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Journal
OSTEOARTHRITIS AND CARTILAGE, 23(9)

ISSN
1063-4584

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Publication Date
2015

DOI
10.1016/j.joca.2015.04.023

Peer reviewed

Osteoarthritis and Cartilage 23 (2015) 1595–1604

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Racial differences in biochemical knee cartilage composition between African-American and Caucasian-American women with 3 T MR-based T2 relaxation time measurements – data from the Osteoarthritis Initiative

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A R T I C L E I N F O

Article history:
Received 16 September 2014
Accepted 21 April 2015

Keywords:
MRI
T2 relaxation time
Cartilage
Knee
Race

S U M M A R Y

Objective: To determine whether knee cartilage composition differs between African-American and Caucasian-American women at risk for Osteoarthritis (OA) using *in vivo* 3 T MRI T2 relaxation time measurements.

Methods: Right knee MRI studies of 200 subjects (100 African-American women, and 100 closely matched Caucasian-American women) were selected from the Osteoarthritis Initiative (OAI). Knee cartilage was segmented in the patellar (PAT), medial and lateral femoral (MF/LF), and medial and lateral tibial compartments (MT/LT)). Mean T2 relaxation time values per compartment and per whole joint cartilage were generated and analyzed spatially via laminar and grey-level co-occurrence matrix (GLCM) texture methods. Presence and severity of cartilage lesions per compartment were graded using a modified WORMS grading. Statistical analysis employed paired t- and McNemar testing.

Results: While African-American women and Caucasian-Americans had similar WORMS cartilage lesion scores ($P = 0.970$), African-Americans showed significantly lower mean T2 values (~1 ms difference; ~0.5SD) than Caucasian-Americans in the whole knee cartilage ($P < 0.001$), and in the subcompartments (LF: $P = 0.001$, MF: $P < 0.001$, LT: $P = 0.019$, MT: $P = 0.001$) and particularly in the superficial cartilage layer (whole cartilage: $P < 0.001$, LF: $P < 0.001$, MF: $P < 0.001$, LT: $P = 0.003$, MT: $P < 0.001$). T2 texture parameters were also significantly lower in the whole joint cartilage of African-Americans than in Caucasian-Americans (variance: $P = 0.001$; contrast: $P = 0.018$). In analyses limited to matched pairs with no cartilage lesions in a given compartment, T2 values remained significantly lower in African-Americans.

Conclusion: Using T2 relaxation time as a biomarker for the cartilage collagen network, our findings suggest racial differences in the biochemical knee cartilage composition between African-American and Caucasian-American women.

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http://dx.doi.org/10.1016/j.joca.2015.04.023
1063-4584/

Introduction

Osteoarthritis (OA) is the most common form of arthritis and is characterized by progressive cartilage loss, osteophyte formation, subchondral bone changes, and synovitis[1]. It is a chronic musculoskeletal disorder with an increasing prevalence worldwide[2]. Estimates suggest that by the year 2020, about 59.4 million people will suffer from OA in the United States, accounting for about 18% of the population[3,4], and similar numbers are projected for Europe[5]. OA can affect every joint, but is specifically predominant at knee, hips and hands causing substantial pain and disability[6]. Several factors have been identified that play a role in OA risk including age, gender, genetics, behavioral factors and ethnicity[7]. Among those, the risk factor ethnicity has attracted limited research attention so far, although several radiographic studies demonstrated that African-Americans and in particular African-American women showed higher prevalence of radiographic knee OA than Caucasians[8–10]. The reasons for this ethnic difference in OA development are currently unclear, but could involve ethnic differences in cartilage composition, in cartilage degradation, or in sociocultural behavior, such as different coping[11] and belief-systems[12] leading to a higher prevalence of OA in African-American women. First epidemiologic evidence evolving from the Johnston County Osteoarthritis Project suggests racial differences in cartilage composition or degradation, but further data are lacking. In this cohort, African-American women were found to have higher serum levels of cartilage oligomeric matrix protein (COMP) compared to Caucasian women[13], a glycoprotein that is predominantly synthesized in articular cartilage[14]. Another study emerging from the same population-based cohort reported differences in serum hyaluronan levels among African-American and Caucasian-Americans[15], providing further clues that the composition of cartilage might differ by race.

