Osteoarthritis and Cartilage (2009) **17,** 304–312

doi:10.1016/j.joca.2008.07.016

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Evaluation of a Photographic Chondropathy Score (PCS) for pathological samples in a study of inflammation in tibiofemoral osteoarthritis

D. A. Walsh F.R.C.P., Ph.D.†‡*, A. Yousef F.R.C.S., M.Sc.§, D. F. McWilliams Ph.D.†, R. Hill†, E. Hargin B.Sc.† and D. Wilson‡

† *Academic Rheumatology, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK*

‡ *Back Pain Unit, Sherwood Forest Hospitals NHS Foundation Trust, Mansfield Road, Sutton in Ashfield NG17 4JL, UK*

§ *Orthopaedics and Trauma, Sherwood Forest Hospitals NHS Foundation Trust, Mansfield Road, Sutton in Ashfield NG17 4JL, UK*

Summary

Objective: Severity of structural change in knee osteoarthritis (OA) can be measured radiologically, macroscopically or microscopically. Existing methods have limitations for use in laboratory studies. We have developed a Photographic Chondropathy Score (PCS) for use with pathological samples. We have compared the ability of the different severity measures to distinguish between samples obtained at total knee replacement surgery or postmortem (PM), and to detect associations between structural severity and synovitis.

Method: Tibial plateaux and femoral condyles were collected from 84 patients undergoing surgery or PM. Each sample was photographed and scored. Limits of agreement and repeatability coefficients were calculated for PCS. Scores for radiological joint space narrowing (JSN) and osteophytes, histological cartilage changes (Mankin), and synovitis were assigned. Data were analysed using Mann–Whitney *U* tests, Spearman's correlation coefficient or logistic regression.

Results: A total of 116 knees were analysed from 84 patients. Both medial tibial plateaux and total joint PCS showed good repeatability, internal consistency and reliability between observers. PCS, radiographic and Mankin's scores were all modestly positively correlated (*r* values 0.28–0.55). PCS and Mankin scores were greater in surgical than PM samples. Synovial inflammation was associated with higher PCS and radiological JSN scores (*r* values 0.43–0.48), irrespective of diagnosis.

Conclusion: Macroscopic, microscopic and radiographical severity scores are complementary measures of structural severity in knee OA. Synovial inflammation was associated with increased OA structural severity, suggesting a possible role of chronic synovitis in cartilage damage.

Key words: Arthroscopy, Osteoarthritis, Cartilage, Inflammation, Grading.

Abbreviations: PM postmortem, OST osteophyte, JSN joint space narrowing, EDTA ethylenediaminetetraacetic acid, PCS photographic cartilage osteoarthritis severity score, SFA Système Française D'Arthroscopie, TKR total knee replacement.

Introduction

Osteoarthritis (OA) of the knee is a common cause of pain and disability and is of great socioeconomic importance. The current treatments of OA address symptoms of pain, disability and distress, with little impact on structural disease progression.

A variety of methods have been described for measuring structural change in OA. Changes in cartilage structure, chondrocyte phenotype, and loss of matrix components can be detected by histology. Fibrillation, fissuring and loss of articular cartilage may be macroscopically apparent at the joint surface. Loss of articular cartilage contributes to joint space narrowing (JSN) on weight-bearing radiographs, and new bone formation results in the formation of osteophytes (OSTs). Different methods are used to measure OA structural change in different types of studies, depending on the scientific question, local expertise and practicalities.

Histological grading is most commonly used in laboratory research. Methods based on that described by Mankin are sensitive to pathological change, but require invasive tissue sampling[1–4]. Histological methods permit associations to be explored between severity and other pathological processes in the same region, although it may not always be valid to generalise results to the joint as a whole.

