Skeletal Radiol (1994) 23:535–539

Skeletal Radiology

# Magnetization transfer contrast (MTC) and MTC-subtraction: enhancement of cartilage lesions and intracartilaginous degeneration in vitro

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**Abstract.** Human articular cartilage from 16 cadaveric or amputated knees was studied using standard magnetic resonance imaging (MRI), on-resonance magnetization transfer contrast (MTC) and MTC-subtraction MRI. Results were compared with subsequent macroscopic and histopathological findings. MTC-subtraction and T2-weighted spin-echo images visualized cartilaginous surface defects with high sensitivity and specificity. MTC and T2-weighted spin-echo images revealed intra-cartilaginous signal loss without surface defects in 80% of the cases, corresponding to an increased collagen concentration. It is concluded that MTC is sensitive to early cartilage degeneration and MTC-subtraction can be helpful in detecting cartilage defects.

**Key words:** Magnetization transfer contrast – Cartilage – MTC-subtraction – Collagen

Magnetic resonance imaging (MRI) is a helpful imaging technique for detecting cartilaginous lesions. Several sequences have been used to increase its sensitivity in detecting surface lesions. Three-dimensional spoiled gradient-echo techniques with short repetition times (TR 40–50 ms), short echo times (TE 5–10 ms), and intermediate flip angles (30°–60°) achieve sensitivities in detecting chondroid lesions of more than 80% [1–3]. With injection of gadolinium-DTPA into the joint (MR arthrography), sensitivity can be increased to 86% [4, 5]. Fat-suppressed spin-echo sequences are also quite sensitive to surface defects as well as focal water loss [ 6, 7]. A combination of gradient-echo imaging and fat-suppression can even approach a sensitivity of 96% [16].

Recently, magnetization transfer contrast (MTC), a new MRI technique, has been introduced. This technique is based on a magnetization exchange (magnetization transfer) and relaxation exchange (cross relaxation) between macromolecule-bound and free protons. These exchange processes depend on the relationship of free water to macromolecules and are both different and characteristic for various tissues. Cartilage in particular is known to be sensitive to magnetization transfer effects [8].

In this study we wish to establish the value of MTC imaging of human articular cartilage for the imaging of surface defects and cartilage itself.

## Materials and methods

Sixteen cadaveric and amputated knees were studied. The patient's age at death or amputation ranged from 25 to 91 years ($\bar{x}$ = 60 ± 14 years). The cause of death or amputation was cardiac failure ($n$ = 4), malignancy ($n$ = 2), and arterial occlusive disease ($n$ = 10). There was no prior history of any knee operation or severe knee complaint apart from osteoarthritis in three patients. The positioning of the knee specimen for MRI was kept constant. The knees were first imaged using MRI and then arthrotomized. We used a 0.5 superconducting MRI system (T5, Philips). A section thickness of 4 mm, a field of view of 160 × 160 mm$^2$, a matrix of 256$^2$, the volume knee coil, two excitations, and sagittal and axial planes were chosen for all sequences. For standard spin-echo T1-weighted (T1-W) sequences a TR of 600 ms and a TE of 18 ms was used. For spin-echo T2-weighted (T2-W) sequences a TR of 2000 ms and a TE of 80 ms was used. For MTC images the T1-W spin-echo sequence was combined with a four-element composite on-resonance prepulse (1$\bar{1}\bar{1}$1). Each prepulse element had a flip angle of 180°, 1 ms duration, and shortest interval time. In five cases this MTC protocol was also combined with a nonspoiled gradient-echo sequence (FFE) with a TR of 400 ms, a TE of 13.8 ms (i.e., in-phase echo-time at 0.5 tesla) and a flip angle of 30°. In order to produce MT-subtraction images, FFE and MT-FFE images were subtracted using the regular postprocessing software provided by the manufacturer (Philips Medical, Gyroscan release 3).

After MRI the knees were arthrotomized by an orthopedic surgeon. All visible cartilaginous lesions were staged according to the Outerbridge classification grading lesions from 1 to 4 as follows: grade 1, cartilage swelling and softening; grade 2, cartilage thinning less than 50 %; grade 3 cartilage thinning more than 50 % but without exposure of subchondral bone; grade 4 complete loss of cartilage with subchondral bone exposure.

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MR images were analyzed by two radiologists. Cartilage abnormalities were divided into surface defects rating from Outerbridge grade 2 to 4 and signal inhomogeneities within the cartilage below a regular surface. For each group the decision was made by consensus as to which sequence best visualized the abnormality.

In three knees with intracartilaginous signal inhomogeneities but no visible surface defects, corresponding cross-sections were obtained. For histological correlation hematoxylin-eosin (HE) staining was performed. In order to visualize the collagen distribution within the cartilage van Gieson stains, and in order to visualize mucopolysaccharides alcian blue staining was performed.

