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Sex- and Age-Dependence of Region- and Layer-Specific Knee Cartilage Composition (Spin-Spin-Relaxation Time) in Healthy Reference Subjects

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SUMMARY

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 (54y). 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 45–78y. The findings suggest that a

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Competing interests

- Wolfgang Wirth is co-owner and has a part time employment at Chondrometrics GmbH (Ainring, Germany), a company providing medical image analysis service to academic researchers and to industry. He has provided consulting services to MerckSerono.
- Susanne Maschek is co-owner and has a part time employment at Chondrometrics GmbH.
- Felix Eckstein is CEO and co-owner of Chondrometrics GmbH. He provides consulting services to MerckSerono, Synarc and Servier, and has held educational lectures for Medtronic. He has received funding support (for studies not related to the current one) from Pfizer, Eli Lilly, Stryker, Novartis, MerckSerono, Glaxo Smith Kline, Wyeth, Contocor, Abbvie, Kolon, Synarc, Ampio, and Orthotrophix.

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.

Keywords

Cartilage Composition; Transverse Relaxation Time (T2); Magnetic Resonance Imaging; Osteoarthritis Initiative; Healthy Reference; Knee

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, 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 (Figure 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 P, 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) (Figure 1). Similarly, the cMF and cLF were divided into central (ccMF/ccLF), external (ecMF/ecLF, and internal (icMF/icLF) subregions (Wirth and Eckstein, 2008) (Figure 1). To account for the spatial association between cartilage T2 times and tissue depth (Dardzinski and Schneider, 2013; Mosher and Dardzinski, 2004), each of the four cartilage plates and 16 subregions was computationally divided into a superficial and a deep layer after segmentation has been completed, comprising 50% of the distance between the segmented cartilage surface and the bone interface, respectively (Wirth et al., 2014). For reference purposes, we also report the cartilage thickness for each cartilage plate and subregion, as determined from a morphometry-specific cartilage imaging sequence described in an earlier publication (Eckstein et al., 2010).

The average deep and superficial layer cartilage T2 times in the entire femorotibial joint (FTJ) were computed as the average T2 times of all 4 cartilages (FTJ = Average(MT, LT, cMF, cLF)). The average deep and superficial layer cartilage T2 times in the medial and lateral compartment (MFTC/LFTC) were computed as the average deep and superficial layer cartilage T2 times of the respective cartilages (MFTC = Average(MT, cMF), LFTC = Average(LT, cLF)). The average deep and superficial layer cartilage T2 times in the combined central subregion of the medial and lateral compartment (cMFTC/cLFTC) were computed as the average deep and superficial layer cartilage T2 times of the respective central subregions (cMFTC = Average(cMT, ccMF), cLFTC = Average(cLT, ccLF)).

2.2 Statistical analysis

All statistical analyses were performed using IBM SPSS 22 (IBM Corporation, Armonk, NY). The deep and superficial layer T2 times in combined measures, cartilage plates, and subregions were described using the mean, the standard deviation, and the 95% confidence intervals.

To test, whether cartilage composition differed significantly between femorotibial subregions within each cartilage plate, non-parametric Friedman tests were applied to superficial and deep cartilage, respectively. To explore the specific pattern of the subregional deep and superficial cartilage T2 times, subregional T2 was compared to the average T2 in the same cartilage plate, using a non-parametric Wilcoxon signed rank tests. The significance level was set to p=0.01 for this explorative analysis, to account for the multiple parallel comparisons.

To determine whether deep and superficial cartilage T2 times differed between and men and women and between participants in the youngest (45 – 48 years) and oldest (58 – 78 years) quartile, non-parametric Mann-Whitney-U tests were used. The primary analytic focus for these two comparisons was the deep and superficial cartilage T2 time in the entire FTJ. Cartilage T2 times in the MFTC and LFTC were considered a secondary focus. Cartilage T2 times in individual cartilage plates and subregions were considered exploratory. The significance level was adjusted to p=0.0083 (p=0.05/6) to account for the six parallel comparisons (2 layers, 3 analytical measures).

3. Results

Cartilage T2 was consistently longer in the superficial than in the deep layer, and longer in femoral than in tibial cartilage (Table 1). The superficial vs. deep layer T2 ratio ranged from 1.22 ± 0.09 (95% CI: [1.20, 1.23]) in cLF to 1.37 ± 0.07 (95% CI: [1.35, 1.38]) in LT.

3.1. Subregional distribution of deep and superficial layer cartilage T2 times

The T2 values differed significantly between cartilage subregions, both for the superficial and for the deep cartilage layer ($p<0.001$). In the superficial layer, cartilage T2 times were longer in the central femoral subregions when compared to the total cartilages plate (Table 1 & Figure 2). In the LT, T2 times were shorter in the central subregion than for the entire cartilage plate, but were longer in the posterior subregion (Table 1 & Figure 2). Longer T2 times than average were also observed in the external subregions of both the MT and the LT, and in the internal subregion of the cMF (Table 1 & Figure 2). In contrast, shorter T2 times than average were observed in the internal subregions of both the MT and LT, and in the external subregions of both the cMF and cLF (Table 1 & Figure 2).

In the deep layer, the cartilage T2 times were generally shorter than average in the central subregions (Table 1 & Figure 2). Shorter T2 times were also observed in the internal subregion of the MT and the external subregion of the cMF. Longer T2 times than average were observed in the external subregions of MT, LT, and cLF, in the internal subregions of LT, cMF, and cMF, and in the posterior subregions of both MT and LT (Table 1 & Figure 2).

