Concise report

Ultrasonographic predictors for clinical and radiological progression in knee osteoarthritis after 2 years of follow-up

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Abstract

Objective. The aim of this study was to investigate the association between a set of US features and radiographic and clinical progression of knee OA after 2 years of follow-up.

Methods. A total of 125 patients fulfilling ACR 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 Osteoarthritis Research Society International responder criteria or progression to total knee replacement. Radiological progression was defined as a ≥2 point increase in Altman score or progression to total knee replacement. Regression analyses were performed with baseline ultrasonographic features as independent variables and progression (two separate models for clinical progression and radiographic progression) as the dependent variable.

Results. A total of 31 (25%) patients fulfilled the criteria of clinical progression and 60 (48%) patients fulfilled the criteria of radiological progression. The presence of Baker’s cyst showed a statistically significant association with clinical [odds ratio (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 radiological 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 2 years.

Key words: knee osteoarthritis, musculoskeletal ultrasonography, disease progression.

Introduction

Pathophysiology of 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 of rapid worsening and guide future research on therapeutic interventions.

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

In contrast to conventional radiography, US is able to visualize these (peri)articular soft tissue structures and has been shown to be more sensitive than clinical examination [4]. Compared with 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 scarce. One study found an association between effusion detected by US and subsequent knee replacement after 3 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 2 years of follow-up.

**Patients and methods**

**Study design/patients**

This prospective, observational study was carried out within 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 radiological outcome at 2 years were eligible for inclusion in this study. All patients fulfilled the ACR clinical criteria for knee OA [11]. At inclusion, demographic and clinical data were collected. The local Medical Research Ethics Committee, Arnhem-Nijmegen (The Netherlands) region, approved the study (study number 2009/095). All patients signed 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 (KL) systematics [13]. Radiological progression was defined by a ≥2 point score increase in the sum JSN score or osteophyte score or ≥1-point score increase in both domains over 2 years or progression to total knee replacement.

**Clinical progression**

The WOMAC [14] was used as the primary patient-reported outcome measure. Pain and function scores were transformed in a way where 0 indicates no complaints and 100 indicates maximum complaints. Also Patient Global Assessment (PGA) on a numerical rating scale from 0 to 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 point (absolute) increase in pain, or a minimum of 50% and 20 point (absolute) decrease in function or worsening in two of three domains (pain, function, PGA) of 20% and 10 points (absolute). Patients who underwent total knee replacement during follow-up were also classified as clinical progressors.

**Ultrasoundography**

Ultrasonography was performed by a rheumatologist (K.B.) and a post-doctoral physician, who were trained in musculoskeletal US and previously involved in interreader reliability research of the applied US protocol [7, 16]. The investigator performing US was unaware of the clinical and radiographic results. The US 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 (≥4 mm), synovial hypertrophy (≥2 mm), meniscal protrusion, infrapatellar bursitis, Baker’s cyst and cartilage thickness (mm). Except for cartilage thickness, all items were scored dichotomously.

**Statistical analysis**

Data were checked for missing information and assumptions of normality. Descriptive statistics were computed, with mean (s.d.) or median (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 the dependent variable (two separate models for radiographic and clinical progression). Infrapatellar bursitis was not included in the regression analyses because of the very low prevalence (6%) of this US feature, which 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 a 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 a potential confounder was dropped because of collinearity (r = 0.82 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 ≥10% when adding the potential confounder to the model using a forward selection approach. All steps were performed for clinical as well as radiological progression. Statistical analyses were
performed using the statistical software package Stata10 (StataCorp, College Station, TX, USA).

**Results**

A total of 125 patients fulfilling the inclusion 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. Sixty patients (48%) did not fulfil any progression criterion.

**Regression analyses**

The results of the final regression analyses are shown in Table 2. The presence of Baker’s cyst on US at baseline shows a statistically significant association with clinical and radiological progression. For synovial hypertrophy, a large but non-significant association with clinical and radiological progression was found.

**Discussion**

In this study we demonstrated an association between Baker’s cyst on US 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 fluctuate more 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, Baker’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 that 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 advanced 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 capable of reliably visualizing the presence of the pathology of interest in this study.

The US protocol could be questioned with respect to the 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 may have led to an underestimation of the total amount of effusion and theoretically to a (false) absent association between effusion and progression.

**TABLE 1** Baseline data: clinical and radiographic data of study participants

<table>
<thead>
<tr>
<th>Population, n</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (s.d.), years</td>
<td>57 (9.4)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>68 (54)</td>
</tr>
<tr>
<td>BMI, mean (s.d.), kg/m²</td>
<td>27.8 (7.8)</td>
</tr>
<tr>
<td>Duration of complaints, mean (s.d.), years</td>
<td>8.7 (10.0)</td>
</tr>
<tr>
<td>WOMAC&lt;sup&gt;a&lt;/sup&gt; mean (s.d.)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>52.6 (16.8)</td>
</tr>
<tr>
<td>Function</td>
<td>51.5 (18.4)</td>
</tr>
<tr>
<td>Altmann score&lt;sup&gt;b&lt;/sup&gt;, mean (s.d.)</td>
<td></td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>1.6 (1.3)</td>
</tr>
<tr>
<td>Osteophyte score, mean</td>
<td>4.1 (2.9)</td>
</tr>
<tr>
<td>Kellgren and Lawrence score (0-4), mean (s.d.)</td>
<td>1.9 (1.1)</td>
</tr>
<tr>
<td>US pathology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Effusion</td>
<td>21 (17)</td>
</tr>
<tr>
<td>Synovial hypertrophy</td>
<td>27 (22)</td>
</tr>
<tr>
<td>Meniscal protrusion</td>
<td>79 (63)</td>
</tr>
<tr>
<td>Infrapatellar bursitis</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Baker’s cyst</td>
<td>33 (26)</td>
</tr>
<tr>
<td>Cartilage thickness, mean (s.d.), mm</td>
<td>2.0 (0.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup>: WOMAC score: normalized data (0-100) in which 0 indicates no complaints and 100 indicates maximal complaints.

<sup>b</sup>: Altmann score: total score for joint space narrowing, 0-6; osteophyte score, 0-12.

**TABLE 2** Multivariate associations (adjusted for confounders) of US features and radiological/clinical progression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiological progression</th>
<th>Clinical progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Effusion</td>
<td>2.39 (0.82, 6.97)</td>
<td>0.11</td>
</tr>
<tr>
<td>Synovial hypertrophy</td>
<td>2.11 (0.80, 5.57)</td>
<td>0.13</td>
</tr>
<tr>
<td>Baker’s cyst</td>
<td>2.84 (1.17, 6.90)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

<sup>a</sup>: Not retained in the final model. *Statistically significant (P < 0.05).
Since patients in this cohort received a multimodal treatment protocol comprising NSAIDs and IA injection with triamcinolone acetate if indicated, one could argue that the effects that are observed are treatment effects 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 a decrease in inflammation on US/MRI and a subsequent decrease in inflammation and clinical improvement in OA has not yet been demonstrated. Also, IA glucocorticoids are known to have a rather short-lived effect and are unlikely to affect clinical outcome at 2 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 to other active knee OA cohorts 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 2 years in established knee OA, and to a lesser extent for synovial hypertrophy. This finding needs confirmation, but US assessment of these features might be a candidate to help define knee OA patients with worse prognosis, which may be useful in research as well as daily clinical practice.

Acknowledgements

References