pezen, spieren en slijmbeurzen in beeld te brengen. Daar deze onderdelen waarschijnlijk een belangrijke rol spelen in het ziekteproces, is het aantrekkelijk om echografie in te zetten in het onderzoek naar artrose. Europese en Amerikaanse wetenschappelijke verenigingen hebben een onderzoeksagenda opgesteld waarin is vastgelegd dat het van belang is om beeldvormende technieken in te zetten in het onderzoek naar pijn, het ziekteproces en prognose van artrose.

ECHOGRAFIE

Echografie is een beeldvormende techniek die gebruik maakt van ultrageluid (geluidsgolven buiten het door de mens hoorbare domein). Deze techniek maakt gebruik van het feit dat verschillende weefsels een verschillende dichtheid hebben en de geluidsgolven op een andere manier weerkaatsen of doorlaten. Een geluidsgolf wordt

uitgezonden door een transducer, verplaatst zich door weefsels en wordt op overgangen verschillend teruggekaatst en vervolgens weer opgevangen. De teruggekaatste golven worden omgezet in een elektrisch signaal en verwerkt tot een plaatje in grijswaarden op het beeldscherm. Geluidsgolven kunnen het bot niet passeren en hebben dus beperkte doordringbaarheid. Volwassen hersenen kunnen bijvoorbeeld niet met echografie onderzocht worden, omdat er een schedel omheen zit. Echografie heeft een aantal voordelen: het onderzoek is volledig onschuldig, er is geen contrastvloeistof nodig, het is mogelijk een dynamisch onderzoek te doen (bv patiënt tijdens onderzoek spieren laten aanspannen), het is relatief goedkoop en kan vrijwel overal uitgevoerd worden (klein apparaat, makkelijk te vervoeren). Echografie heeft echter ook een belangrijk nadeel: het is een onderzoeker-afhankelijk meetinstrument; de beelden worden geïnterpreteerd tijdens het onderzoek. Dat betekent dat het lastig te standaardiseren is en dat de resultaten dus sterk afhangen van de kennis en kunde van degene die het onderzoek uitvoert.

Concluderend kan gezegd worden dat er behoefte is aan meer kennis over pijn, het ziektebeloop en de prognose van artrose. Het lijkt erop dat de weke delen van een gewricht een belangrijke rol spelen in dit ziekteproces. Vandaar dat het zinvol lijkt om een relatief goedkope en veilige onderzoeksmethode in te zetten, die goed in staat is weke delen in beeld te brengen om meer te weten te komen over de pathofysiologie en prognose van artrose.

In **hoofdstuk 2** komt het onderwerp standaardisering aan bod. Als je een onderzoeker-afhankelijk meetinstrument in het onderzoek wilt inzetten, zal je je eerst moeten vergewissen van het feit dat het mogelijk is om meetresultaten te reproduceren, dus dat twee onderzoekers onafhankelijk van elkaar tot hetzelfde resultaat komen bij dezelfde patiënt. Om dit te onderzoeken is er eerst een protocol vastgesteld van de onderdelen van de knie die onderzocht zouden worden in knie artrose. Op grond van (weliswaar beperkt) eerder onderzoek werden 6 items vastgesteld:

1. Verdikt gewrichtskapsel (> 2 mm; ja/nee)
2. Vocht in het gewricht (> 4mm; ja/nee)
3. Kniekuilcyste (ja/nee)
4. Slijmbeursontsteking bij knieschijfpees (ja/nee)
5. Uitpuilen meniscus binnenzijde knie (>3 mm; ja/nee)
6. Kraakbeendikte (in mm).

Twee onderzoekers voerden vervolgens kalibratiesessies uit. Dat wil zeggen dat patiënten onderzocht werden met echografie door beide onderzoekers samen, waarbij afspraken gemaakt werden over hoe het onderzoek moest worden uitgevoerd en wat als afwijkend zou worden bestempeld om zo goed mogelijk vooraf af te stemmen. Vervolgens werden 60 patiënten door beide onderzoekers apart onderzocht. Na analyse bleek dat voor 5 van de 6 echo onderdelen goede overeenstemming werd bereikt. Alleen voor de dikte van het gewrichtskapsel was dit onbevredigend. Geconcludeerd werd dat er desondanks voldoende basis was, om verder onderzoek met echografie bij knie artrose te rechtvaardigen en dat de resultaten voor het verdikte gewrichtskapsel nog verbeterd dienden te worden.