The strongest deviations of superficial layer cartilage T2 times from average were observed in the ecMF (−5.0 ±2.8 [−5.6, −4.4] ms) and eLT (+3.8 ±3.5 [3.1, 4.5] ms), and those of deep layer T2 in ccMF (−4.3±2.2 [−4.7, −3.8] ms), cLT (−4.3±1.8 [−4.7, −3.9] ms) and icMF (+5.4±3.5 [4.7, 6.1] ms, Table 1 & Figure 2).

3.2. Sex differences in cartilage T2 times

Cartilage T2 averaged across the total femorotibial joint did not differ significantly between men and women in either the superficial (45.6±2.1 [44.9, 46.3] ms vs. 45.3 ±2.5 [44.6, 45.9] ms, $p=0.26$, Table 2) or deep cartilage layers (35.5±1.7 [34.9, 36.1] ms vs. 36.0±1.8 [35.5, 36.5] ms, $p=0.32$, Table 3). In the MFTC, the superficial T2 times tended to be longer in men (46.2±2.7 [45.3, 47.1] ms) than in women (45.1±2.9 [44.3, 45.9] ms), but the difference did not reach the adjusted significance level ($p=0.029$, Table 2). Deep layer LFTC T2 times, in contrast, tended to be longer in women (35.7±2.0 [35.2, 36.3] ms) than in men (34.8±1.7 [34.2, 35.4] ms), but again the difference did not meet the adjusted significance level ($p=0.018$, Table 3).

In the exploratory analyses, significant differences between men and women were observed in the superficial layer of the MT (Table 2), specifically in aMT (Table 2), and in the deep layer of iLT and icLF (Table 3).

3.3. Age-related differences in cartilage T2 times

Cartilage T2 averaged across the total femorotibial joint did not differ significantly between participants in the youngest versus participants in the oldest quartile in either the superficial

(45.8±3.1 [44.4, 47.1] ms vs. 45.7 ±1.8 [44.9, 46.4] ms, p=0.94, Table 4) or the deep cartilage layer (36.3±2.2 [35.3, 37.2] ms vs. 35.9±1.5 [35.2, 36.5] ms, p=0.27, Table 5). Also, no significant age differences were observed in the medial and lateral femorotibial compartment, cartilage plates, and subregions (Tables 4 & 5) or when comparing deep and superficial cartilage T2 times between participants older and younger than the median age of 54 years (data not shown).

4. Discussion

This is the first study to characterize subregional (layer-specific) compositional differences in femorotibial cartilage by MRI spin-spin (transverse) relaxation time (T2) in healthy adults, and to relate T2 systematically throughout different subregions and layers with sex and age. The study identified significant differences in both superficial and deep cartilage T2 between subregions, whereas no relevant sex- or age-dependency was observed for the age range of adult healthy subjects examined here. These findings suggest that men and women, and subjects aged 45–78 years may be pooled in analyses of subregional and layer specific cartilage T2, if these are acquired in truly healthy knees without symptoms, signs or risk factors of OA.

The limitations of the current study are that cartilage T2 was examined in only two layers, each comprising 50% of the full cartilage thickness, whereas histologically, at least 3 zones can be identified based on the collagen orientation and other structural features, that cover various percentages of the cartilage thickness (Glaser and Putz, 2002). However, the in plane resolution of 0.3125 mm (and 3 mm slices thickness) of the MESE sequence precluded the analysis of a higher number of cartilage laminae, in view of cartilage thickness values of < 2 mm in some of the peripheral femorotibial subregions. Yet, a strength of the study was the use of 3T MRI that permitted acquisition of MESE images at a high in-plane resolution (Peterfy et al., 2008). Another limitation is the small sample size, but the subjects included were rigorously selected to be free of symptoms, signs and risk factors of knee OA, and thus can be viewed as “super-normals” when compared to reference groups commonly used in epidemiological studies. Finally, limitations arise from the number of parallel comparisons that had to be performed in exploring potential differences between regions, and for the comparison between men and women, and youngest vs. oldest subjects, but the significance level was adjusted to account for the parallel tests, and a clear hierarchical set of tests was defined upfront for the comparison between men and women, and youngest vs. oldest participants.

When taking the average of the deep and superficial T2 times as an approximation of the bulk T2 times in the cartilage plates, the bulk T2 times observed in the tibial cartilages were up to 3ms longer and the bulk T2 times observed in the central medial femur were up to 4 ms shorter than the medial femoral condyle T2 times reported by Pan et al. for a different subset of participants from the OAI reference cohort (Pan et al., 2011). These differences can potentially be attributed to methodological factors including different segmentation methods or the inclusion of the 1st echo for the calculation of the cartilage T2 times in the study by Pan et al. (Pan et al., 2011), whereas in the current study, the 1st echo was excluded to reduce the impact of stimulated echoes (Mosher and Dardzinski, 2004).