In the past, analysis of cartilage composition was challenging, as it required the harvesting of biological specimens during arthroscopy or in cadaveric specimens. With the advent of quantitative MRI techniques such as cartilage T2 mapping, an effective tool has emerged allowing for the non-invasive assessment of structural and biochemical cartilage composition and integrity[16]. Several studies have demonstrated that MRI T2 mapping is particularly sensitive to the cartilage water content[17], and serves in first line as a measure of collagen network integrity[18] which accounts for approximately 15–20% weight of the extracellular cartilage matrix (ECM)[19]. In contrast, T2 mapping is relatively insensitive to the change in proteoglycans content that account for about 3–6% of the weight of the ECM[19]. It has been demonstrated that cartilage damage due to degeneration of the collagen matrix is associated with elevated water content within the cartilage and therefore will increase cartilage T2 relaxation time measurements[20,21].

Unlike standard T2 relaxation time techniques, advanced methods such as laminar[22] and texture grey-level co-occurrence matrix (GLCM) analyses[23,24] can be utilized to better understand the spatial and laminar distribution of T2 values within the cartilage. Cartilage T2 laminar analysis generates information on the horizontal organization of articular cartilage by averaging T2 values over a superficial layer, adjacent to the joint fluid and over a deep cartilage layer adjacent to the subchondral bone[25]. Texture analysis via grey-level co-occurrence matrices allows to extract information on the organizational relationship of neighboring pixels by computing features such as entropy, contrast and variance[25]. Using T2 MRI relaxation time measurements of knee cartilage as a sensitive measure of cartilage collagen network, this is the first human *in vivo* and MRI study aiming to investigate ethnic differences in knee cartilage composition, texture and laminar structure between African-American and Caucasian women. Our study focused on women as they have a higher disease burden of OA than men[26].

We hypothesized that knees without radiographic OA in African-American women and Caucasian women would differ in their knee cartilage composition as assessed by MRI T2 relaxation time measurements. Furthermore, we hypothesized that the knee cartilage in African-American women would exhibit a different texture than knee cartilage in Caucasian-American women.

Material and methods

Subjects

A subset of 200 African-American and Caucasian-American women was identified from the Osteoarthritis Initiative (OAI) incidence and progression subcohorts as illustrated in Fig. 1. The OAI is a large-scale, multi-center, longitudinal cohort study which is dedicated to investigate the role of MRI-based imaging biomarkers in knee OA. It consists of 4796 participants who either have at baseline no OA and no OA risk factors (=normal cohort), or have no OA but possess risk factors to develop OA (=incidence cohort), or experienced frequent knee symptoms in the past 12 months and have radiographic evidence of OA (progression cohort, Kellgren–Lawrence (KL)-score of ≥2). The OAI is set up as a huge publicly accessible repository providing collected imaging and clinical data, such as e.g., data on physical activity (PASE) or on OA risk factors for further research use[27]. The study protocol, amendments, and informed consent documentation including analysis plans were reviewed and approved by local institutional review boards.

To be included in the study, all women had to be non-Hispanic and had to self-report their racial background as either Black or African-American or Caucasian or White. The 45 Asians enrolled in the OAI were not included in this study. As OA prevention is most effective in younger individuals and as T2 measurements have been shown to be less useful in subjects with more advanced OA, we only included women aged less than 70 years old[28]. A body mass index between of 22.5–39.5 kg/m^2 was also required. To allow for a sufficiently large sample size we included subjects with no or doubtful OA in right baseline knee radiographs as defined by KL scores[29] of ≤1 (71% KL0 subjects, 29% KL1 subjects). The purpose of this latter inclusion criterion was to identify participants with no OA or in the very early stage of the OA disease process, when cartilage was still well-preserved and matrix imaging biomarkers, such as T2 relaxation time, could be used to measure differences in cartilage composition. Exclusion criteria comprised all women with a positive history of rheumatoid arthritis, other inflammatory arthritis, or knee surgery at the right knee. Using these inclusion and exclusion criteria, 140 African-American women were available in the overall OAI cohort. These were matched by KL grade (0 or 1), baseline age (45–54, 55–64, 65–69 years) and BMI strata (≥20–25, ≥25–30, ≥30–35, ≥35–40 kg/m^2), subcohort and clinical site. Caucasian-American controls were randomly selected from each stratum. 38 African-American women failed to have a Caucasian match and therefore were not included in the study. An additional two subjects could not be analyzed due to the incomplete MRI imaging data set. In total 100 subjects per group were finally studied.

