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RESEARCH ARTICLE

Sex- and age-dependence of region- and layer-specific knee cartilage composition (spin–spin–relaxation time) in healthy reference subjects

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ABSTRACT

Compositional measures of articular cartilage are accessible in vivo by magnetic resonance imaging (MRI) based relaxometry and cartilage spin–spin transverse relaxation time (T2) has been related to tissue hydration, collagen content and orientation, and mechanical (functional) properties of articular cartilage. The objective of the current study was therefore to evaluate subregional variation, and sex- and age-differences, in laminar (deep and superficial) femorotibial cartilage T2 relaxation time in healthy adults. To this end, we studied the right knees of 92 healthy subjects from the Osteoarthritis Initiative reference cohort (55 women, 37 men; age range 45–78 years; BMI 24.4 ± 3.1) without knee pain, radiographic signs, or risk factors of knee osteoarthritis in either knee. T2 of the deep and superficial femorotibial cartilages was determined in 16 femorotibial subregions, using a multi-echo spin-echo (MESE) MRI sequence. Significant subregional variation in femorotibial cartilage T2 was observed for the superficial and for the deep (both $p < 0.001$) cartilage layer (Friedman test). Yet, layer- and region-specific femorotibial T2 did not differ between men and women, or between healthy adults below and above the median age (54 years). In conclusion, this first study to report subregional (layer-specific) compositional variation of femorotibial cartilage T2 in healthy adults identifies significant differences in both superficial and deep cartilage T2 between femorotibial subregions. However, no relevant sex- or age-dependence of cartilage T2 was observed between age 45–78 years. The findings suggest that a common, non-sex-specific set of layer-and region-specific T2 reference values can be used to identify compositional pathology in joint disease for this age group.

1. Introduction

Compositional and morphological changes are known to occur in human articular cartilage with age-related structural pathology, such as osteoarthritis (OA) (Grushko et al., 1989; Liess et al., 2002; Meachim, 1971; Meachim et al., 1977). Differences in the risk of developing knee OA between women and men (Neogi and Zhang, 2013) may be suggestive of potential differences in cartilage composition between sexes. Characterization of sex-specific and age-related cartilage composition in healthy subjects is a prerequisite for distinguishing between normal aging processes and disease related pathological alterations, such as those occurring in OA.

One of the most robust techniques for the in vivo assessment of the cartilage composition is the magnetic resonance imaging (MRI)-based spin–spin (transverse) (T2) relaxometry (Dardzinski and Schneider, 2013; Mosher et al., 2011; Mosher and Dardzinski, 2004) and cartilage T2 times have been reported to be associated with cartilage composition, in particular hydration, collagen integrity and orientation (Baum et al., 2013; Liess et al., 2002; Mosher and Dardzinski, 2004). Although not specific to a single compositional measure, cartilage T2 was shown to correlate with histological grading (David-Vaudey et al., 2004; T. Kim et al., 2014) and with the mechanical properties (Lammentausta et al., 2006; Mosher and Dardzinski, 2004) of articular cartilage, providing a link between cartilage composition and function. Therefore, cartilage T2 has gained interest as an imaging biomarker for “early” stages of OA (Baum et al., 2013; Joseph et al., 2011; Jungmann et al., 2013; Mosher and Dardzinski, 2004), in which therapeutic intervention is potentially more successful than at more advanced disease stages.

In accordance with marked differences in collagen orientation between the superficial and deep cartilage layer (Glaser and Putz,

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2002), cartilage T2 times have been shown to vary substantially between the bone interface and cartilage surface in healthy cartilage (Dardzinski and Schneider, 2013; Smith et al., 2001), and to differ between cartilage plates in the knee (Dardzinski and Schneider, 2013; Joseph et al., 2015).

In vitro studies have reported change in human cartilage composition with age, such as a decline of proteoglycan synthesis and content (DeGroot et al., 1999) and a reduction in interstitial water content (Grushko et al., 1989). Biomechanical experiments have described a reduction in compressive (Armstrong et al., 1979; Armstrong and Mow, 1982) and tensile (Kempson, 1991) stiffness of cartilage with age, whereas other studies suggested cartilage may become stiffer due to age-related alterations in matrix composition (Bank et al., 1998). Early T2 relaxometry studies failed to identify sex-differences in cartilage T2 in young healthy participants (Mosher et al., 2004a), but reported T2 values to become longer with advanced age in the superficial layer of patellar cartilage (Mosher et al., 2004b). In a cross sectional study, skeletal maturation in children was reported to result in a sequential decrease in cartilage T2 relaxation times that was sex-dependent (H.K. Kim et al., 2014). Following adolescent athletes longitudinally, a decrease in cartilage T2 was confirmed in the deep layers of the medial femorotibial compartment cartilages, that did not differ between males and females (Wirth et al., 2014). No such compositional change during maturation was, in contrast, observed in the superficial layers, or in the deep or superficial layers of knee cartilages of mature athletes in the same study (Wirth et al., 2014).