Cartilage T2 relaxation times are known to depend on the orientation of the collagen fibers relative to the main magnetic field (magic-angle effect) (Mosher and Dardzinski, 2004), in particular in the deep, radial zone (Xia et al., 2002). In the current study, we have calculated the vector normal to the subchondral bone surface area as an approximation of the collagen orientation in the deep layer, to estimate the impact of the angular dependency between the collagen orientation and the orientation of the main magnetic field on subregional T2 times (data not shown). The orientation of the central, external, and anterior subregions in the main magnetic field was observed to be similar to the orientation of the respective entire cartilage plates, whereas somewhat larger angles were observed for the posterior and the internal subregions. When compared to the laminar T2 times in the respective entire cartilage plates, we observed both shorter and longer T2 times in subregions with similar orientations (e.g. internal subregions) indicating that the orientation of the subregions relative to the main magnetic field is unlikely to explain the variation between subregional T2 times. This can probably be attributed to the fact that the average angles observed for the subregions (4° – 26°) were much smaller than the magic angle (54.7°), where the cartilage T2 times reach their maximum (Xia et al., 2002). Previous studies have also shown that the relative proportion of radial, transitional, and superficial cartilage varies between the central and the peripheral parts of the cartilages (Clark, 1991) and that the composition and biomechanical properties differ between areas of high and low weight-bearing (Akizuki et al., 1986; Gomez et al., 2000; Xia, 2000). The observed spatial pattern of subregional cartilage T2 times is therefore most likely caused by a combination of the above effects, but the specific contribution of these effects needs to be quantified in future studies. It is also worth noting that the combined central medial femorotibial compartment displayed longer cartilage T2 than the combined central lateral femorotibial compartment, with the medial compartment commonly taking more of the load transfer compared with the lateral one (Johnson et al., 1980). We have no reasonable explanation, however, as to why, from a biomechanical point, femoral cartilage subregions displayed substantially longer T2 than tibial subregions, both for the superficial and for the deep cartilages.

The reference values reported in the current study were based on normal-weight OAI healthy reference cohort participants aged 45 to 78 years, which had no signs or risk factors for developing knee OA. Although no significant association was observed between age and cartilage T2 times in the current study, reference values for other, younger cohorts may potentially differ from the reference values reported in the current study. The age of the participants included in the current study, however, covered the age range typically analyzed in knee osteoarthritis studies. Cartilage T2 times for cohorts with different BMI characteristics will most likely also differ from the reference values reported here, given that previous studies reported significant associations between BMI and cartilage T2 times (Joseph et al., 2015; Serebrakian et al., 2015). Obesity has, however, been identified as an important risk factor for developing knee OA (Felson et al., 1997) and cohorts with higher BMI should therefore not be used as basis for providing normal reference values.

Previous reports have been inconsistent with regard to reporting sex- and age-differences in cartilage T2. Our present study shows that, if strictly healthy (i.e. supernormal) subjects are studied, no significant association of cartilage T2 with sex or age are observed. In particular, the variation between men and women, and that of older vs. younger adults was much

smaller than that between cartilage layers (superficial vs. deep), between plates (femoral vs. tibial), and between subregions. The inconsistent findings previously reported (H. K. Kim et al., 2014; Mosher et al., 2004a, 2004b) may be due to OA related structural pathology, in particular cartilage lesions, becoming more frequent with age, even in the absence of radiographic signs of knee OA (Guermazi et al., 2012). Hence, the age-dependency of cartilage T2 observed in previous studies may be due to cartilage pathology rather than normal cartilage aging, and may not be observed when risk factors of knee OA are rigorously eliminated. Similar considerations apply to sex-differences previously reported for cartilage T2, given that women have a higher prevalence of knee OA than men (Neogi and Zhang, 2013). The lack of sex-differences as well as that of an age-dependence in cartilage T2 across the age range studied here greatly simplifies the identification of pathological compositional change of cartilage T2 in joint disease (OA), as it suggests that the same reference values can be used for men and women and for an age range of 45–78 years that applies to most studies of knee OA.

In conclusion, this is the first study to report subregional, layer-specific compositional variation in femorotibial cartilage T2 (spin-spin/transverse) relaxation time in healthy adults, and the first study to report significant differences between femorotibial subregions in both the superficial and deep cartilage layers. No relevant sex- or age-dependency of cartilage T2 was, however, detected between age 45 and 78, suggesting that a common set of layer-and region-specific T2 reference values can be used for this age range to identify compositional pathology in joint disease.

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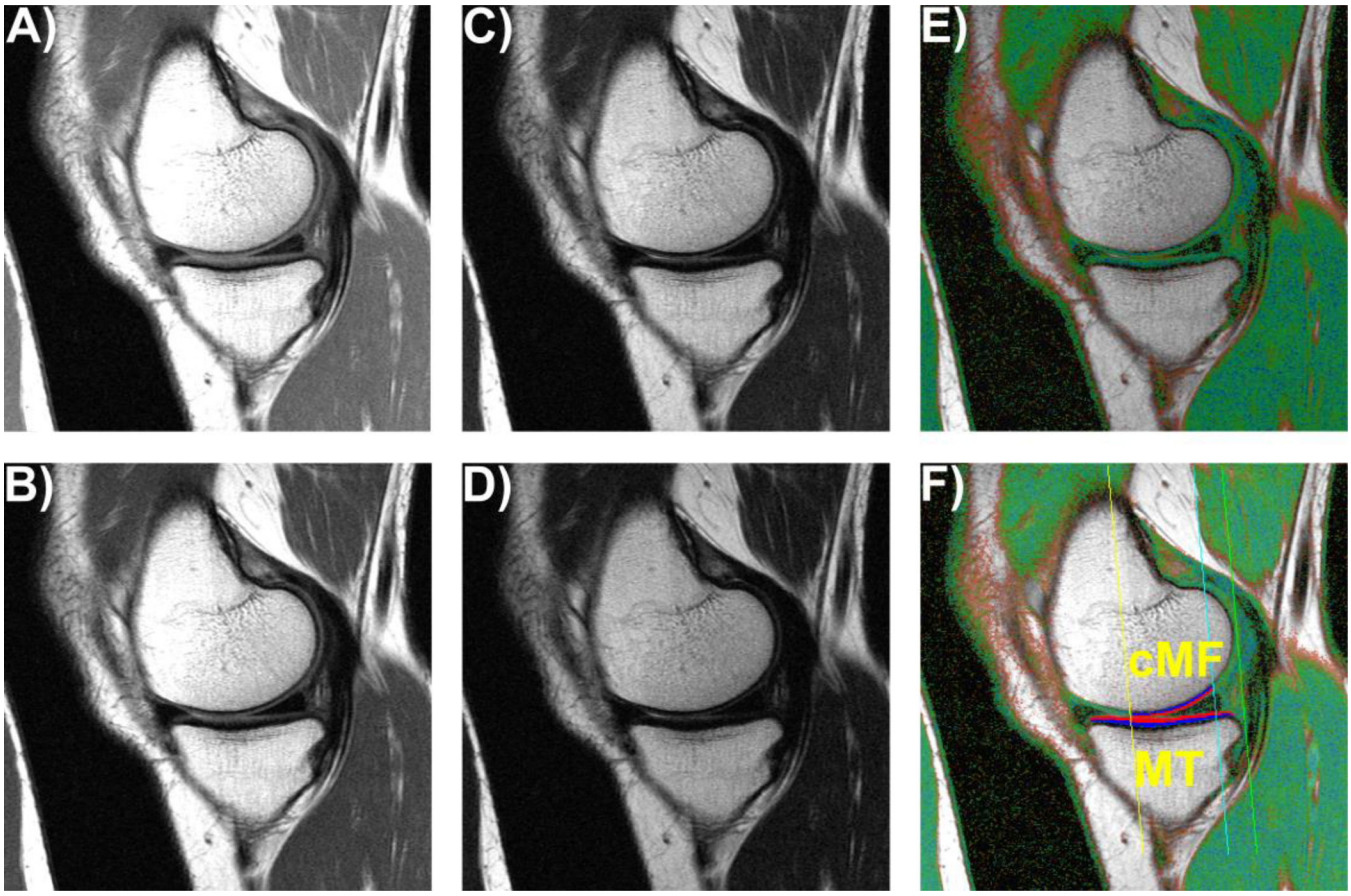

