MRI of bioregenerative approaches in cartilage repair: Differentiation of repair tissue after matrix-associated autologous chondrocyte transplantation using a hyaloronic acid-based or a collagen-based scaffold with advanced morphological scoring and biochemical T2 relaxation time mapping

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Introduction: Over the past decade, one of the most active areas of biomaterials research has involved cartilage repair (1). After the first human autologous chondrocyte transplantation (ACT) reported by Brittberg and co-corkers in 1994, the development of new techniques, the so-called second and third generations of ACT, have led investigators to focus on bioregenerative approaches using tissue engineering techniques with chondrocytes cultured on biomaterials . These biologic scaffolds, as carrier vehicles and matrices for cartilage repair, are in many of the reported techniques based on collagen or hyaluronic acid (HA) (2,3). To measure the morphological integration and the biochemical constitution of the cartilage repair tissue noninvasively, magnetic resonance imaging (MRI) is the method of choice. A validated scoring system for the morphological MR evaluation of cartilage repair sites is the magnetic resonance observation of cartilage repair tissue (MOCART) system (4). The biochemical evaluation of the ultrastructural organization of the repair tissue can be achieved by biochemical MR techniques. Whereas T1 relaxation time in the presence of Gd-DTPA^{2-} (delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)) reflects the proteoglycan content of articular cartilage, T2 relaxation time is sensitive to the integrity and orientation of the collagen network and hydration (5). Together with chondrocytes, the collagen fiber ultrastructure and the matrix contribute to the zonal appearance of hyaline cartilage, which explains its complex biomechanical profile.

The two main goals of matrix-associated ACT (MACT) using HA- or collagen-based scaffolds are (i) the integration into the surrounding cartilage, and (ii) the ability to proliferate and phenotypically express chondrocytic functions, producing extracellular matrix and type II collagen. Based on this, the aim of the present study was to compare cartilage repair tissue after MACT of the femoral condyle using Hyalograft® C (HC), an HA-based scaffold, to cartilage repair tissue after MACT of the femoral condyle using CaReS®, a collagen-based scaffold, noninvasively with morphological MOCART scoring and biochemical T2 mapping.

Material and Methods: Twenty patients who had undergone MACT were included in the study. The scaffold used for MACT was Hyalograft® C in ten patients and CaReS® in the ten other patients. HC is entirely based on the benzylic ester of hyaluronic acid (HYAFF11®). CaReS® is composed of chondrocytes seeded on a three-dimensional collagen type I gel. The patients with a post-operative follow-up of 24 months were selected from a larger cohort and prospectively included in this study, with the aim to, as much as possible, guarantee the comparability of cartilage repair tissue built after MACT using CaReS® to repair tissue after MACT with HC within the two groups (CaReS® (28.9 ± 6.1 years) versus HC (30.7 ± 5.2 years) (p=0.237)). MRI was performed on a 3 T MR scanner (Siemens, Erlangen, Germany); the protocol for both groups was identical and consisted of a morphological coronal 3D true–fast imaging with steady-state precession sequence for the morphological assessment, and a sagittal, multi-echo spin-echo (SE) sequence using six echoes for quantitative T2 mapping. Morphological evaluation was performed by the MOCART score with a maximum score of 100, achievable in the evaluation of the nine variables: repair filling (1), integration of the cartilage repair tissue (2), structure of the surface (3), structure of the repair tissue (4), signal intensity (5), constitution of the subchondral lamina (6), and the subchondral bone (7), possible adhesions (8), and effusion (9). T2 maps were obtained in-line by a pixel-wise, mono-exponential, non-negative least squares (NNLS) fit analysis (MapIt, Siemens, Erlangen, Germany). A ´mean and zonal (deep and superficial) region of interest (ROI) analysis was performed in the areas of cartilage repair and in the native surrounding control cartilage. Comparison of the two groups was performed by statistical analysis of variance.

Results: When comparing the MOCART score of all patients in the CaReS® group (76.5 ± 12.7) and all patients in the HC group (70.0 ± 9.4), no significant difference could be found (p=0.210). The single variables of the MOCART scoring system revealed no significant difference in eight of nine variables (p=0.331 to p=1.000). The surface of the repair tissue, however, appeared to be in better condition in the CaReS® group compared to the HC group (p=0.004).