Imaging

Radiographs

Baseline standing postero-anterior fixed flexion knee radiographs were acquired as described in detail in the OAI Radiographic Procedure Manual freely accessible at http://www.oai.ucsf.edu. A

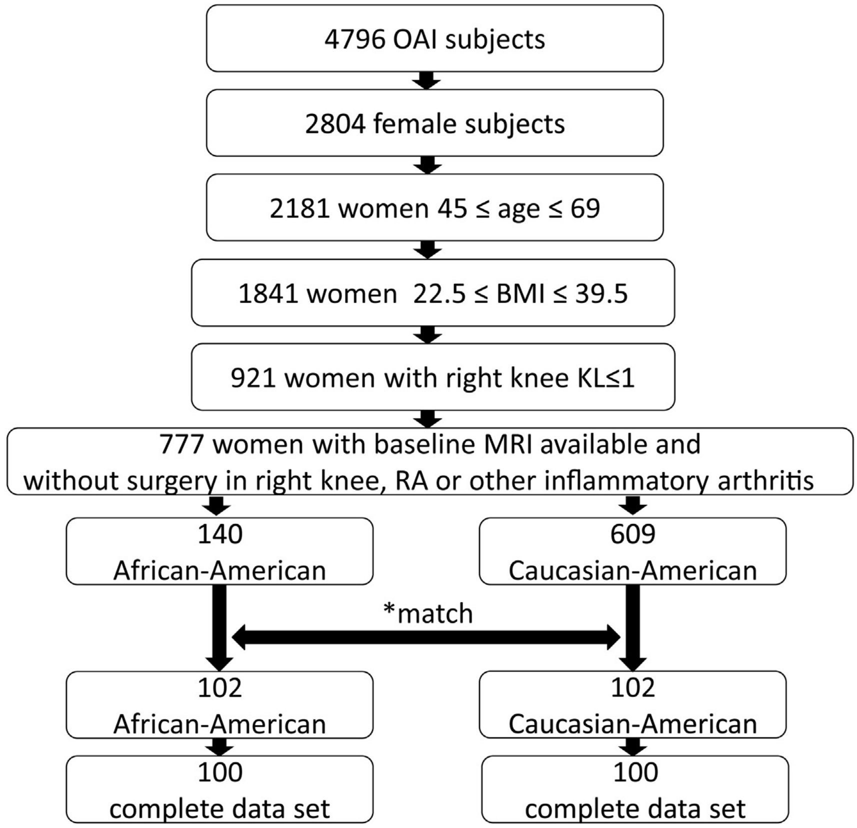

Fig. 1. Schematic illustration showing selection of subjects. 100 African-American women and 100 Caucasian-American women fulfilled the inclusion and exclusion criteria. *Subjects were matched by cohort, KL score, site, baseline age and by BMI strata, and randomly selected from the eligible knees in each stratum. Thirty-eight African-Americans failed to match.

Plexiglas frame (SynaFlexer, CCBR-Synarc, Newark, CA, USA) was used for image acquisition. Knees were placed in 20–30° flexion and 10° internal rotation of the feet. A focus-to-film distance of 72 inches was used. All knee radiographs were graded by a central reading center for KL scores[29,30].