Fig. 1.

Sagittal multi-echo spin-echo (MESE) images showing the cartilages in the medial compartment; A) – D) MESE images acquired at echo times of 10, 30, 50, and 70 ms; E) Color-coded T2map; F) T2 map as in E), showing the femoral region of interest (ROI) and the segmented cartilage of the medial tibia (MT) and the central medial femur (cMF) divided into the superficial (red) and deep (blue) cartilage layers.

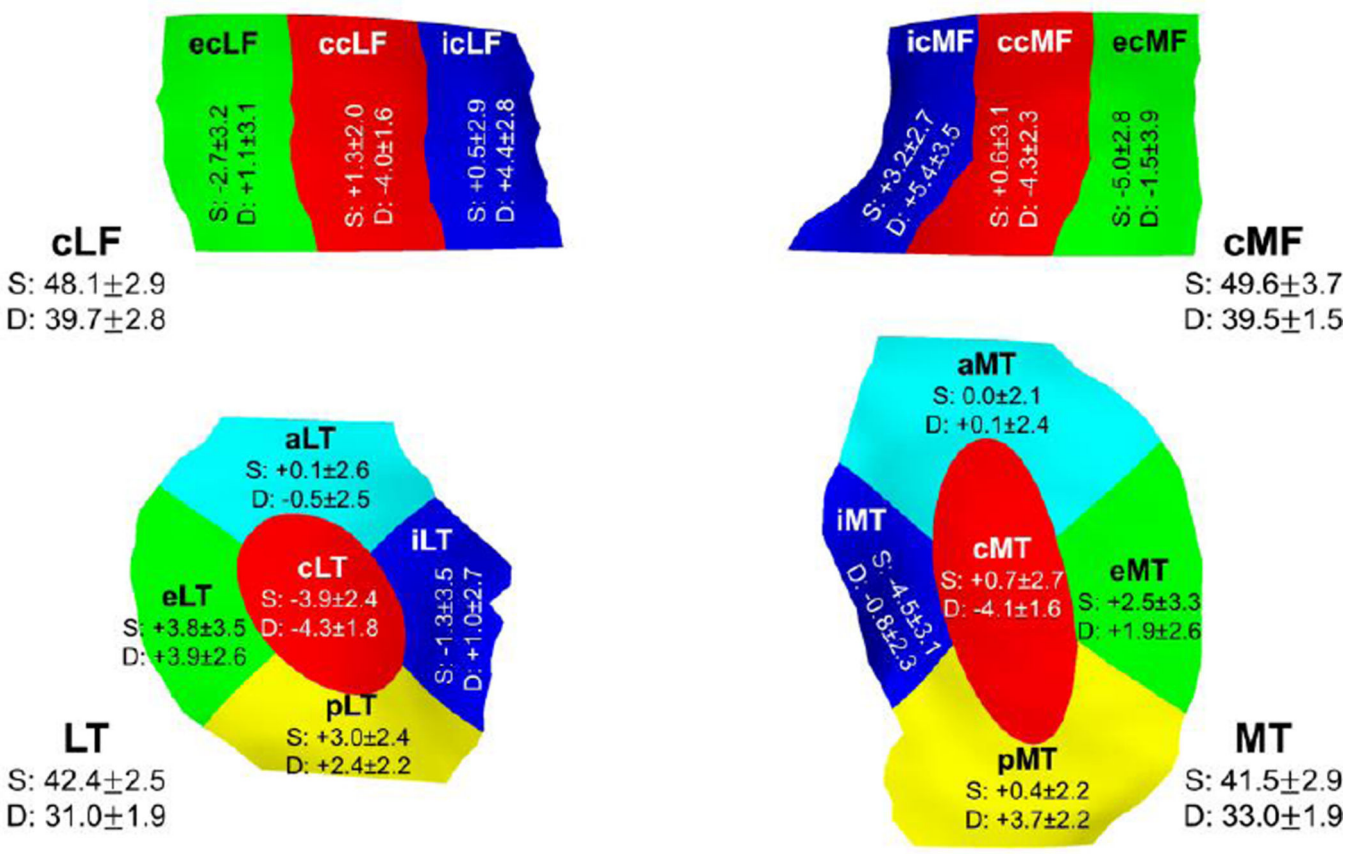

Fig. 2.