Macroscopic methods for scoring the appearance of articular surfaces have been most extensively developed for arthroscopic studies[5]. The Système Française D'Arthroscopie (SFA) system is based on global assessment of OA changes in the articular surfaces of the knee, and has been validated across the range from mild chondropathy to severe OA[6–8]. The SFA system builds on a macroscopic severity score that was developed by Collins using

*Address correspondence and reprint requests to: Dr D. A. Walsh, Academic Rheumatology, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK. Tel: 44-(0)-115-8231751; Fax: 44-(0)-115-8231757; E-mail: david.walsh@nottingham.ac.uk

Received 22 February 2008; revision accepted 24 July 2008.

pathological samples[9,10], was based on factor analysis of data from arthroscopic examinations, and later simplified giving a scale from 0 to 100[7]. Macroscopic methods require access to intact tissues, but can be used to derive global scores for the joint or joint compartment as a whole.

Radiography permits serial weight-bearing measurements in living subjects. Radiographic methods may be less sensitive to OA cartilage change than are histological or macroscopic methods, especially in the lateral tibiofemoral compartment[8,11–14]. Other imaging methods such as MRI may display higher sensitivity in detecting OA cartilage change, but greater cost[15].

Structural disease progression in OA is multifactorial. Inflammation is increasingly recognised as a potential contributor to structural change. Rapidly progressing OA is associated with higher baseline circulating levels of the acute phase reactant, C-reactive protein[16,17]. Cytokines that are expressed by the inflamed osteoarthritic synovium increase chondrocyte catabolic activity[18] and enhance angiogenesis[19], and proteases produced by inflammatory cells may directly compromise cartilage structure[20]. Synovitis therefore may contribute to cartilage damage in OA. Indeed, clinical and arthroscopic synovitis have been associated with radiological progression in human OA[21,22].

We aimed to develop and validate a measure of OA disease severity for use in pathological samples of tibiofemoral joints from both clinical and cadaveric cases. We have developed and tested three Photographic Chondropathy Scores (PCSs), based on the Collins and SFA systems. We have compared the PCS systems with other histological, macroscopic and radiographic measures of structural severity, and have used these methods to explore possible associations between histological synovitis and the severity of OA structural changes.

Materials and methods

Informed consent was gained from each donor (surgical cases) or next of kin (postmortem [PM] cases) according to protocols approved by the North Nottinghamshire Research Ethics Committee and Nottingham Research Ethics Committee 1 (Projects NNHA/420, NNHA/544, NNHA/673 and 05/Q2403/24)[23]. Tibial plateaux, femoral condyles and synovium were collected from 56 patients undergoing total knee replacement (TKR), all of whom fulfilled the American College of Rheumatology revised criteria for OA[24].

Additional samples were obtained from both knees of 28 recently deceased patients (PM). It was anticipated that OA would be prevalent in PM cases, but at milder severity than in patients undergoing TKR. Clinical data for PM cases were obtained by case notes review, by interview with the patient's bereaved relatives and by clinical examination PM. Relatives reported that they were unaware of any attendance with a doctor for knee pain in the last 12 months by PM cases. Four PM cases were believed to have had OA by their relatives. No Heberden's nodes, rheumatoid nodules or OSTs were apparent at the point of sample collection.

Patients with rheumatoid arthritis and other arthritides were excluded from the study. Four patients (all TKR) displayed clinical evidence of nodal OA in the hands.

PHOTOGRAPHIC CHONDROPATHY SCORES (PCSs)

Tibial and femoral plateaux were photographed from a fixed distance of 23 cm using a Kaiser RS 2 XA camera stand, under standard illumination with a Sony DSC-S85 CyberShot digital camera fitted with a Carl Zeiss lens at 4× zoom (Carl Zeiss Ltd., Welwyn Garden City, UK). Uncompressed images were stored using Tagged Image File Format (TIFF) at a resolution of 2272×1704.

The severity and extent of loss of surface integrity of articular cartilage were recorded on a Clinical Report Form for each of four articular surfaces from each knee; medial and lateral tibial plateaux and femoral condyles, using a method adapted from Dougados *et al.*[6] (Fig. 1). Patellae and trochlear regions were excluded from the photographic scoring system due to their typical absence from pathological samples obtained at TKR surgery.