MR imaging protocol

MR images of the right knee were obtained in all subjects, using identical 3.0 T scanners (Siemens Magnetom Trio, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, Oh, USA) at four clinical sites. A standardized[31,32] sagittal T2 map 2-D Multi-Slice Multi-Echo (MSME) spin-echo sequence (TR 2700 ms, TE1–TE7 10 ms, 20 ms, 30 ms, 40 ms, 50 ms, 60 ms, and 70 ms, in-plane spatial resolution of 0.313 mm × 0.446 mm (0.313 mm × 0.313 mm after reconstruction), slice thickness 3.0 mm, gap 0.5 mm) was used for measuring T2 relaxation times. For WORMS cartilage scoring, a coronal intermediate-weighted (IW) 2D fast spin-echo (FSE) sequence (TE/T2 29/3700, flip angle 180°), a sagittal 3D dual-echo in steady state (DESS) with selective water excitation (WE) (TE/TR 4.7/16.3, flip angle 25°) and a sagittal 2D IW fat suppressed FSE sequence (FS) (TE/TR 30/3200, flip angle 180°) were analyzed. More detailed information on the OAI MRI sequence parameters can be found in Peterfy *et al.*[31].

Quantitative T2 relaxation time measurements

T2 relaxation time measurements were carried out in all 200 subjects as described in detail previously[33]: Articular knee cartilage of the right knee was first segmented on MRI T2 sequences by two board certified musculoskeletal radiologists using an in-house developed, semi-automated, spline-based software implemented in MATLAB (The Mathworks Inc., Natick, MA)[34]. For each knee, five cartilage compartments consisting of the patellar, lateral/medial femoral and lateral/medial tibial cartilage were segmented on all image slices throughout the sagittal image stack in which the cartilage was clearly depictable and free of partial-volume effects. The trochlea was excluded because of interfering flow artifacts from the popliteal artery. In a second step, T2 relaxation time measurements were calculated based on the Levenberg–Marquardt algorithm[22]. This algorithm uses a mono-exponential decay model as fitting function. The first echo time was dropped as suggested by recent studies to optimize signal-to-noise ratio[35,36]. Mean T2 relaxation time measures were generated for the cartilage of each compartment (patella, medial and lateral femur, medial and lateral tibia). In addition, a global T2 value for the overall cartilage of the joint was obtained by calculating the mean of all compartments.

Laminar and GLCM texture analysis

Cartilage laminar analysis was performed in all 200 women using in house-software that has been utilized in previous studies[22]. This technique separates the cartilage on a slice-by-slice basis into a deep layer adjacent to the bone cartilage interface and a superficial articular layer of equal thickness resulting in an average layer thickness of about 3.5 (medial tibia) to 7 pixels (patella) per layer (Fig. 2). Furthermore, cartilage GLCM texture analysis was performed to evaluate the spatial distribution of cartilage T2 values within each compartment, based on the method as described by Haralick *et al.*[23]. GLCM texture parameters including variance, contrast and entropy were calculated in each cartilage region. The GLCM parameters reflect heterogeneity of T2 values throughout the cartilage matrix[20,37]. GLCM variance indicates how much pixel

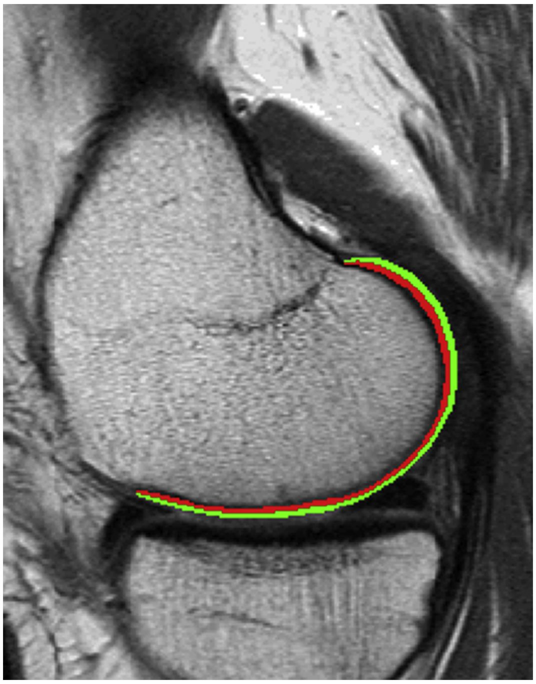

Fig. 2. Representative example of laminar regions of interest shown for the medial femoral cartilage. The green region corresponds to the superficial layer, while the red region corresponds to the deep cartilage layer.