To evaluate the MT effect, signal intensities within regions of interest of cartilage, muscle, bone-marrow, posterior cruciate ligament, and background were measured. As a reference phantom we used a tube of copper sulfate solution with no expected MT effect, but with short T1 and long T2 relaxation times.

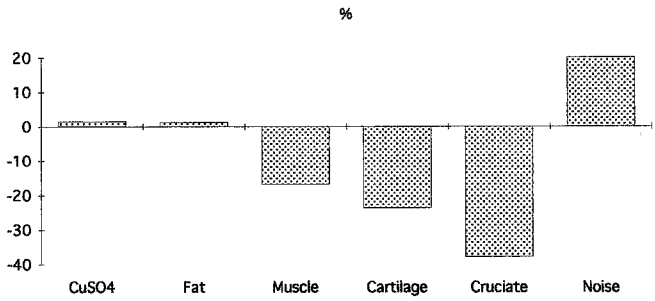


**Fig. 1.** Signal intensity changes in percent after application of the magnetization transfer contrast (MTC) pulse. $CuSO_4$, copper sulfate solution; *Noise*, standard deviation of background signal

## Results

MTC effects were most intense within cartilage and the cruciate ligaments. Fat and copper sulfate solution did not show MT effects (Figs. 1, 2).

Arthrotomy revealed ten superficial cartilage lesions of the femoropatellar cartilage. There were one grade 2, three grade 3, and six grade 4 lesions. All of these were rated correctly by MRI using T2-weighted spin-echo images (Fig. 3). T1-weighted spin-echo and MT images showed poor visualization of surface defects due to an inferior contrast between cartilage and joint fluid. Subtraction MT images achieved improved visualization of these surface defects (Fig. 4).

MRI revealed a focal or geographic reduction of the signal intensity within the cartilage in areas with an intact surface in 13 cases. These signal inhomogeneities were best shown on T2-weighted spin-echo images (Fig. 5). T1-weighted spin-echo images did not show significant signal variances. The MT images also showed a decrease in signal intensity. The signal reduction on MT images, however, was not as clear as on the T2-weighted images and could be sufficiently appreciated in six cases only.

Histological examination of cartilage which revealed signal reduction on T2-weighted spin-echo and MT images showed areas of increased color concentration using van Gieson stain (Fig. 6). This corresponds to an increased collagen concentration. The alcian blue stain showed an irregular staining pattern, corresponding to inhomogeneous proteoglycan concentration. Sections with hematoxylin and eosin staining did not show abnormalities within these areas. Normal areas on the MR images had corresponding by normal color distribution and sections.

## Discussion

Our results confirm MRI as a highly sensitive and specific diagnostic tool in visualization of cartilage lesions. However, discussion about the best sequence to use continues. Two basic contrasts for cartilage display have to be considered:

1. Cartilage of high signal intensity contrasting with low-signal-intensity joint fluid, synovium, etc.
2. Cartilage of low signal intensity contrasting with surrounding tissues of high signal intensity.

Techniques displaying contrast of type I (bright cartilage) are T1-weighted spin-echo, T1-W or mixed weighted gradient-echo sequences, and fat-saturated sequences. A recent in vivo study advocated a fat-suppressed spoiled gradient-echo sequence with short TR and TE and large flip angle as the best technique in cartilage imaging [9].

Techniques generating images of the second type of contrast (relatively dark cartilage) are the T2-W spin-echo sequences and MR arthrography.

We found a 100% sensitivity and specificity in detecting cartilaginous lesions using the T2-weighted spin-echo sequence. This in vitro finding, however, may not be transferable to in vivo studies, since there were no arterial pulsation and movement to alter image quality. Another limitation is the small number of lesions. However, since our goal was to investigate the possibilities of MT imaging for human articular cartilage, this was not a major drawback.

The new MT technique can be used to image cartilage with the first type of contrast (bright cartilage) by subtraction. We found encouraging results using this technique. Due to hardware and software upgrading, subtraction could not be applied to all images and our comparative results using subtraction are therefore somewhat limited. However, image quality was impressive and further studies should compare MTC subtraction with fat-suppressed gradient-echo sequences. The highest possible MT energy deposition within the limits of the official SAR values yielded the best results, since cartilage signal reduction was then highest. The subtracted image in these cases results in highest signal intensity for articular cartilage and better contrast with surrounding tissues, including fluid with little or no signal. In a preliminary study in addition to the present one we found no major quality differences between using on-resonance and off-resonance tech-niques at 1.5 or 0.5 tesla magnetic field strength.

