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Perfusion of subchondral bone marrow in knee osteoarthritis: A dynamic contrast-enhanced magnetic resonance imaging preliminary study

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ABSTRACT

The role of inflammation in the pathogenesis of osteoarthritis is being given major interest, and inflammation is closely linked with vascularization. It was recently demonstrated that dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) could identify the subchondral bone marrow vascularization changes occurring in osteoarthritis in animals. These changes appeared before cartilage lesions were visible and were correlated with osteoarthritis severity. Thus the opportunity to obtain an objective assessment of bone vascularization in non-invasive conditions in humans might help better understanding osteoarthritis pathophysiology and finding new biomarkers.

We hypothesized that, as in animals, DCE-MRI has the ability to identify subchondral bone marrow vascularization changes in human osteoarthritis. We performed knee MRI in 19 patients with advanced knee osteoarthritis. We assessed subchondral bone marrow vascularization in medial and lateral femorotibial compartments with DCE-MRI and graded osteoarthritis lesions on MR images. Statistical analysis assessed intra- and inter-observer agreement, compared DCE-MRI values between the different subchondral zones, and sought for an influence of age, sex, body mass index, and osteoarthritis garde on these values.

The intra- and inter-observer agreement for DCE-MRI values were excellent. These values were significantly higher in the femorotibial compartment the most affected by osteoarthritis, both in femur and tibia ($p < 0.0001$) and were significantly and positively correlated with cartilage lesions ($p = 0.02$) and bone marrow oedema grade ($p < 0.0001$) after adjustment.

We concluded that, as in animals, subchondral bone marrow vascularization changes assessed with DCE-MRI were correlated with osteoarthritis severity in humans.

1. Introduction

Providing a better understanding of non-cartilage articular pathology in osteoarthritis (OA) is a research priority [1]. Among these issues, the role of inflammation in the pathogenesis of osteoarthritis is being given major interest [2]. Data suggest that inflammatory processes may be closely linked to the neovascularization occurring in the subchondral bone of osteoarthritic joints [3]. It has therefore been hypothesized that angiogenesis could play a key role in OA pathogenesis and could thus become a future target in OA treatment [3].

Abbreviations: AUC, area under the curve; DCE-MRI, dynamic contrast enhanced MRI; OA, osteoarthritis; PDFS, proton density with fat suppression; SCBM, subchondral bone marrow.

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Subchondral bone marrow (SCBM) vascularization can be assessed using dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI). This quantitative imaging method can be added in routine protocols on clinical MRI devices in minimally invasive conditions, as it only requires standard gadolinium injection [4].

Its ability to identify alteration of SCBM vascularization, and thus to serve as a potential biomarker, has been recently demonstrated in an animal model of advanced spontaneous OA in Dunkin-Hartley guinea pig [5]. In this study, the vascularization changes were correlated to OA severity. To the best of our knowledge, no equivalent work has been performed in humans. Yet, differences exist between animal and human diseases, and this was specifically demonstrated in the angiogenesis occurring in Dunkin-Hartley guinea pig models of OA [6]. As the extrapolation of animal models to human is a constant research issue, we intended to assess subchondral bone marrow vascularization with DCE-MRI in patients.

We hypothesized that, as in animals, DCE-MRI has the ability to identify SCBM vascularization changes in human osteoarthritis. Our secondary hypothesis was that SCBM perfusion modifications were correlated with OA severity.

Therefore, the purpose of the present study was to investigate SCBM vascularization with DCE-MRI in patients with advanced knee OA.

2. Materials and methods

2.1. Ethical statement

This prospective monocentric preliminary study was authorized by our Institutional Research Ethics Board and declared to our local Ethics Committee (Comité de Protection des Personnes Nord-Ouest IV). Oral and written information was given. Written informed consent was obtained.

2.2. Population

Patients with knee OA, classified Kellgren-Lawrence 3 or 4, with asymmetric femorotibial joint space narrowing, were included.

Exclusion criteria were: MR contra-indication, chronic renal failure (creatinine clearance < 30 ml/min), contrast media allergy, orthopaedic hardware around the knee. We also excluded patients in whom motion artifacts impaired image analysis.

Age, sex and body mass index were registered.