Difference between laminar subregional cartilage T2 times (mean ± SD difference in ms) and the cartilage T2 times in the superficial (S) and deep (D) layers of the respective total cartilages (mean ± SD in ms).The 3D illustration also shows the central (c), external (e), and internal (i) subregions of the central part of the medial (cMF) and lateral (cLF) femur and the central (c), external (e), internal (i), anterior (a), and posterior (p) subregions of the medial (MT) and lateral (LT) tibia.

Table 1

Superficial and deep layer cartilage transverse relaxation time (T2) and cartilage thickness in various compartments, plates, and subregions of the femorotibial joint

	Superficial Layer			Deep Layer			Cartilage Thickness	
	Mean ± SD	**[95% CI]**	**P-Value**	**Mean ± SD**	**[95% CI]**	**P-Value**	**Mean ± SD**	**[95% CI]**
Composite measures:								
FTJ	45.4 ± 2.3	[44.9, 45.9]		35.8 ± 1.8	[35.4, 36.2]		7.4 ± 0.9	[7.2, 7.5]
MFTC	45.6 ± 2.8	[45.0, 46.1]		36.3 ± 2.2	[35.8, 36.7]		3.5 ± 0.5	[3.4, 3.6]
LFTC	45.3 ± 2.4	[44.8, 45.8]		35.4 ± 2.0	[35.0, 35.8]		3.8 ± 0.5	[3.7, 3.9]
cMFTC	46.2 ± 3.3	[45.5, 46.9]		32.1 ± 2.6	[31.6, 32.6]		4.6 ± 0.7	[4.5, 4.7]
cLFTC	44.0 ± 3.1	[43.3, 44.6]		31.2 ± 2.1	[30.7, 31.6]		5.3 ± 0.8	[5.2, 5.5]
Medial tibia (MT):								
MT	41.5 ± 2.9	[40.9, 42.1]		33.0 ± 1.9	[32.6, 33.4]		1.7 ± 0.2	[1.7, 1.7]
cMT	42.2 ± 4.1	[41.4, 43.1]	0.027	29.0 ± 2.1	[28.5, 29.4]	<0.001	2.4 ± 0.4	[2.3, 2.4]
eMT	44.0 ± 4.2	[43.1, 44.9]	<0.001	34.9 ± 3.1	[34.3, 35.5]	<0.001	1.5 ± 0.2	[1.4, 1.5]
iMT	37.0 ± 3.8	[36.2, 37.8]	<0.001	32.2 ± 3.9	[31.4, 33.0]	0.001	1.8 ± 0.2	[1.8, 1.9]
aMT	41.5 ± 3.8	[40.8, 42.3]	0.953	33.1 ± 2.4	[32.6, 33.6]	0.469	1.5 ± 0.2	[1.5, 1.5]
pMT	41.9 ± 3.6	[41.2, 42.7]	0.066	36.3 ± 2.5	[35.7, 36.8]	<0.001	1.4 ± 0.2	[1.4, 1.5]
Central medial femur (cMF):								
cMF	49.6 ± 3.7	[48.8, 50.4]		39.5 ± 3.5	[38.8, 40.2]		1.8 ± 0.3	[1.8, 1.9]
ccMF	50.2 ± 4.2	[49.3, 51.0]	0.007	35.2 ± 4.0	[34.4, 36.1]	<0.001	2.2 ± 0.4	[2.2, 2.3]
ecMF	44.6 ± 4.2	[43.7, 45.4]	<0.001	38.0 ± 4.0	[37.2, 38.8]	<0.001	1.3 ± 0.2	[1.3, 1.3]
icMF	52.8 ± 4.9	[51.8, 53.8]	<0.001	44.9 ± 5.7	[43.7, 46.1]	<0.001	1.9 ± 0.3	[1.9, 2.0]
Lateral tibia (LT):								
LT	42.4 ± 2.5	[41.9, 42.9]		31.0 ± 1.9	[30.6, 31.4]		2.1 ± 0.3	[2. 0, 2.2]
cLT	38.5 ± 3.8	[37.7, 39.3]	<0.001	26.7 ± 2.6	[26.2, 27.2]	<0.001	3.3 ± 0.6	[3.1, 3.4]
eLT	46.2 ± 3.9	[45.4, 47.0]	<0.001	34.9 ± 3.0	[34.3, 35.5]	<0.001	1.7 ± 0.2	[1.6, 1.7]
iLT	40.9 ± 4.5	[40.0, 41.9]	<0.001	32.0 ± 3.7	[31.2, 32.7]	0.002	2.0 ± 0.4	[2.0, 2.1]
aLT	42.5 ± 3.0	[41.8, 43.1]	0.738	30.5 ± 2.6	[29.9, 31.0]	0.020	1.7 ± 0.3	[1.6, 1.7]
pLT	45.4 ± 3.6	[44.6, 46.1]	<0.001	33.4 ± 3.3	[32.8, 34.1]	<0.001	1.9 ± 0.3	[1.9, 2.0]
Central lateral femur (cLF):								
cLF	48.1 ± 2.9	[47.5, 48.7]		39.7 ± 2.8	[39.2, 40.3]		1.7 ± 0.2	[1.7, 1.8]

