Osteoarthritis and Cartilage 21 (2013) 434–442

Osteoarthritis and Cartilage

In vivo comparison of delayed gadolinium-enhanced MRI of cartilage and delayed quantitative CT arthrography in imaging of articular cartilage

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ARTICLE INFO

Article history:
Received 2 July 2012
Accepted 16 December 2012

Keywords:
Articular cartilage
MRI
Contrast-enhanced computed tomography
Arthroscopy
Osteoarthritis
Knee joint

SUMMARY

Objective: To compare delayed gadolinium-enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) and delayed quantitative computed tomography (CT) arthrography (dQCTA) to each other, and their association to arthroscopy. Additionally, the relationship between dGEMRIC with intravenous ($dGEMRIC_{IV}$) and intra-articular contrast agent administration ($dGEMRIC_{IA}$) was determined.
Design: Eleven patients with knee pain were scanned at 3 T MRI and 64-slice CT before arthroscopy. dQCTA was performed at 5 and 45 min after intra-articular injection of ioxaglate. Both $dGEMRIC_{IV}$ and $dGEMRIC_{IA}$ were performed at 90 min after gadopentetate injection. dGEMRIC indices and change in relaxation rates (ΔR_1) were separately calculated for $dGEMRIC_{IV}$ and $dGEMRIC_{IA}$. dGEMRIC and dQCTA parameters were calculated for predetermined sites at the knee joint that were International Cartilage Repair Society (ICRS) graded in arthroscopy.
Results: dQCTA normalized with the contrast agent concentration in synovial fluid (SF) and $dGEMRIC_{IV}$ correlated significantly, whereas $dGEMRIC_{IA}$ correlated with the normalized dQCTA only when $dGEMRIC_{IA}$ was also normalized with the contrast agent concentration in SF. Correlation was strongest between normalized dQCTA at 45 min and $\Delta R_{1,IV}$ ($r_s = 0.72$ [95% CI 0.56–0.83], $n = 49$, $P < 0.01$) and $\Delta R_{1,IA}$ normalized with ΔR_1 in SF ($r_s = 0.70$ [0.53–0.82], $n = 52$, $P < 0.01$). Neither dGEMRIC nor dQCTA correlated with arthroscopic grading. $dGEMRIC_{IV}$ and non-normalized $dGEMRIC_{IA}$ were not related while $\Delta R_{1,IV}$ correlated with normalized $\Delta R_{1,IA}$ ($r_s = 0.52$ [0.28–0.70], $n = 50$, $P < 0.01$).
Conclusions: This study suggests that dQCTA is in best agreement with $dGEMRIC_{IV}$ at 45 min after CT contrast agent injection. dQCTA and dGEMRIC were not related to arthroscopy, probably because the remaining cartilage is analysed in dGEMRIC and dQCTA, whereas in arthroscopy the absence of cartilage defines the grading. The findings indicate the importance to take into account the contrast agent concentration in SF in dQCTA and $dGEMRIC_{IA}$.

Introduction

In osteoarthritis (OA) articular cartilage is progressively degenerated. One of the earliest signs of cartilage degeneration is loss of glycosaminoglycan (GAG) side chains of proteoglycans[1,2], particularly at the superficial layer. Other early degenerative changes in cartilage include the deterioration of the collagen network and an increase in water content[1,3]. There are several factors predisposing to OA, including age, obesity, joint injuries, and genetics[2,4]. Further,

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1063-4584/$ – see front matter
http://dx.doi.org/10.1016/j.joca.2012.12.009

cartilage injuries, *e.g.*, after joint trauma, lead often to the development of OA[2,5]. There are different treatment options for focal cartilage lesions[6–8] and thus, early and accurate diagnosis of the cartilage lesions and degenerative changes are important.

Clinical diagnosis of OA is based on the physical examination and observation of changes on plain radiographs, occasionally followed by magnetic resonance imaging (MRI) or arthroscopy. Unfortunately, current clinical imaging methods are not sensitive enough to detect cartilage lesions and early OA changes in cartilage. Arthroscopy is still considered as the gold standard for the evaluation of cartilage lesions, although it is based on subjective visualization and palpation, hence, it includes large inter-observer and moderate intra-observer variability[9–11].

When aiming at earlier diagnosis of the lesions and early OA changes in cartilage, noninvasive determination of structural and compositional changes of cartilage tissue is an advantage. One approach to probe the composition of articular cartilage is to use negatively charged contrast agent to enhance MR or computed tomography (CT) imaging. These methods are based on assumption that negatively charged contrast agent distributes into cartilage in an inverse relation to the fixed charge density in cartilage associated with GAG content of the cartilage[12,13]. Therefore, higher concentration of anionic contrast agent diffuses into degraded cartilage than into intact cartilage. Diffusion and distribution of contrast agent are, however, influenced also by other factors in cartilage, *e.g.*, collagen and water content[14–17].

With regard to MRI, a technique called delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is based on the aforementioned properties and it has been proposed for quantitative estimation of the GAG concentration in cartilage[12,13,18]. The dGEMRIC method has been applied both *in vitro*[18–20] and *in vivo*[13,21,22]. While the specificity of dGEMRIC to GAG has been recently questioned[14,17,23], it is reported to sensitively detect degenerative changes in cartilage[21].