values vary from the compartment mean. The higher the variance the more T2 co-occurrences are dispersed from the GLCM mean. The parameter contrast is defined as the probability of finding neighboring pixels with a large T2 difference. Therefore an elevated contrast signifies that there is a high probability of finding neighbouring pixels with large T2 differences. The GLCM parameter entropy is a measure of disorder in an image and indicates how irregular pixel pairs occur within an image. The higher the entropy the less organized an image and the rarer to find common pixel pairs[38].

Whole-Organ Magnetic Resonance (WORMS) cartilage lesion scoring. MR images were evaluated independently by two board-certified radiologists for presence and severity of cartilage lesions using a semi-quantitative modified Whole-Organ Magnetic Resonance Imaging Score (WORMS)[32,39]. In case of disagreement, a consensus reading was performed with a senior musculoskeletal radiologist with 24-years of experience (TML). Cartilage lesions were assessed in five compartments (patella, medial/lateral femur, and medial/lateral tibia) using an 8-point scale as outlined in Table I.

Table I
WORMS cartilage lesion scoring system adopted from Peterfy *et al.* and utilized to score the frequency and severity of cartilage lesions in the five knee cartilage compartments (lateral femur, medial femur lateral tibia, medial tibia and patella). Each cartilage lesion was scored on the following eight-point scale

0	Normal cartilage thickness and signal intensity
1	Normal cartilage thickness or swelling with abnormal signal on fluid-sensitive sequences
2	Single partial-thickness focal cartilage lesion <1 cm in greatest width
2.5	Single full-thickness focal cartilage lesion <1 cm in greatest width
3	Multiple areas of partial-thickness (grade 2) cartilage lesions intermixed with areas of normal cartilage thickness or a grade 2 cartilage lesion wider than 1 cm but <75% of the region
4	Diffuse (≥75% of the region) partial-thickness cartilage loss
5	Multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region
6	Diffuse (≥75% of the region) full-thickness cartilage loss

Statistical analysis

Statistical analysis was performed using STATA version 12 software (StataCorp LP, College Station, TX) and SPSS 20 (SPSS Inc., Chicago, IL, USA). Normal distribution of numeric variables was explored by visualization of histograms and Shapiro Wilk tests. Paired *t*-tests were used to assess differences in numeric variables between pairs of African-American and Caucasian-American women. To determine intergroup differences in categorical variables such as knee alignment (evaluated in physical exam via goniometer), physical activity score and OA risk factors, McNemar's tests were used. Statistical significance was defined as $P < 0.05$.

We assessed interracial differences in mean cartilage T2 and in mean GLCM variance as primary outcomes. GLCM variance was chosen over other texture parameters based on the rationale that it is highly correlated with GLCM contrast[38] and has proven to be a useful and sensitive biomarker for detection of early extracellular matrix changes in patients at risk for OA[37]. As an exploratory secondary outcome and to verify our results we calculated and reported the differences between African-American and Caucasian-American cartilage T2 values in the superficial and deep cartilage layer, as well as between other texture parameters such as entropy and contrast.

For WORMS grading analysis we treated the score as a numeric outcome. As sensitivity analysis we also analyzed cartilage damage on MRI in each of the five compartments as dichotomous outcomes (first as abnormality present if WORMS grade ≥2 and secondly using the more stringent definition as abnormalities present if WORMS grade ≥1). We additionally performed a sub-analysis in all matched pairs that were free of any cartilage lesion in a given compartment (WORMS = 0 or 1).

