Osteoarthritis and Cartilage 25 (2017) 976–985

Osteoarthritis and Cartilage

Cartilage MRI T2* relaxation time and perfusion changes of the knee in a 5/6 nephrectomy rat model of chronic kidney disease

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ARTICLE INFO

Article history:
Received 16 August 2016
Accepted 14 December 2016

Keywords:
Chronic kidney disease
Dynamic contrast enhanced MRI
MRI T2* relaxation time
5/6 Nephrectomy
Cartilage
Knee

SUMMARY

Objective: Chronic kidney disease (CKD) is characterized by metabolic disturbances in calcium and phosphorus homeostasis as kidney function declines. Alterations in blood perfusion in bone resulting from arteriosclerosis of bone vessels may relate to the progression of CKD. Herein, change in dynamic contrast enhanced (DCE) MRI parameters (*A*: *amplitude*, k_{el}: *elimination constant*, and k_{ep}: *permeability rate constant*) and MRI T2* relaxation time of the knee cartilage were measured in a rodent nephrectomy model in order to (1) examine the relationship of peripheral blood perfusion to CKD and (2) demonstrate the feasibility of using DCE-MRI parameters and MRI T2* as imaging biomarkers to monitor disease progression.

Design: Two groups of male Sprague–Dawley rats received either (1) no intervention or (2) 5/6 nephrectomy.

Results: We found that the CKD group (compared with the control group) had lower *A* and k_{el} values and similar k_{ep} value in the lateral and medial articular cartilages beginning at 12 weeks ($P < 0.05$); statistically significantly higher T2* values in the lateral and medial articular cartilages beginning at 18 weeks ($P < 0.05$); statistically significantly decreased inner luminal diameter of the popliteal artery, and altered structure of the lateral and medial articular cartilages ($P < 0.05$).

Conclusion: Perfusion deficiency and CKD may be related. DCE parameters and MRI T2* could serve as imaging biomarkers of cartilage degeneration in CKD progression.

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Introduction

Chronic kidney disease (CKD), also known as chronic renal disease, is characterized by progressive loss of kidney function over a period of months or years. Its pathophysiology is associated with diverse cardiovascular, hematological, gastrointestinal, immune, endocrine, neurological, and musculoskeletal system complications[1,2]. A bone–vascular axis linkage between systemic arterial stiffness (atherosclerosis of the aorta and the main peripheral arteries) and CKD was proposed by London *et al.*[3,4]. Bridgeman mentioned that bone marrow blood vessels are subject to atherosclerosis with reduction in blood supply[5]. However, few studies have addressed the impact of the peripheral vascular system and peripheral blood flow change on CKD pathogenesis[6,7]. The knee subchondral bone marrow and cartilage have direct anatomical and functional connections[8]. Degeneration of the articular cartilage and associated changes in subchondral bone results in osteoarthritis-related joint pain and dysfunction[9]. Although cartilage is

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http://dx.doi.org/10.1016/j.joca.2016.12.019
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considered a non-vascularized tissue, according to several studies, microvessels can be found both in calcified and uncalcified cartilage[10–13]. Blood from the subchondral bone crosses the calcified cartilage and enters the basal regions of uncalcified cartilage through microchannels[14,15]. Perfusion accounts for about 50% of the nutrition supplied to the articular cartilage, half of which enters by diffusion from the synovial fluid. Alterations in the blood flow might cause the composition of the extracellular matrix and the chondrocyte response in cartilage to deteriorate. Mild changes in the chondrocyte environment can slow the synthesis of proteoglycans; alter osmotic pressure, ionic concentrations, and pH; decrease matrix accumulation; increase matrix turnover, and cause tissue weakness[16,17].

