ORIGINALARBEIT

Comparison of multiple quantitative MRI parameters for characterization of the goat cartilage in an ongoing osteoarthritis: dGEMRIC, $T_{1\rho}$ and sodium

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Abstract

Rationale and Objectives: *Osteoarthritis (OA) is a degenerative joint disease leading to cartilage deterioration by loss of matrix, fibrillation, formation of fissures, and ultimately complete loss of the cartilage surface. Here, three magnetic resonance imaging (MRI) techniques, dGEMRIC (delayed Gadolinium enhanced MRI of cartilage; $dG_1=T_{1,post}$; $dG_2=1/T_{1,post}-1/T_{1,pre}$), $T_{1\rho}$,and sodium MRI, are compared in a preclinical in vivo study to evaluate the differences in their potential for cartilage characterization and to establish an examination protocol for a following clinical study.*

Materials and Methods: *OA was induced in 12 caprine knees (6 control, 6 therapy). Adipose derived stem cells were injected afterwards as a treatment. The animals were examined healthy, 3 and 16 weeks postoperatively with all three MRI methods.*
Using statistical analysis, the OA development and the degree of correlation between the different MRI methods were determined.

Results: *A strong correlation was observed between the dGEMRIC indices dG_1 and dG_2 (r=–0.87) which differ*

Vergleich mehrerer quantitativer MRT Parameter zur Charakterisierung des Ziegenknorpels während einer fortschreitenden Arthrose: dGEMRIC, $T_{1\rho}$ und Natrium

Zusammenfassung

Einleitung und Problemstellung: *Die Arthrose ist eine degenerative Gelenkserkrankung, die zu einem Knorpelverschleiß führt. Dies beinhaltet den Umbau der strukturellen Zusammensetzung, wie die Auffaserung der Oberfläche, Fibrillation bis hin zu tiefen Fissuren oder dem kompletten Verlust des Knorpels. In dieser Arbeit werden drei Magnetresonanztomographische (MRT) Methoden – dGEMRIC (verzögerte und durch Gadolinium verstärkte MRT des Knorpels; $dG_1=T_{1,post}$; $dG_2=1/T_{1,post}-1/T_{1,pre}$), $T_{1\rho}$, und Natrium-MRT – in einer präklinischen In-vivo-Studie miteinander verglichen, um deren Potential zur Knorpelcharakterisierung zu evaluieren und ein Untersuchungsprotokoll für eine klinische Folgestudie zu etablieren.*

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only in considering or not considering the T_1 baseline. Moderate correlations were found between $T_{1\rho}$ and dG_1 (r=0.55), $T_{1\rho}$ and dG_2 (r=0.47) and at last, sodium and dG_1 (r=0.45).
The correlations found in this study match to the biomarkers which the methods are sensitive to.

Conclusion: *Even though the goat cartilage is significantly thinner than the human cartilage and even more in a degenerated cartilage, all three methods were able to characterize the cartilage over the whole period of time during an ongoing OA.*
Due to measurement and post processing optimizations, as well as the correlations detected in this work, the overall measurement time in future goat studies can be minimized. Moreover, an examination protocol for characterizing the cartilage in a clinical study was established.

Keywords: Osteoarthritis, cartilage, MRI, preclinical study

Material und Methoden: *12 Ziegen (6 Therapie-, 6 Kontrollgruppe) wurden eine Arthrose im Kniegelenk induziert. Der Therapiegruppe wurden aus Fettgewebe gewonnene Stammzellen als Therapie re-injiziert. Alle Tiere wurden gesund, 3 und 16 Wochen nach der Operation mit allen drei MRT-Methoden untersucht.*
Mit statistischen Analysen wurden die Entwicklung der Arthrose und das Maß der Korrelation zwischen den einzelnen MRT-Methoden bestimmt.

Ergebnisse: *Zwischen den beiden dGEMRIC-Indizes dG_1 und dG_2, die sich in der Berücksichtigung einer T_1-Normierung unterscheiden, wurde eine starke Korrelation festgestellt (r=–0.87). Des Weiteren ergaben sich moderate Korrelation zwischen $T_{1\rho}$ und dG_1 (r=0.55), $T_{1\rho}$ und dG_2 (r=0.47) und zuletzt Natrium und dG_1 (r=0.45).*

Zusammenfassung: *Obwohl der Ziegenknorpel signifikant dünner ist als beim Menschen und das Volumen des Ziegenknorpels während einer Arthrose noch zusätzlich abnimmt, konnte der Knorpel mit allen drei MRT-Methoden über die gesamte Studiendauer charakterisiert werden.*
Durch Optimierungen von Messung und Nachbearbeitung sowie die in dieser Arbeit ermittelten Korrelationen kann die Gesamtmesszeit in zukünftigen Ziegenstudien minimiert werden. Weiterhin konnte ein Untersuchungsprotokoll zur Knorpelcharakterisierung für eine klinische Studie etabliert werden.

Schlüsselwörter: Arthrose, Knorpel, MRT, Präklinische Studie

Introduction

Osteoarthritis (OA) is a degenerative joint disease leading to a loss of matrix, fibrillation, formation of fissures, and ultimately complete loss of the cartilage surface. Up to date, no efficient therapy is available to treat OA completely [1–3].

For the development of new therapy strategies preclinical studies are mandatory. The European medicines agency (EMA) recommends the goat as the large animal model for cartilage repair of the knee [4]. Nevertheless, there are only few studies published on monitoring and characterization of the goat knee cartilage using magnetic resonance imaging (MRI) [5,6].

Cartilage can be divided into four layers: superficial, middle, radial and calcified region [7–9]. The structure and composition of the cartilage varies with the depth. A healthy hyaline cartilage consists of few chondrocytes (1% of the volume), an extracellular matrix containing mainly water (65–80%), a macromolecular matrix with proteoglycans (PG; 3–10%) and type-II collagen (15–20%). Attached to the PGs, there are glycosaminoglycans (GAG), which are negatively charged and therefore attract free floating positive charged sodium ions Na^+ [7,10] (cf. Figure 1a). In early stages of an ongoing OA, a depletion of PGs and GAGs can be observed directly proportional to the severity of the disease (cf. Figure 1b). Taking into account, that more than half of the population above the age of 65 is affected by this disease [11–13], the possibility of an early diagnosis and the development of an efficient treatment is absolutely mandatory.

Because of the slow progression of OA (10–20 years in humans), prophylactic medical examinations and validating the efficiency of treatments in humans requires noninvasive monitoring techniques that can directly assess molecular changes associated with early stages of cartilage degeneration that precede morphological changes like lesions or joint narrowing.

Due to its superior soft-tissue contrast, MRI has emerged to be the favorable imaging technique for the assessment of articular cartilage. In the clinic, mostly conventional MRI sequences are routinely used to detect morphological changes by providing T_1, T_2 and spin density weighted images. In research, advanced MRI techniques have been developed