Na hernieuwde kalibratie en opnieuw onderzoeken van een aantal patiënten door 2 onderzoekers apart, bleken de resultaten voor dikte van het gewrichtskapsel afdoende en die voor de overige onderdelen verbeterd, zodat de volgende stap in het onderzoek gezet kon worden.

In **hoofdstuk 3** is vervolgens onderzoek gedaan naar oorzaken van pijn bij artrose. De ernst van artrose wordt vaak weergegeven in de ernst van de röntgenafwijkingen. Het blijkt echter dat pijn en de door röntgenonderzoek geconstateerde schade vaak niet hand in hand gaan. Zo zijn er mensen met forse röntgenschade en nauwelijks pijn en mensen met minimale afwijkingen op de foto en veel pijn. Dat heeft tot het inzicht geleid, dat pijn wellicht niet veroorzaakt wordt door kraakbeenverlies, maar door afwijkingen in de weke delen van het gewricht. Er zijn al studies gedaan die uitwijzen dat er een relatie bestaat tussen bv ontstekingsverschijnselen (vocht, zwelling kapsel) en pijn. In dit onderzoek werden 180 patiënten onderzocht met echografie en werd tegelijkertijd de pijn die de patiënt op dat moment ervoer vastgelegd. Vervolgens werd bekeken of er een relatie was tussen afwijkingen in de weke delen en pijn. Dit was echter zonder resultaat. Dat kan betekenen dat pijn in de knie daadwerkelijk niet uit de weke delen voortkomt (pijn is een complex proces en waarschijnlijk multifactorieel) of dat echografie niet goed in staat is om bijvoorbeeld vocht en kapselzwelling in de volle omvang in beeld te brengen. Deze bevinden zich namelijk in meerdere compartimenten van het gewricht en standaardisering is niet eenvoudig als men alle compartimenten wil onderzoeken. Al met al lijkt het niet aantrekkelijk om echografie verder in te zetten voor onderzoek naar de oorzaken van pijn.

Hoofdstuk 4 is gewijd aan de mogelijk voorspellende waarde van echografie voor een gewichtsinjectie met prednison. Het is bekend dat een injectie met prednison in de knie bij patiënten met knie artrose een goed (hoewel meestal kort: 4 weken) effect kan hebben op de pijn. 40% reageert positief op deze behandeling. In de huidige behandelrichtlijnen staat beschreven dat dit een optie is voor patiënten met veel pijn, vooral als ze ook ontstekingsverschijnselen (bv kniezwelling) hebben, omdat prednison een ontstekingsremmer is. Op grond hiervan werd verondersteld dat ontstekingsverschijnselen bij echografie wellicht zouden kunnen voorspellen of iemand goed op een injectie reageert. Dit is aantrekkelijk, omdat dan een aantal overbodige injecties voorkomen zou kunnen worden. Om dat te onderzoeken ondergingen 62 patiënten eerst een echo en kregen vervolgens een injectie in de knie. Pijn voor en na injectie werd gedocumenteerd op aangeven van de patiënt. Het bleek dat geen enkel onderdeel van de echografie voorspellend was voor het effect van de injectie. Eerder onderzoek toonde al wisselende resultaten over de relatie tussen ontstekingsverschijnselen en de reactie op prednison injecties aan. Wellicht werkt het pijnstillende effect van prednison niet via ontstekingsremming. Het advies in de behandelrichtlijn om een injectie juist te geven als er ontstekingsverschijnselen zijn, staat hiermee ter discussie.

Hoofdstuk 5 is gericht op het ziektebeloop. Dit is een meer beschrijvende studie waarin aan bod komt wat er met de afwijkingen van de weke delen in de loop van een jaar gebeurt. Hiervoor ondergingen ruim 50 patiënten een knie echo op 3 tijdstippen: bij aanvang van de studie, na 3 maanden en na een jaar. Hieruit werd duidelijk dat ontstekingsverschijnselen zoals zwelling van het gewrichtskapsel en/of vocht in het gewricht in iets minder dan de helft van de gevallen op enig moment in de loop van

het jaar voorkwam en dat deze ontstekingen niet stabiel waren (wisselden in de loop van de tijd). Daarnaast bleken er ook stabiele factoren te zijn zoals de kniekuilcyste en het uitpuilen van de mensicus. Het is van belang om te weten of afwijkingen permanent of wisselend aanwezig zijn, omdat de permanente verschijnselen bruikbaarder zijn in onderzoek naar prognostische factoren.