	Superficial Layer			Deep Layer			Cartilage Thickness	
	Mean ± SD	**[95% CI]**	**P-Value**	**Mean ± SD**	**[95% CI]**	**P-Value**	**Mean ± SD**	**[95% CI]**
ccLF	49.4 ± 3.8	[48.7, 50.2]	<0.001	35.7 ± 3.2	[35.0, 36.3]	<0.001	2.1 ± 0.3	[2.0, 2.1]
ecLF	45.5 ± 3.6	[44.7, 46.2]	<0.001	40.8 ± 3.5	[40.1, 41.6]	0.002	1.5 ± 0.2	[1.4, 1.5]
icLF	48.6 ± 4.4	[47.7, 49.6]	0.241	44.2 ± 4.3	[43.3, 45.1]	<0.001	1.6 ± 0.2	[1.6, 1.7]

SD: standard deviation; 95% CI: 95% confidence intervals; P: Wilcoxon signed rank test for differences between subregional T2 and T2 in the respective cartilage. Cartilage thickness for the n=92 participants measurements were adapted from (Eckstein et al., 2010). FTJ: femorotibial joint; MFTC/LFTC: medial/lateral femorotibial compartment; cMFTC/cLFTC: central medial/lateral compartment; c/e/i/a/p M/LT: central/external/internal/anterior/posterior medial/lateral tibia; c/e/i cM/LF: central/external/internal medial/lateral femur.

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Table 2

Sex differences in superficial layer cartilage transverse relaxation time (T2) in various compartments, plates, and subregions of the femorotibial joint

	Men		Women		
	Mean ± SD	**[95% CI]**	**Mean ± SD**	**[95% CI]**	**P-Value**
Composite measures:					
FTJ	45.6 ± 2.1	[44.9, 46.3]	45.3 ± 2.5	[44.6, 45.9]	0.257
MFTC	46.2 ± 2.7	[45.3, 47.1]	45.1 ± 2.9	[44.3, 45.9]	0.029
LFTC	45.0 ± 2.0	[44.4, 45.7]	45.4 ± 2.6	[44.7, 46.1]	0.491
cMFTC	46.6 ± 3.3	[45.5, 47.7]	45.9 ± 3.3	[45.0, 46.8]	0.240
cLFTC	43.2 ± 2.8	[42.2, 44.1]	44.5 ± 3.2	[43.6, 45.4]	0.037
Medial tibia (MT):					
MT	42.6 ± 2.9	[41.7, 43.6]	40.7 ± 2.6	[40.0, 41.4]	0.002
cMT	43.4 ± 4.4	[41.9, 44.8]	41.5 ± 3.8	[40.4, 42.5]	0.034
eMT	45.0 ± 3.9	[43.7, 46.3]	43.3 ± 4.2	[42.2, 44.5]	0.028
iMT	37.7 ± 3.6	[36.5, 38.9]	36.6 ± 4.0	[35.5, 37.7]	0.281
aMT	43.0 ± 3.5	[41.8, 44.2]	40.6 ± 3.6	[39.6, 41.6]	0.008
pMT	42.9 ± 3.9	[41.6, 44.2]	41.3 ± 3.3	[40.4, 42.2]	0.043
Central medial femur (cMF):					
cMF	49.8 ± 3.5	[48.6, 50.9]	49.5 ± 3.9	[48.5, 50.6]	0.438
ccMF	49.9 ± 4.2	[48.4, 51.3]	50.4 ± 4.2	[49.2, 51.5]	0.741
ecMF	44.7 ± 4.5	[43.2, 46.2]	44.5 ± 4.0	[43.5, 45.6]	0.670
icMF	53.5 ± 4.6	[51.9, 55.0]	52.4 ± 5.1	[51.0, 53.7]	0.138
Lateral tibia (LT):					
LT	42.5 ± 2.3	[41.8, 43.3]	42.3 ± 2.7	[41.5, 43.0]	0.636
cLT	38.1 ± 3.2	[37.0, 39.2]	38.7 ± 4.2	[37.6, 39.8]	0.442
eLT	47.4 ± 3.4	[46.3, 48.6]	45.4 ± 4.0	[44.3, 46.4]	0.014
iLT	40.4 ± 3.9	[39.1, 41.7]	41.3 ± 4.9	[40.0, 42.6]	0.438
aLT	42.8 ± 3.1	[41.8, 43.9]	42.2 ± 3.0	[41.4, 43.0]	0.438
pLT	46.0 ± 3.2	[44.9, 47.0]	45.0 ± 3.8	[43.9, 46.0]	0.162
Central lateral femur (cLF):					
cLF	47.5 ± 2.5	[46.7, 48.3]	48.6 ± 3.1	[47.7, 49.4]	0.110
ccLF	48.2 ± 3.8	[47.0, 49.5]	50.3 ± 3.5	[49.3, 51.2]	0.014

	Men		Women		
	Mean ± SD	**[95% CI]**	**Mean ± SD**	**[95% CI]**	**P-Value**
ecLF	45.7 ± 2.7	[44.8, 46.6]	45.3 ± 4.1	[44.2, 46.4]	0.765
icLF	47.9 ± 3.9	[46.6, 49.2]	49.1 ± 4.6	[47.9, 50.4]	0.225

For abbreviations used, please see table 1

Table 3

Sex differences in deep layer cartilage transverse relaxation time (T2) in various compartments, plates, and subregions of the femorotibial joint

