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Histopathological subgroups in knee osteoarthritis

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SUMMARY

Objective: Osteoarthritis (OA) is a heterogeneous, multi-tissue disease. We hypothesised that different histopathological features characterise different stages during knee OA progression, and that discrete subgroups can be defined based on validated measures of OA histopathological features.
Design: Medial tibial plateaux and synovium were from 343 post-mortem (PM) and 143 OA arthroplasty donations. A 'chondropathy/osteophyte' group ($n = 217$) was classified as PM cases with osteophytes or macroscopic medial tibiofemoral chondropathy lesions ≥grade 3 to represent pre-surgical (early) OA. 'Non-arthritic' controls ($n = 48$) were identified from the remaining PM cases. Mankin histopathological scores were subjected to Rasch analysis and supplemented with histopathological scores for subchondral bone marrow replacement and synovitis. Item weightings were derived by principle components analysis (PCA). Histopathological subgroups were sought using latent class analysis (LCA).
Results: Chondropathy, synovitis and osteochondral pathology were each associated with OA at arthroplasty, but each was also identified in some 'non-arthritic' controls. Tidemark breaching in the chondropathy/osteophyte group was greater than in non-arthritic controls. Three histopathological subgroups were identified, characterised as 'mild OA', or 'severe OA' with mild or moderate/severe synovitis.
Conclusions: Presence and severity of synovitis helps define distinct histopathological OA subgroups. The absence of a discrete 'normal' subgroup indicates a pathological continuum between normality and OA status. Identifying specific pathological processes and their clinical correlates in OA subgroups has potential to accelerate the development of more effective therapies.

Introduction

Osteoarthritis (OA) is clinically heterogeneous[1], and associations between joint pathology and clinical features such as pain are often weak[2]. Earlier understanding of OA as a disease of articular cartilage has been supplemented by evidence of synovial inflammation[3] and subchondral bone marrow lesions (BML), often associated with fibrovascular replacement of marrow spaces[4]. Synovium and subchondral bone might contribute to OA symptoms, as well as pathogenesis[5–8]. The extent to which different histopathological features reflect clinical heterogeneity, disease severity or stage, or discrete pathological subgroups remains uncertain.

Histopathological OA characteristics were scored by Mankin in order to generate a measure of OA severity[9]. Despite widespread research use, the Mankin score has been subjected to only limited validation[10], and its measurement properties have not been defined. It has limited ability to distinguish OA from healthy controls[11], and focuses on chondropathy, rather than reflecting the multi-tissue nature of OA. The relevance of the each component of the Mankin score (cartilage surface integrity, proteoglycan loss, chondrocyte morphology and tidemark breaching) to OA pathogenesis has not been fully elucidated[12]. More recently an Osteoarthritis Research Society International (OARSI) working group addressed some of the limitations of Mankin's system[13]. The OARSI

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system combines several histopathological features within each grade together with staging the extent of articular surface involved, and provides a robust measure of structural severity, but does not permit identification of contributions from discrete histopathological changes. Synovitis and BML have been identified in magnetic resonance imaging (MRI) studies as key pathological correlates of symptoms in OA[5–7], although their histological correlates (e.g., fibrovascular replacement of subchondral marrow) are not included in the Mankin or OARSI systems. Separate scoring systems have been described that evaluate the severity of synovitis in OA[14,15].

The measurement properties of scoring systems where individual component (or item) scores are summed (such as in the Mankin score) to produce a total score can be explored using Rasch analysis. Rasch analysis is used to validate or reform scoring systems[16]. The measurement properties of the Oxford knee score[17], and the ordinal MRI score for knee OA[18] have been evaluated using Rasch analysis. However, Rasch analysis has not previously been used for histological methods in OA.

Clinical heterogeneity has led to the identification of discrete clinical subgroups, for example based on lower extremity muscle strength[19], psychological phenotype[20] or on patterns of co-existing MRI lesions[21]. Identifying homogenous subgroups of OA patients is important to allow for stratification of treatments, by focussing on those in whom they are most likely to modify disease progression and improve outcomes. Increasing attention is being paid to early disease, in the hope of developing interventions that might retard OA progression. Histopathological scores have largely been developed using joint tissues representative of end stage OA collected at arthroplasty, and their validity in early disease or other clinical subgroups remains uncertain.