Reproducibility measurements

Previous studies on T2 relaxation time measurements from our group using this segmentation technique found minimal reproducibility errors in the same dataset. For intra-reader reproducibility, the mean T2 RMS (root mean square) errors by compartment were as follows: lateral femur (LF) 1.52%, lateral tibia (LT) 1.02%, medial femur (MF) 1.18%, medial tibia (MT) 2.36%, patella (Pat) 1.19%, and mean of all compartments 1.46%. For inter-reader reproducibility, the mean T2 RMS errors by compartment were as follows: LF 1.39%, LT 1.86%, MF 1.63%, MT 1.45%, Pat 1.22%, and mean of all compartments 1.57%[34].

Results

Subject characteristics

African-American women and matched Caucasian-American women exhibited comparable age, BMI, and physical activity levels and demonstrated similar knee alignment (Table II). Both racial groups consisted to 71% of subjects without any sign of radiographic OA (KL = 0). 29% of subjects of both groups had doubtful OA on knee radiographs (KL = 1). WORMS cartilage lesion scoring revealed that cartilage in both racial groups had no or a very low and similar prevalence of cartilage lesions in all tibiofemoral compartments and in the whole joint cartilage (medial femur: $P = 0.306$, lateral femur: $P = 0.804$; medial tibia: $P = 0.150$; lateral tibia: $P = 0.686$, whole joint cartilage: $P = 0.970$, WORMS grade 0, Table III). This remained true, even when we subdivided the groups according to their WORMS cartilage grading (Total WORMS,

Table II
Subject characteristics at time of baseline visit

Parameter	Subjects		P − value
	African American	Caucasian American	
	$n = 100$	$n = 100$	
Age*	55.89 ± 6.02	55.32 ± 6.46	0.138
BMI*	29.20 ± 4.02	29.16 ± 3.81	0.816
Physical Activity Score (average PASE)*	151.2 ± 80.4	167.1 ± 78.7	0.160
Alignment†			
Neither	32 (32.0)	32/98 (32.7)	
Varus	16 (16.0)	19/98 (19.4)	0.869
Valgus	52 (52.0)	47/98 (48.0)	
OA risk factors†			
History of knee injury	26 (26.0)	31 (31.0)	0.423
Knee symptoms in the past 12 months	47/99 (47.5)	31/99 (31.3)	0.029‡
Family history of knee replacement surgery	15/99 (15.2)	15/99 (15.2)	0.842

BMI body mass index.
* Values are given as mean ± SD.
† Values are number (%).
‡ Statistically significant ($P < 0.05$).

WORMS grade 0 and 1, and WORMS grade ≥2). Most lesions were found in the patella, but were similar in severity and frequency in African-American women and Caucasians ($P = 0.337$). African-American women exhibited higher percentages of knee symptoms compared to Caucasian-American women ($P = 0.029$). With respect to other OA risk factors such as history of knee injury and family history of knee replacement surgery, no differences between African-American and Caucasian-American females were detected ($P > 0.05$).

Table III
WORMS cartilage lesion scoring presented for both cohorts. The cartilage was scored per compartment on an 8-point scale from 0 to 6, with 0 meaning "normal (healthy) cartilage", to 6 representing "highly degenerated cartilage with ≥75% of areas with full thickness cartilage loss".† Results were pooled to derive an overall cartilage lesion score for the whole knee joint