Histologically, human articular cartilage is composed of four zones [10]. The superficial or tangential zone comprises about 2%–3% of the cartilage thickness, re-

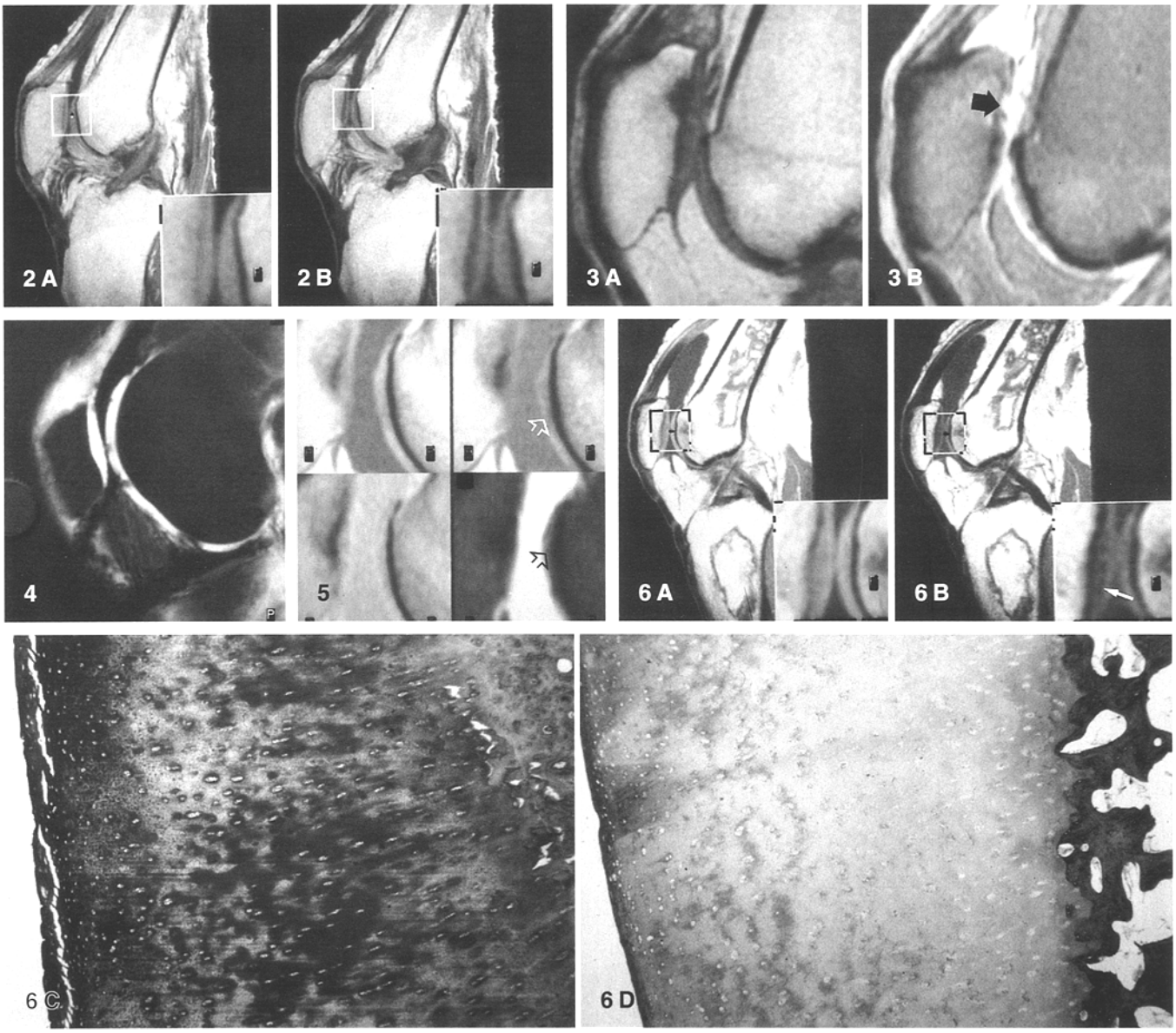


**Fig. 2A, B.** Cadaveric knee **A** without and **B** with application of an MTC prepulse, showing signal reduction of the anterior cruciate ligament, cartilage, and muscles. The signal reduction of cartilage in this case is most marked in the basal region. No signal change of fat is seen

**Fig. 3A, B.** Osteoarthritis of the knee. Grade 4 cartilaginous lesion of the patellar cartilage. **A** MTC image, **B** T2-weighted spin-echo image. Due to improved fluid/cartilage contrast, the lesion is shown better on the T2-weighted image (*arrow*)

**Fig. 4.** MTC subtraction image revealing low-grade femoral cartilage lesions. The copper sulfate phantom in front of the patella demonstrates good subtraction quality