We aimed to first define histopathological features of early OA by comparing post-mortem (PM) cases who had early signs of OA but had not sought a total knee replacement (TKR) ("chondropathy/osteophyte") cases with non-arthritic PM controls and end-stage OA (arthroplasty) cases. Second we aimed to identify the contribution of subchondral bone and synovial changes to OA histopathological classification. We finally used severity of OA histopathological scores for medial tibial plateau, subchondral bone and synovium to investigate possible discrete OA subgroups. We hypothesised the existence of discrete 'normal' and OA groups (rather than a continuum between normality and disease), in addition to pathological subgroups of OA.

Materials and methods

The study was approved by Nottingham Research Ethics Committee 1 (05/Q2403/24) and Derby Research Ethics Committee 1 (11/H0405/2).

Patients

Medial tibial plateaux and synovia were from 343 consecutive PM donations, plus 143 consecutive patients at TKR surgery for end-stage OA who satisfied American College of Rheumatology (ACR) classification criteria[22]. PM samples were from people with no history of rheumatoid arthritis or pseudogout. In order to test validity of histological features as characteristics of OA, we defined subgroups of the total sample group that (1) satisfied ACR criteria for OA based on symptoms and radiography (TKR), and (2) non-arthritic controls ($n = 48$ PM cases) that had no history of OA, no reported pain in the knee during the last year of life, no Heberden's nodes, no osteophytes seen on the dissected knee and no macroscopic chondropathy lesions grade 3 or 4 in the medial tibiofemoral compartment[23]. PM cases that had osteophytes or macroscopic chondropathy lesions grade 3 or 4 in the medial tibiofemoral compartment were classified as "chondropathy/osteophyte" cases ($n = 217$).

Data collected before TKR surgery by clinical assessment and from medical notes included symptom duration (<1 year to >5 years), morning and inactivity stiffness in the biopsied joint (<30 min to >2 h), previous fracture or surgery, analgesic medication (classified as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, opiates or anti-neuropathic), effusion, increased warmth and synovial thickening (each present or absent).

Medial and lateral tibial plateaux and femoral condyles were graded on the extent and severity of macroscopic chondropathy (cartilage loss) by an experienced technician (RH). Macroscopic chondropathy scores could range from 0 (normal) to 400 (complete cartilage loss from all four articular surfaces)[24]. Chondropathy grades were as follows; 0 = normal: smooth, unbroken surface, homogeneous white to off-white colour, 1 = swelling and softening: a light brown homogenous colouration, 2 = superficial fibrillation: lightly broken surface, white to off-white/light brown in colour, 3 = deep fibrillation: coarsely broken cartilage surface, dark brown, grey or red in colour, 4 = subchondral bone exposure: stippled white and dark brown/red in colour.

Histopathological grading

All histological scoring was carried out by a single observer blinded to diagnostic categorisation and clinical details. Mid-coronal sections of the middle one-third of the medial tibial plateau and synovial tissues were formalin-fixed and processed as previously described[23], and sections (5 μm) stained with haematoxylin and eosin, or Safranin-O for proteoglycan content. Four aspects of chondropathy were graded after Mankin[9]; cartilage surface integrity (0–6), tidemark integrity (0 or 1), chondrocyte morphology (0–3) and proteoglycan loss (0–4). Subchondral bone marrow replacement was graded 0 (absent) or 1 (present). Subchondral bone marrow replacement was defined as replacement of bone marrow fat spaces with fibrovascular tissue.

Synovial inflammation was graded 0 to 3. Only samples with synovial lining were graded. Normal synovium (grade 0) was defined as synovial lining <4 cells thick, sparse cellular distribution with few or no inflammatory cells. Mild inflammation (grade 1); synovial lining 4 or 5 cells thick, increased cellularity with some inflammatory cells. Moderate inflammation (grade 2); synovial lining 6 or 7 cells thick, dense cellularity with inflammatory cells but no lymphoid aggregates. Severe inflammation (grade 3); synovial lining >7 cells thick, dense cellularity and inflammatory cell inflammation, may contain perivascular lymphoid aggregates[14].

Rasch analysis

Rasch analysis was used to examine the measurement properties of the Mankin score. First, the data set was divided into both a test ($n = 181$ PM and 55 TKR cases) and validation group ($n = 162$ PM and 88 TKR). All cases were scored according to the Mankin criteria. Rasch analysis is a tool used to validate or improve outcome scales[16,25], using RUMM2020 software[26], and the partial credit model[16].

Various fit statistics were used in order to measure the fit of the Mankin score to the Rasch model. Rasch analysis examines an outcome scale, or scoring system, against a mathematical model, for a more detailed review refer to Ref. 16. Each histological component of the Mankin score (cartilage surface integrity,