	Men		Women		
	Mean ± SD	**[95% CI]**	**Mean ± SD**	**[95% CI]**	**P-Value**
Composite measures:					
FTJ	35.5 ± 1.7	[34.9, 36.1]	36.0 ± 1.8	[35.5, 36.5]	0.318
MFTC	36.2 ± 2.4	[35.4, 37.0]	36.3 ± 2.1	[35.7, 36.9]	0.990
LFTC	34.8 ± 1.7	[34.2, 35.4]	35.7 ± 2.0	[35.2, 36.3]	0.018
cMFTC	32.1 ± 2.7	[31.2, 33.0]	32.1 ± 2.5	[31.4, 32.7]	0.777
cLFTC	30.7 ± 1.8	[30.1, 31.3]	31.5 ± 2.3	[30.9, 32.1]	0.076
Medial tibia (MT):					
MT	33.4 ± 1.9	[32.8, 34.0]	32.8 ± 1.8	[32.3, 33.2]	0.135
cMT	29.6 ± 2.3	[28.8, 30.3]	28.5 ± 1.8	[28.0, 29.0]	0.016
eMT	35.6 ± 2.7	[34.7, 36.5]	34.5 ± 3.2	[33.6, 35.3]	0.089
iMT	31.8 ± 3.1	[30.8, 32.8]	32.5 ± 4.4	[31.3, 33.6]	0.771
aMT	33.4 ± 2.5	[32.6, 34.2]	32.9 ± 2.4	[32.2, 33.5]	0.325
pMT	36.7 ± 2.5	[35.9, 37.5]	36.0 ± 2.5	[35.3, 36.6]	0.133
Central medial femur (cMF):					
cMF	39.0 ± 3.5	[37.9, 40.2]	39.8 ± 3.4	[38.9, 40.7]	0.341
ccMF	34.7 ± 3.8	[33.4, 35.9]	35.6 ± 4.2	[34.5, 36.7]	0.392
ecMF	37.4 ± 3.5	[36.3, 38.6]	38.4 ± 4.3	[37.2, 39.5]	0.257
icMF	44.9 ± 6.4	[42.8, 47.0]	44.8 ± 5.2	[43.4, 46.3]	0.833
Lateral tibia (LT):					
LT	30.6 ± 1.8	[30.0, 31.2]	31.3 ± 2.0	[30.7, 31.8]	0.098
cLT	26.5 ± 2.2	[25.8, 27.2]	26.8 ± 2.8	[26.1, 27.6]	0.765
eLT	35.0 ± 3.0	[34.0, 36.0]	34.8 ± 3.0	[34.0, 35.6]	0.548
iLT	30.7 ± 2.8	[29.7, 31.6]	32.9 ± 3.9	[31.8, 33.9]	0.002
aLT	30.1 ± 2.6	[29.3, 31.0]	30.7 ± 2.7	[30.0, 31.4]	0.167
pLT	33.0 ± 3.2	[31.9, 34.1]	33.7 ± 3.3	[32.8, 34.6]	0.291
Central lateral femur (cLF):					
cLF	39.1 ± 2.4	[38.3, 39.9]	40.2 ± 2.9	[39.4, 41.0]	0.023
ccLF	34.9 ± 3.0	[33.9, 35.9]	36.2 ± 3.3	[35.3, 37.1]	0.041

	Men		Women		
	Mean ± SD	**[95% CI]**	**Mean ± SD**	**[95% CI]**	**P-Value**
ecLF	41.8 ± 3.5	[40.6, 42.9]	40.2 ± 3.4	[39.3, 41.1]	0.031
icLF	42.5 ± 3.6	[41.3, 43.7]	45.3 ± 4.4	[44.1, 46.5]	0.002

For abbreviations used, please see table 1

Table 4

Age differences in superficial layer cartilage transverse relaxation time (T2) in various compartments, plates, and subregions of the femorotibial joint

	1st Quartile		4th Quartile		
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**	**P-Value**
Composite measures:					
FTJ	45.8 ± 3.1	[44.4, 47.1]	45.7 ± 1.8	[44.9, 46.4]	0.939
MFTC	46.0 ± 3.7	[44.4, 47.6]	46.0 ± 2.8	[44.8, 47.2]	0.956
LFTC	45.6 ± 3.0	[44.3, 46.8]	45.3 ± 1.7	[44.6, 46.0]	0.733
cMFTC	46.7 ± 4.3	[44.9, 48.5]	46.4 ± 3.3	[45.0, 47.9]	0.818
cLFTC	44.3 ± 3.4	[42.8, 45.7]	44.0 ± 2.6	[42.9, 45.1]	0.956
Medial tibia (MT)					
MT	42.2 ± 2.9	[41.0, 43.5]	41.9 ± 3.6	[40.3, 43.5]	0.531
cMT	43.3 ± 4.3	[41.4, 45.1]	42.5 ± 4.8	[40.4, 44.6]	0.546
eMT	45.8 ± 3.6	[44.2, 47.4]	43.7 ± 4.4	[41.7, 45.6]	0.036
iMT	37.3 ± 3.6	[35.8, 38.9]	37.7 ± 4.5	[35.7, 39.6]	0.869
aMT	41.9 ± 3.3	[40.4, 43.3]	42.1 ± 4.0	[40.3, 43.8]	0.701
pMT	42.3 ± 3.4	[40.8, 43.8]	42.6 ± 4.4	[40.7, 44.5]	0.974
Central medial femur (cMF):					
cMF	49.8 ± 4.9	[47.6, 51.9]	50.1 ± 3.3	[48.7, 51.6]	0.684
ccMF	50.1 ± 5.6	[47.7, 52.5]	50.3 ± 3.3	[48.9, 51.7]	0.784
ecMF	44.6 ± 5.2	[42.3, 46.8]	45.1 ± 4.2	[43.3, 46.9]	0.921
icMF	53.3 ± 6.3	[50.6, 56.0]	53.7 ± 4.7	[51.7, 55.8]	0.652
Lateral tibia (LT):					
LT	42.7 ± 2.8	[41.5, 43.9]	42.8 ± 2.8	[41.6, 44.0]	0.575
cLT	39.0 ± 3.6	[37.5, 40.6]	38.9 ± 4.3	[37.1, 40.8]	0.784
eLT	46.1 ± 3.5	[44.6, 47.6]	45.2 ± 3.6	[43.7, 46.7]	0.215
iLT	41.3 ± 4.6	[39.3, 43.3]	43.0 ± 4.3	[41.2, 44.9]	0.150
aLT	42.8 ± 2.9	[41.6, 44.0]	43.4 ± 3.2	[42.0, 44.8]	0.475
pLT	45.5 ± 3.9	[43.8, 47.1]	44.8 ± 3.5	[43.3, 46.4]	0.606
Central lateral femur (cLF):					
cLF	48.4 ± 3.8	[46.8, 50.1]	47.8 ± 1.5	[47.2, 48.4]	0.448