2.3. MR protocol

Patients were examined using a 3T MR scanner (MR 750W, General Electrics, Milwaukee, WI) with a dedicated knee coil.

The knee was assessed morphologically with 3D T1-weighted and coronal proton density with frequency-selective fat suppression (PDFS) sequences. These are adapted to cartilage assessment and visualization of bone attrition, osteophytes and bone marrow oedema [7].

The T1 spin-echo sequence consisted in 182 slices acquired in the sagittal plane without gap in 2 min and 53 s. Slice thickness was 0.6 mm, field of view was 180 × 144 mm, matrix was 352 × 288, time of repetition was 600 ms, and time of echo was 18 ms.

The PDFS sequence consisted in 20 slices acquired with a 0.5 mm gap in 3 min and 5 s. Slice thickness was 3 mm, field of view was 160 × 160 mm, matrix was 416 × 384, time of repetition was 2500 ms, and time of echo was 45 ms.

The 3D T1-weighted DCE-MRI sequence was based on fast spoiled gradient echo. Forty slices were acquired in the coronal plane without gap in 4 min and 13 s. The main parameters were: field of view = 180 × 162 mm, matrix = 180 × 160, slice thickness = 2 mm, time of repetition = 4.8 ms, time of echo = 2.1 ms, bandwidth = 50 Hz, flip angle = 20°, parallel imaging with an acceleration factor of 2. Four dynamics were acquired to determine baseline. Then, the patient received a bolus injection of gadoteric acid (Dotarem, Guerbet, France) via an antecubital vein at a dose of 0.1 mmol/kg during the fifth dynamic acquisition. This injection was performed via an automatic injector. Nineteen dynamics were acquired. Temporal resolution was 11 s per dynamic. Seven pre-injection variable flip angle sequences were acquired to calculate T1 maps. Flip angles values were: 2°, 5°, 10°, 15°, 20°, 25°, 30°. Each variable flip angle sequence lasted 10 s.

Total acquisition time was 13 min.

2.4. Image analysis

We studied morphological and perfusion features, as detailed below, in four subchondral zones: medial and lateral tibial plateaus and medial and lateral femoral condyles. In each patient, the data were compared between the femorotibial compartment the most affected by OA (termed OA+) and the femorotibial compartment the least affected by OA (termed OA−).

2.5. DCE-MRI analysis

The images were analyzed independently by a senior musculoskeletal radiologist with 8 years experience (JFB) and a senior resident (JD) on anonymized images. The senior musculoskeletal radiologist performed the measurements a second time with a two-week interval. Radiologists were blinded to X-rays.

The enhancement curves were analyzed based on the Tofts pharmacokinetic model with DCE-Tool (an open-source software developed by Kyung Sung, MD, PhD, from the Body MRI research group of Stanford University, CA, USA) on an OsiriX DICOM workstation. T1 maps were calculated from variable flip angle sequences. Arterial input function was determined by drawing one circular region of interest in the popliteal artery.

Four oval regions of interest were drawn in the tibial and femoral SCBM, in medial and lateral compartments, centered halfway between the midpoint and the edge of tibial plateau, as shown in Fig. 1. The weight-bearing zone was defined as the coronal image with the largest medial tibial spine, as described in the BLOKS scoring system [8]. The size of the regions of interest was adjusted in each zone in order to obtain a maximum coverage of the SCBM. For each region of interest, perfusion parameters were obtained from the time-intensity curve fitting: area under the curve (AUC), time to peak, transfer constant Ktrans and rate constant Kep. Because bone enhancement was very weak in many zones, no peak could be identified on the corresponding time-concentration curves (Fig. 1c). In these circumstances, the time to peak could not be measured. Moreover, without proper signal enhancement, the concentration of tracer in the tissue was considered negligible. Hence, Ktrans and Kep could not be calculated reliably [9].

2.6. Analysis of other MR sequences

For each subchondral zone, we graded cartilage damage (8 points), bone marrow oedema (4 points), bone attrition (4 points) and osteophytes (8 points), according to the WORMS scoring system [10]. This was done on the coronal DPFS slice corresponding to the DCE image (Fig. 1). For each region of interest, bone marrow oedema was also defined as present (score = 1) or absent (score = 0).