Reference databases of normal values are an important prerequisite for the diagnosis or for grading the disease severity. In osteoporosis, for instance, bone mineral density reference data from young healthy subjects (t-scores) and from age-matched healthy subjects (z-scores) are used to classify an individual as "normal", "osteopenic" or "osteoporotic" and to express the severity of osteoporosis. A recent paper provided reference data for knee cartilage T2 in participants without (MRI) evidence of cartilage degeneration based on WORMS (Peterfy et al., 2004) cartilage scorings (Joseph et al., 2015) and two studies previously reported cartilage T2 times from larger subsamples of the OAI healthy reference cohort (Pan et al., 2011; Wirth et al., 2016). However, two of these studies (Joseph et al., 2015; Pan et al., 2011) examined "bulk" T2 averages throughout the full depth of the cartilage instead of laminar cartilage T2 times and examined T2 times in the entire femur without taking potential compositional differences between the central, weight-bearing part and the non-weight-bearing parts of the femur into account, and none of these studies assessed cartilage T2 times in subregions (e.g. central vs. peripheral) of knee cartilage plates. In addition, the study by Joseph et al. involved subjects from the incident cohort of the Osteoarthritis Initiative (OAI) with dedicated risk factors of incident OA, which can therefore not be regarded as being strictly healthy (Joseph et al., 2015).

The objective of the current study was therefore, to provide MRI-based T2 relaxation time reference data of layer- and subregion-specific knee cartilage composition in a cohort of healthy adult reference subjects without knee pain, radiographic evidence of OA, and risk factors of OA, and to study the relationship of the layer- and region-specific T2 times with sex and age in cartilage laminae and subregions in this adult healthy reference population.

2. Material and methods

2.1. Study participants

The participants for this study were selected from the healthy reference cohort of the Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu/, clinicaltrials.gov identifier: NCT00080171) (Eckstein et al., 2012), a large epidemiological study designed to study the incidence and progression of knee OA. All OAI participants provided written informed consent, and the study was carried out in accordance with the IRB-approved OAI data user agreement, approved by the Committee on Human Research of the Institutional Review Board for the University of California, San Francisco (UCSF).

The OAI recruited 4796 participants aged 45–79 years, with (or with risk of) knee OA (Eckstein et al., 2012). All participants were free of rheumatoid or other inflammatory arthritis, bilateral end-stage knee OA, inability to walk without aids, and MRI contraindications at the time of enrollment (Eckstein et al., 2012). For reference purposes, the OAI also included a "non-exposed" reference cohort of 122 healthy participants. These participants were free of clinical signs of knee OA (e.g. knee pain), were not exposed to risk factors for developing knee OA (including obesity, knee injury, knee surgery, a family history of TKA in a biological parent or sibling, Heberden's nodes, or repetitive knee bending during daily activities) and had no signs of radiographic abnormalities in either knee according to the OAI clinical site readings (Eckstein et al., 2012). Of these 122 reference cohort participants, 23 were later found to have doubtful (Kellgren & Lawrence grade [KLG] 1) or definite (KLG 2) radiographic OA in at least one knee based on central radiographic readings performed by expert readers from Boston University (Eckstein et al., 2012), resulting in 99 participants, who were confirmed to be bilaterally free of radiographic OA. For the current study, we used data and MR images from 92 of the 99 participants that also had at least one follow-up time point. This sample (n = 92) comprised 37 men and 55 women, aged 54.7 ± 7.5 years (range: 45–78 years) with a BMI of 24.4 ± 3.1 kg/m^2.

2.2. MR imaging and femorotibial cartilage T2 analysis

The OAI acquired sagittal multi-echo spin-echo (MESE) MR images in one of the knees (usually the right one) of all OAI participants (Fig. 1) using 3T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany) and quadrature transmit/receive knee coils (USA Instruments, Aurora, OH) (Eckstein et al., 2012; Peterfy et al., 2008). The slice thickness of the MESE acquisitions was 3 mm, the field of view was 120 mm (matrix: 269 [phase] × 384 [frequency] interpolated to 384 × 384 pixels, in-plane resolution 0.3125 × 0.3125 mm), the repetition time was 2700 ms, and the echo times were 10, 20, 30, 40, 50, 60, and 70 ms (Peterfy et al., 2008).

The femorotibial cartilages, i.e. the medial and lateral tibia (MT/LT) and the central, weight-bearing femoral part of the medial and lateral femoral condyles (cMF/cLF) were manually segmented by an experienced reader (S.M) using the MESE MRIs (Wirth et al., 2014). The tibial cartilage was segmented entirely, whereas the weight-bearing, central part of the femoral condyles was defined as 75% of the distance between the inter-condylar notch and the most posterior aspect of the condyles (Eckstein et al., 2009) (Fig. 1F).

Cartilage T2 times (in ms) were computed for each (segmented) voxel using a non-linear method by fitting a mono-exponential decay curve to the measured signal intensities (Li and Hornak Joseph, 1994). The 1st echo (10 ms) was excluded from the fit, in order to reduce the impact of stimulated echoes (Mosher and Dardzinski, 2004). Voxels with $R^2 < 0.66$ for the curve fitting were not included in the analysis, to avoid contribution from voxels with low image quality (Wirth et al., 2014).

After computing bulk T2 times for each of the 4 segmented cartilage plates, the MT and LT were each computationally divided into one central (cMT/cLT), one external (eMT/eLT), one internal (iMT/iLT), one anterior (aMT/aLT), and one posterior (pMT/pLT) subregion, using a previously published methodology for cartilage thickness measurements (Eckstein et al., 2014, 2012; Wirth and Eckstein, 2008) (Fig. 1). Similarly, the cMF and cLF were