**Fig. 5.** T1-weighted (*left upper*), MTC (*right upper*), proton density-weighted (*left lower*), and T2-weighted (*right lower*) images. The MTC and T2-weighted images show focal signal loss (*arrows*)

**Fig. 6A–D.** Cadaveric knee with several infarcts. **A** T1-weighted spin-echo image showing normal cartilage; **B** MTC image showing a marked signal decrease within the patellar cartilage (*arrow*); **C** histological section with van Gieson staining corresponding to the indented area on the MR images. Note the marked increase in staining due to increased collagen concentration. **D** Van Gieson stain of normal cartilage for comparison

veals flat, spindle-like chondrocytes, and is rich in collagen fibers. The transitional zone comprises 5% of the cartilage thickness and displays more spherical cells. The collagen fibers in the superficial and transitional zone are horizontally orientated. The radial zone comprises 92% of the cartilage thickness. The chondrocytes in this region are the largest in size and organized in vertical columns; collagen in this region is oriented vertically. The basal calcified zone compromises 1% of the cartilage thickness and represents the junction to the subchondral bone plate.

These four histological zones cannot be visualized individually by MRI. However, recent reports indicate that, due to variances in the water content, the superficial

and transitional zones reveal different signal intensities compared with the radial and calcified zones [11, 12]. In one study, signal distribution across normal cartilage corresponded well with the proteoglycan concentration, showing a bell-shaped distribution pattern [13]. We also saw zonal signal intensity variances which were emphasized on T1-W spin-echo images, with a small superficial layer of intermediate signal intensity, a broad middle zone with higher signal intensity, and a small basal zone of signal void. On T2-W spin-echo images, the basal zone, which most suggestive corresponds to the calcified zone, appears broader, probably due to susceptibility effects at the calcifying border to the radial zone. The superficial layer was not visible on the T2-W spin-echo images; instead one high-signal-intensity zone was evident. This might be explained by a poorer signal-to-noise ratio of the T2-W spin-echo images.

The MT images did not demonstrate a zonal pattern of the signal intensity distribution within normal cartilage, apart from the signal void within the basal layer. We saw instead a homogeneous intermediate signal intensity distribution within the cartilage. This might be explained by the overall loss of signal intensity by cartilage after the MTC pulse, minimizing contrast between individual cartilage layers. MTC effects should therefore be different in intensity in the various cartilage layers. Indeed, differences in MTC intensity within cartilage layers were recently demonstrated by MR microscopy at 9.4 and 11.7 tesla [14]. Corresponding to that study, the MTC effect within the tangential zone was highest.

Articular cartilage is an anisotropic tissue, revealing signal variances depending on the orientation within the main magnetic field [15]. Typically, an orientation of 55° causes higher signal intensity of anisotropic tissue due to changes in spin-spin and spin-lattice coupling ("magic angle phenomenon"). These effects have recently been demonstrated to occur particularly within the radial zone of cartilage [15]. In order to avoid signal variations due to this anisotropic effect, all our experiments were performed with identical positioning of the knee specimen. The observed decreases of signal intensity in some cartilage areas of our specimen are therefore not influenced by this magic angle phenomenon.

Our finding of increased collagen concentration within areas of increased MTC corresponds well with other published results [16]. According to one study, the collagen type II molecules are responsible for most of the MTC effect within cartilage [17]. In contrast, proteoglycans are barely sensitive to MTC. These authors postulate the presence of an increased collagen concentration due to focal water loss in early osteoarthritis.

Lesperance and coworkers [18] also demonstrated the dependence of the MT effect on the collagen concentration. These authors additionally found a dependence of MTC on the collagen structure. Heating of the collagen led to increased MT effect due to increased interaction of macromolecule and water protons. Heating beyond the denaturation point, by contrast, caused a decrease in the MT effect. This shows the importance for MTC of the collagen structure in a triple helix form, which is lost with denaturation.

Early osteoarthritis is also known to be accompanied by proteoglycan degradation with a loss of water-binding proteoglycan molecules [15]. However, this change may not be visualized by MTC images, due to the inferior MTC effects of proteoglycans. Changes within the proteoglycan concentration and water content can be better visualized by T2-W sequences and fat-saturated sequences [7]. In our study the T2-W images depicted focal signal loss more frequently than MTC images.

In summary, MTC subtraction images are well suited to visualizing cartilage surface defects. With this technique cartilage is displayed with high signal intensity while effusion or surrounding tissues reveal no or low signal intensity.

MTC images of cartilage are able to depict early intracartilage degeneration due to an increased focal collagen concentration, which leads to a higher signal reduction on MTC images. However, due changes in water content and proteoglycan concentration, T2-W images are more sensitive to intracartilage degeneration.

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