	1st Quartile		4th Quartile		
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**	**P-Value**
ccLF	49.5 ± 4.5	[47.5, 51.5]	49.2 ± 2.5	[48.1, 50.2]	0.668
ecLF	46.8 ± 3.8	[45.1, 48.4]	44.3 ± 2.8	[43.1, 45.5]	0.013
icLF	48.6 ± 4.8	[46.6, 50.7]	49.0 ± 3.7	[47.3, 50.6]	0.818

For abbreviations used, please see table 1

Table 5

Age differences in deep layer cartilage transverse relaxation time (T2) in various compartments, plates, and subregions of the femorotibial joint

	1st Quartile		4th Quartile		
	Mean ± SD	95% CI	Mean ± SD	95% CI	P-Value
Composite measures:					
FTJ	36.3 ± 2.2	[35.3, 37.2]	35.9 ± 1.5	[35.2, 36.5]	0.267
MFTC	36.7 ± 2.5	[35.6, 37.8]	36.2 ± 2.0	[35.4, 37.1]	0.362
LFTC	35.8 ± 2.1	[34.9, 36.7]	35.5 ± 2.0	[34.7, 36.4]	0.560
cMFTC	32.7 ± 2.5	[31.7, 33.8]	32.0 ± 2.7	[30.8, 33.1]	0.258
cLFTC	31.6 ± 2.1	[30.7, 32.6]	31.3 ± 1.8	[30.5, 32.1]	0.560
Medial tibia (MT)					
MT	33.1 ± 1.9	[32.3, 33.9]	33.3 ± 1.9	[32.5, 34.1]	0.590
cMT	29.5 ± 1.9	[28.7, 30.3]	29.1 ± 2.7	[28.0, 30.3]	0.475
eMT	35.2 ± 3.1	[33.8, 36.5]	34.6 ± 2.8	[33.4, 35.8]	0.339
iMT	32.1 ± 4.0	[30.4, 33.8]	32.5 ± 3.1	[31.1, 33.8]	0.621
aMT	33.0 ± 2.7	[31.9, 34.2]	33.5 ± 2.3	[32.5, 34.5]	0.489
pMT	36.0 ± 2.4	[35.0, 37.1]	36.7 ± 2.6	[35.6, 37.8]	0.410
Central medial femur (cMF):					
cMF	40.3 ± 3.9	[38.6, 42.0]	39.2 ± 3.2	[37.8, 40.6]	0.223
ccMF	35.9 ± 4.0	[34.2, 37.7]	34.8 ± 4.2	[33.0, 36.6]	0.184
ecMF	37.7 ± 3.9	[36.0, 39.4]	37.7 ± 4.3	[35.9, 39.6]	0.991
icMF	46.5 ± 6.2	[43.8, 49.1]	44.7 ± 5.6	[42.3, 47.1]	0.199
Lateral tibia (LT):					
LT	31.4 ± 2.1	[30.5, 32.3]	30.9 ± 2.0	[30.1, 31.8]	0.637
cLT	27.2 ± 2.7	[26.0, 28.4]	26.4 ± 2.2	[25.4, 27.3]	0.307
eLT	35.5 ± 3.4	[34.1, 37.0]	34.4 ± 2.7	[33.2, 35.5]	0.106
iLT	31.9 ± 3.3	[30.5, 33.3]	33.1 ± 4.3	[31.2, 34.9]	0.503
aLT	30.6 ± 2.6	[29.4, 31.7]	30.7 ± 2.6	[29.6, 31.8]	0.733
pLT	34.0 ± 3.8	[32.3, 35.6]	32.8 ± 3.1	[31.4, 34.1]	0.287
Central lateral femur (cLF):					
cLF	40.2 ± 2.9	[39.0, 41.5]	40.1 ± 2.9	[38.8, 41.4]	0.684

	1st Quartile		4th Quartile		
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**	**P-Value**
ccLF	36.1 ± 3.3	[34.7, 37.6]	36.2 ± 3.4	[34.7, 37.7]	0.701
ecLF	41.7 ± 3.5	[40.2, 43.2]	41.0 ± 4.4	[39.1, 42.9]	0.621
icLF	44.4 ± 4.8	[42.3, 46.4]	45.0 ± 4.3	[43.1, 46.9]	0.886

For abbreviations used, please see table 1