In **hoofdstuk 6** komt de zoektocht naar prognostische factoren aan bod. 125 patiënten ondergingen een echo bij de start van de studie en werden 2 jaar gevolgd. In deze periode werd geregistreerd of patiënten een knieprothese kregen. Na 2 jaar werden nieuwe röntgenfoto's gemaakt en werden door middel van vragenlijsten de knieklachten gedocumenteerd. Omdat er nog geen definities voor verslechtering van knie artrose bestonden, maar wel criteria voor verbetering gedefinieerd waren, werden deze laatste criteria in tegenovergestelde vorm gebruikt. Er werden 2 definities geformuleerd: voor radiologische- (röntgenfoto) verslechtering en voor klinische verslechtering (klachten). Deze twee gaan, zoals eerder beschreven, niet altijd samen op. De analyse van deze gegevens laat zien dat meer dan de helft van de patiënten in de loop van 2 jaar verslechtert (radiologisch, klinisch of beide). Kniekuilcyste en (in mindere mate) verdikking van het kapsel worden met een slechte prognose geassocieerd. Dat wil zeggen dat het ernaar uitziet dat de mensen met deze 2 afwijkingen een grotere kans hebben om te verslechteren. Het zou zelfs zo kunnen zijn dat deze 2 fenomenen allebei een afspiegeling zijn van ontstekingsactiviteit in de knie, wat weer een argument is voor de cruciale rol van ontsteking in het ziekteproces. Het geeft tevens een kans om bijvoorbeeld patiënten op grond hiervan uit te selecteren voor onderzoek naar mogelijke medicijnen.

Concluderend kan gezegd worden dat echografie een goede en betrouwbare onderzoeksmethode is om een aantal weke delen van de knie in beeld te brengen. Op grond van de studies in dit proefschrift is het niet aanbevelenswaardig om echografie verder in te zetten in het onderzoek naar pijn bij knie artrose, maar lijkt het wel van waarde te kunnen zijn in het onderzoek naar het beloop en met name de prognose van de aandoening. Hierbij werd bevestigd dat ontsteking waarschijnlijk een belangrijke rol in het ziekteproces speelt en dat het in het onderzoek naar de prognose aantrekkelijk is om te focussen op stabiele factoren (zoals bv kniekuilcyste). Deze cyste is van de 6 onderzochte onderdelen in dit proefschrift ook nog eens het meest betrouwbaar te meten met echografie. Op die manier kan de echografie een bijdrage leveren aan het ontrafelen van een complex ziektebeeld als artrose.

CURRICULUM VITAE
DANKWOORD

CURRICULUM VITAE

Karen Bevers werd op 12 november 1970 geboren in Arnhem. Zij behaalde in 1989 haar VWO diploma aan het Rijnlands Lyceum in Oegstgeest en begon in hetzelfde jaar aan de studie geneeskunde aan de Vrije Universiteit in Amsterdam, waar zij in 1996 het artsexamen behaalde. De wetenschappelijke stage deed zij in Indonesië (begeleider prof dr. I.N. Wolffers).

Nadat zij anderhalf jaar gewerkt had als ANIOS interne geneeskunde in het Rijnland ziekenhuis in Leiderdorp, begon zij in 1998 aan de opleiding tot internist; de eerste 2 jaar in het Jeroen Bosch ziekenhuis in Den Bosch (opleider: dr. P.M. Netten) en vervolgens in het Radboud UMC (opleiders: prof. dr. J.W.M. van der Meer, prof. dr. P.M.J. Stuyt en prof. dr. J. de Graaf). Na 4 jaar opleiding interne geneeskunde maakte zij in 2003 de overstap naar de reumatologie. Zij doorliep het academische deel in het Radboud UMC (opleider: prof. dr. P.L.C.M. van Riel). De opleiding werd vervolgens in 2006 afgerond in de St. Maartenskliniek (opleider: dr. M.J.A.M. Franssen).

Sindsdien is zij als reumatoloog werkzaam in de St. Maartenskliniek, waar zij sinds 2011 ook opleider is. In 2010 werd de start gemaakt met het promotietraject: *pathophysiologic and prognostic value of ultrasonography in knee osteoarthritis* onder begeleiding van prof. dr. J.W.J. Bijlsma dr. A.A. den Broeder en dr. C.H.M. van den Ende. De resultaten zijn beschreven in dit proefschrift en gepresenteerd tijdens (inter)nationale congressen.

Karen heeft 2 zoons: Samuel (2000) en Noah (2002).

DANKWOORD

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