The healthy reference cartilage showed comparable T2 relaxation times (ms), with mean values of 51.9±8.8 for the CaReS® group and 49.9±7.4 for the HC group (p=0.398). When looking at the cartilage repair tissue, mean T2 relaxation times were significantly higher for the CaReS® group (55.5±10.4) compared to the HC group (48.2±8.5) (p=0.011). For the zonal T2 values, comparable results were found. The zonal increase in the T2 values between the deep and the superficial cartilage aspects was significant for the reference cartilage (p<0.001) and the cartilage repair tissue (p<0.05) for both groups. The also-evaluated difference between the reference cartilage and the cartilage repair tissue revealed a significant increase for the deep zone (p=0.031), but not for the superficial zone (p=0.166) in the CaReS® group, and no significant difference in the deep (p=0.933) or the superficial (p=0.079) zone in the HC group.

Discussion: In the present study, morphological results evaluated with the MOCART score were comparable in patients after MACT with CaReS® and/or HC for eight of nine variables. Only the surface of the repair tissue seemed to be of superior quality in the patients from the CaReS® group compared to the HC group. The biochemical MR assessment, however, revealed a difference between MACT based on HC and MACT based on CaReS®, when looking at the quantitative T2 values of the respective cartilage repair tissues. Although there are severe limitations, the present initial study is, to our knowledge, the first *in vivo* approach to the differentiation of two different scaffolds used for MACT in a patient study. The impact of the reported differences in the morphological and the biochemical description of the cartilage repair tissue must be clarified in future studies. Nevertheless, higher T2 values for the cartilage repair tissue based on a collagen scaffold (CaReS®), compared to the hyaloronic-acid based scaffold (HC), may indicate differences in the composition of the repair tissue, even two years after implantation. These results point out that different scaffolds may cause differences in T2 relaxation times, which must be taken into account when T2 mapping is used to biochemically assess the composition of the repair tissue in the follow-up after MACT.

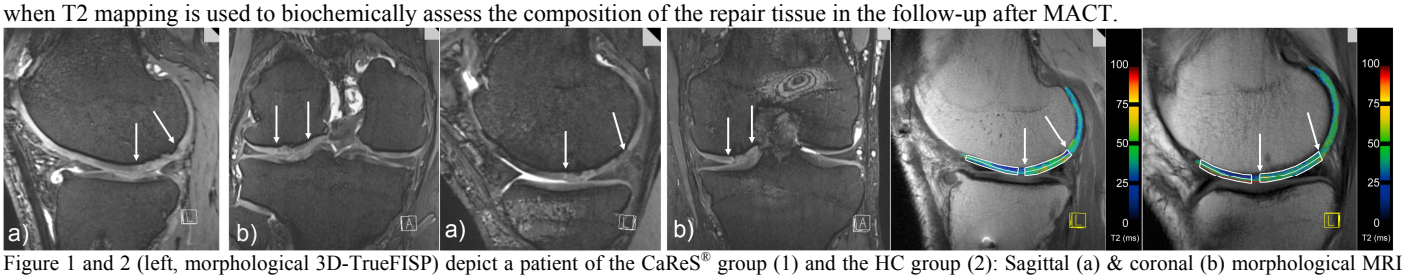

Figure 1 and 2 (left, morphological 3D-TrueFISP) depict a patient of the CaReS® group (1) and the HC group (2): Sagittal (a) & coronal (b) morphological MRI based on the MPR of a 3D-TrueFISP data set. Arrows mark the cartilage repair tissue after MACT of the femoral condyle. Figures 3 and 4 (right, T2 maps) visualize the same patients of the CaReS® group (3) and the HC group (4) with the ROI of the repair tissue (arrows) and the native control cartilage.

References: 1. Galois L et al. *Biorheology.* 2004. 2. Marlovits S et al. *European Journal of Radiology.* 2006 3. McNickle AG et al. *Sports Med Arthrosc.* 2008 4. Marlovits S et al. Eropean Journal of Radiology 2006. 5. T.J. Mosher et al. Semin Musculoskelet Radiol. 2004.