Loss of surface integrity was graded according to appearance on the photographic image. Grade 0; normal – smooth, unbroken surface, homogeneous white to off-white colour. Grade 1; swelling and softening – a light brown homogeneous colouration. Grade 2; superficial fibrillation – lightly broken surface, white to off-white/light brown in colour. Grade 3; deep fibrillation – coarsely broken cartilage surface, dark brown, grey or red in colour. Grade 4; subchondral bone exposure – stippled white and dark brown/red in colour. The extent of each grade of surface change was delineated freehand on standardised diagrams of each articular surface. The percentage of each articular surface area attributed to each grade was estimated by the assessor.

Scores were based on data from the Clinical Report Form. Three scoring methods were applied to each of the four articular surfaces, and total scores derived by summation of each of the four component scores. Data are presented for the total scores, and scores for the medial tibial plateaux alone. The medial tibial plateau was selected as this is the commonest site of tibiofemoral OA, and was sampled for histological analysis.

The grading method of Collins[9] was interpreted as a classification tree for articular surface change (Fig. 2). The phrases 'more extensive' and 'large areas', which define Grade I:II and III:IV boundaries according to Collins, were arbitrarily interpreted as >50% of the articular surface. The medial tibial plateau Collins grade gave values that could range from 0 to 4, and the total Collins grade had a possible range from 0 to 16.

'Original SFA' scores were derived using the two original formulae described by Dougados *et al.*[6], depending on whether a compartment was medial or lateral, and on the percentage of articular surface that is allocated to each severity grade[6]:

$$\text{Medial score} = -2.2 + (\text{Grade } 1 \times 1.3) + (\text{Grade } 2 \times 2.2) + (\text{Grade } 3 \times 3.4) + (\text{Grade } 4 \times 7.2)$$

$$\text{Lateral score} = -2.4 + (\text{Grade } 1 \times 0.8) + (\text{Grade } 2 \times 2.3) + (\text{Grade } 3 \times 5.0) + (\text{Grade } 4 \times 6.1)$$

The medial tibial plateau PCS gave values that could range from −2.2 to +717.8. Total PCS was calculated as the sum of the scores for the four regions (both tibial plateaux and femoral condyles), giving a possible range from −9.2 to +2650.8.

'Revised SFA' scores were derived using modifications of the original SFA formulae described by Ayral *et al.*[7]. Revised SFA scores have possible ranges of 0–100 for each articular surface, or 0–400 for the total score. For each articular surface

$$\text{Score} = (\text{Grade } 1 \times 0.14) + (\text{Grade } 2 \times 0.34) + (\text{Grade } 3 \times 0.65) + \text{Grade } 4$$

Inter-observer reliability was determined by two observers (RH and EH) who independently derived scores from the photographic images of 98 knees (56 PM), each blinded to the scores allocated by the other observer.

In order to evaluate the validity of using photographs for scoring articular surface changes, 'macroscopic pathological scores' were derived for a subset of 77 knees (56 PM) using the methods described above, with direct visualisation and probing of fresh pathological samples, comparable with assessment at arthroscopy.

Additional validation was undertaken during the development of the photographic scoring system using a subset of 24 knees (16 PM). In order to evaluate the overall repeatability of the photographic scoring system, photographs of the 24 knees were re-graded and the extent of graded changes redrawn and re-scored by a single observer (RH) at least 2 weeks after and blinded to his initial grading. In order to evaluate the repeatability of estimating the extent of graded changes, one of us (RH) repeated his estimation of the extent of graded changes, using his original set of 24 diagrams, at least 2 weeks after and blinded to his previous estimations.

RADIOGRAPHIC SCORING

Pre-operative postero-anterior knee radiographs were obtained from all patients undergoing joint replacement surgery and were examined by an observer who was blinded to patient details and histological and macroscopic findings. Radiographs were not available for PM cases. JSN and OST scores were assigned to tibiofemoral joints for each case using a line drawing atlas[25]. A total Radiological OA Severity Score was calculated as the sum of the JSN and OST scores. Possible scores ranged from 0 to 6 and 0 to 12 for JSN and OST scores, respectively, and from 0 to 18 for total Radiological OA Severity Score, with higher scores indicating greater severity.

HISTOLOGICAL GRADING OF SEVERITY OF OA CHANGES IN ARTICULAR CARTILAGE

Samples of medial tibial plateaux and synovium were fixed in neutral-buffered formalin and then wax embedded. A mid-coronal slice across the entire