In the dGEMRIC method, the contrast agent (gadopentetate, charge −2) can be administered either intravenously ($dGEMRIC_{IV}$) or intra-articularly ($dGEMRIC_{IA}$). Intravenously injected contrast agent may enter the cartilage both through the cartilage surface and from the subchondral bone whereas intra-articularly injected contrast agent can diffuse only through the surface[13]. Although diffusion of the contrast agent from the subchondral bone was slow or negligible in recent *in vitro* and *in vivo* studies[14,17,23], the transportation of the contrast agent into the cartilage in the intravenous and intra-articular dGEMRIC methods may be different. At the moment, there are no *in vivo* studies comparing the intravenous and intra-articular dGEMRIC methods in a knee joint of a same patient.

Contrast-enhanced CT, an analogous X-ray technique to dGEMRIC, also employs contrast agent (*e.g.*, anionic ioxaglate, charge −1). There are a range of *in vitro* studies in which the contrast-enhanced CT technique has shown its potential in assessment of GAG content[24–28] and biomechanical properties[24,29] of cartilage, as well as in detection of cartilage injuries[30,31]. Contrast-enhanced CT, referred to as delayed quantitative CT arthrography (dQCTA) in the present study, has recently been tested *in vivo*[32], but it has not been thoroughly validated in clinical settings.

Although the dGEMRIC and contrast-enhanced CT techniques were initially designed to probe GAG content of the cartilage as well as degenerative stage of cartilage[12,13,25,33–36], they have not been systematically compared *in vivo* for the same patients. In the present study, both dGEMRIC and dQCTA were conducted *in vivo* for patients referred to a knee arthroscopy because of knee pain symptoms. The hypotheses of the study were: (1) a strong linear correlation between dGEMRIC and dQCTA parameters should be found, (2) both dGEMRIC and dQCTA parameters should be related to arthroscopic grading of cartilage, and (3) $dGEMRIC_{IV}$ should be significantly related to $dGEMRIC_{IA}$.

Methods

Study subjects

Eleven consecutive patients (eight females and three males) referred to an arthroscopic surgery of the knee because of persistent knee pain symptoms were enrolled in the present study (Table I). One patient declined arthroscopy but completed all imaging studies and one patient was excluded from the analysis due to irregular distribution of contrast agent in joint. Before arthroscopy, MRI (three imaging sessions) and CT (two imaging sessions) examinations were performed as described in Fig. 1. Informed consent was obtained from all patients. The study was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland (No. 33/2010).

MRI

For MRI, each patient was scanned three times on a 3 T scanner (Siemens Skyra, Siemens Healthcare, Erlangen, Germany) with a dedicated 15-channel transmit/receive knee coil (Quality Electrodynamics (QED), MayField Village, OH, USA). For anatomical imaging, double echo steady state (DESS) sequence with water excitation (repetition time (TR)/time to echo (TE) = 14.1/5 ms, field of view (FOV) = 150*150 mm^2, matrix = 256*256, slice thickness = 0.6 mm) was performed in first imaging session whereas T_1 relaxation times were measured in all three sessions. Prior to contrast agent administration, single-slice T_1 mapping was performed at the centre of medial and lateral condyles using an inversion recovery fast spin echo (IR-FSE) sequence (TR/TE/inversion time (TI) = 4060/8.6/50, 100, 200, 400, 800, 1600, 3200, and 3900 ms; FOV = 120*120 mm^2; matrix = 256*256; slice thickness = 3 mm). Subsequently, 0.2 mM/kg (double dose) of gadopentetate (Gd-$DTPA^{2-}$, Magnevist™) was injected intravenously, followed by active flexion-extension exercises of the knee for 5 min and walking for 5 min. T_1 measurements were repeated at 90 min after intravenous administration of Gd-$DTPA^{2-}$ using the same imaging parameters[21,33]. Two weeks after the previous imaging session, $dGEMRIC_{IA}$ was performed after a 20 ml dose of an ioxaglate − Gd-$DTPA^{2-}$ contrast agent mixture (105 mM Hexabrix™ 320, Guerbet, Roissy, France and 2.5 mM Magnevist™, Bayer HealthCare Pharmaceuticals, Berlin, Germany; diluted in 0.9% saline;

Table I
Description of the patients and their preliminary diagnosis according to international classification of diseases (ICD)-10 codes

Patient	Gender	Age (years)	Height (cm)	Weight (kg)	Body mass index (BMI) (kg/m^2)	Preliminary diagnosis (ICD-10)
1	Male	66	170	71	24.6	M23.2
2	Male	59	176	101	32.6	M23.2
3	Female	55	165	75	27.5	M23.2
4	Female	63	167	73	26.2	M23.2
5	Female	61	167	70	25.1	S83.2
6	Female	40	163	73	27.5	M17.1
7	Female	50	168	90	31.9	M23.2
8	Female	68	152	67	29.0	S83.2
9	Female	55	170	98	33.9	M23.2
10	Female	58	164	55	20.4	M23.2

M17.1 = other primary arthrosis of the knee.
M23.2 = derangement of meniscus due to old tear or injury.
S83.2 = current tear of meniscus.