Magnetic resonance imaging (MRI) has proven to be a useful tool for the noninvasive assessment of osteoarthropathic disorders. In addition to detecting structural changes, quantitative MRI techniques have been shown to be sensitive to changes in tissue biochemistry and macromolecular content. Although the morphological characteristics of end-stage renal disease (ESRD) on MRI have been well described in the literature, there is a paucity of published quantitative MRI findings regarding the characteristics of articular cartilage in early stage CKD. Dynamic contrast-enhanced (DCE) MRI provides a valuable noninvasive method to measure bone vascularization and hemodynamics, and identify relevant perfusion parameters[18]. Previous DCE-MRI studies have successfully shown statistically significant alteration of perfusion in bone marrow and cartilage[13,19,20]. Roberto Sanz Requena *et al.* successfully applied DCE-MRI with pharmacokinetic modeling to the patellar cartilage to differentiate healthy human knees from knees affected by diseases such as OA and osteomalacia[13,21]. Martí-Bonmatí L *et al.* reported the reproducibility of the pharmacokinetic calculations for sequences acquired on two different magnetic field systems used to assess changes in cartilage structure. Using 24 acquisitions, they showed a very low test-retest root mean square coefficient of variation[22]. Although there are few reported DCE-MRI studies of cartilage due to its low perfusion and limitations on spatial and temporal resolution, we think that pharmacokinetic modeling of DCE-MRI data has potential for quantitative assessment of cartilage and should be further investigated. MRI $T2^*$ mapping is the method of choice because of its rapid acquisition time and noninvasiveness, and can be used to sensitively probe cartilage for changes in matrix composition including collagen structure and hydration status[23–25]. MRI $T2^*$ techniques can reflect similar compositional changes as T2 and T1rho in the articular cartilage and have the advantages of reducing specific absorption rate, shortening image acquisition time, and providing a higher resolution image[26,27]. The inner zone of the cartilage near the deteriorated osteochondral junction which has a relatively short T2 relaxation time is an important image biomarker of early phase degeneration. Increased multi-slice efficiency, higher spatial resolution with shorter echo time (TE), and higher sensitivity of inner zone detection make MRI $T2^*$ even more suitable for assessing cartilage structure[28]. More information about the physiological processes underlying altered cartilage perfusion and changes in matrix composition after CKD can be obtained from the details of cartilage perfusion kinetics beyond the bone–vascular axis.

We hypothesized that impaired blood supply and nutrient delivery to cartilage in CKD might be related to cartilage degeneration. Thus, the aims of the present study were to (1) conduct a longitudinal study of the relationship of DCE-MRI parameters and MRI

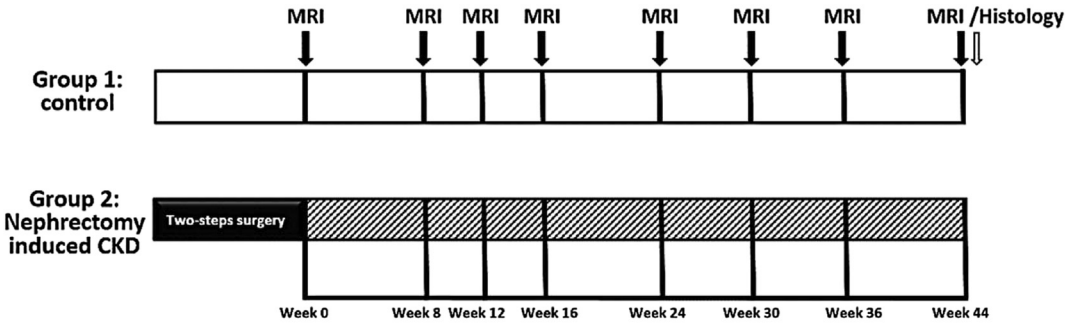

Fig. 1. A schematic illustration of the protocol design in this study. (↓) indicates MRI (⇩); indicates histologic examination.

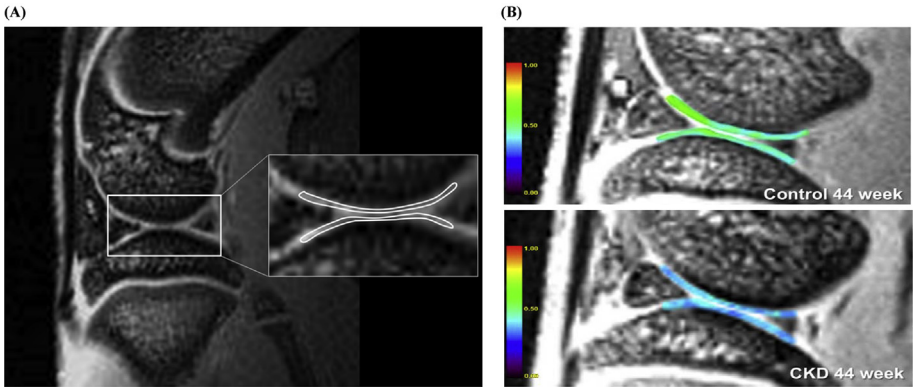

Fig. 2. ROI in a representative knee cartilage. (A) ROIs (white) in the articular cartilage were selected using the DCE first-frame and MRI $T2^*$ first-echo sagittal images. The lateral and medial articular cartilages were measured in the same manner. (B) The DCE results (amplitude *A* map) of medial femoral and tibial cartilages of the right knee in 44-week-old control and CKD rats. Significant hypoperfusion in knee articular cartilage can be noted in the CKD group (lower) but not in the control group (upper).

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