WORMS cartilage	Subjects		P − value
	African American	Caucasian American	
	$n = 100$	$n = 100$	
WORMS cartilage lesion score*			
Global knee joint	3.61 [3.03–4.17]	3.62 [3.14–4.10]	0.970
Lateral femur	0.32 [0.17–0.46]	0.29 [0.16–0.42]	0.804
Lateral tibia	0.57 [0.39–0.77]	0.62 [0.45–0.76]	0.686
Medial femur	0.58 [0.36–0.79]	0.45 [0.28–0.61]	0.306
Medial tibia	0.09 [0.00–0.17]	0.02 [−0.01–0.05]	0.150
Patella	2.05 [1.76–2.34]	2.26 [1.97–2.55]	0.337
WORMS grade = 0			
Lateral femur (n %)	83 (100)	80 (100)	0.578
Lateral tibia (n %)	64 (100)	54 (100)	0.157
Medial femur (n %)	72 (100)	74 (100)	0.732
Medial tibia (n %)	95 (100)	98 (100)	0.257
Patella (n %)	14 (100)	9 (100)	0.297
WORMS grade = 0 and 1			
Lateral femur (n %)	88 (100)	93 (100)	0.251
Lateral tibia (n %)	85 (100)	89 (100)	0.394
Medial femur (n %)	82 (100)	85 (100)	0.549
Medial tibia (n %)	98 (100)	100 (100)	0.157
Patella (n %)	45 (100)	39 (100)	0.396
WORMS grade ≥ 2			
Lateral femur (n %)	12 (100)	7 (100)	0.251
Lateral tibia (n %)	15 (100)	11 (100)	0.394
Medial femur (n %)	18 (100)	15 (100)	0.549
Medial tibia (n %)	2 (100)	0 (0)	0.157
Patella (n %)	55 (100)	61 (100)	0.396

* Data are given as mean values [95% confidence intervals].
† A detailed outline of the WORMS cartilage lesion scoring system is given in Table I.

T2 measurements

African-American women exhibited significantly lower mean T2 values than Caucasian-American women in the pooled analysis of global knee cartilage ($P < 0.001$) as well as in each compartmental analysis (lateral femur $P = 0.001$, medial femur $P < 0.001$, lateral tibia $P = 0.019$, medial tibia $P = 0.001$), except for the patella ($P = 0.147$) (Table IV). Figure 3 shows representative color-coded sagittal T2 maps of the medial femur of an African-American women [Fig. 3(A)] and the correspondent Caucasian-American women [Fig. 3(B)]. The sub-analysis which included only those matched African-American and Caucasian pairs without focal cartilage lesions (WORMS = 0 or 1), showed similar results: mean T2 values in African-Americans were generally lower than those in Caucasians. Differences were most pronounced in the lateral femur ($P = 0.001$), the medial femur ($P = 0.012$), and the medial tibia ($P = 0.029$).

Laminar cartilage analysis

Results of laminar superficial and deep layer analysis are displayed in Table V. Mean superficial cartilage layer T2 values in African-American women were significantly lower than mean superficial T2 values in Caucasian-American women in each compartment and global knee joint except in the patella (lateral and medial femur, medial tibia and global knee joint: $P < 0.001$; lateral tibia: $P = 0.003$). The deep layer global T2 values were also significantly lower in the African-American women compared to Caucasian-American women ($P = 0.031$). Differences were most pronounced at the deep T2 layers of the lateral femur, medial femur, and patella (lateral femur: $P = 0.019$, medial femur: $P = 0.038$, patella: $P = 0.018$), while deep layer T2 values of the tibial compartments were not significantly different among both races (lateral tibia: $P = 0.529$, medial tibia: $P = 0.160$).

GLCM texture analysis

With respect to GLCM texture parameters, articular knee cartilage of African-American women exhibited a more homogenous spatial distribution of T2 values than the knee cartilage of Caucasian-American women (Tables IV and V). All three GLCM-

Table IV
Cartilage T2 values (in ms) and mean GLCM parameters

Parameter	Subjects		P − value
	African American	Caucasian American	
	$n = 100$	$n = 100$	
Mean cartilage T2*	32.03 [31.71–32.35]	32.86 [32.49–33.22]	**<0.001**
LF T2	33.61 [33.16–34.06]	34.54 [34.10–34.98]	**0.001**
LT T2	27.77 [27.32–28.21]	28.52 [27.99–29.05]	**0.019**
MF T2	36.92 [36.44–37.40]	38.02 [37.49–38.54]	**<0.001**
MT T2	28.92 [28.55–29.28]	29.77 [29.35–30.19]	**0.001**
PAT T2	32.94 [32.44–33.44]	33.43 [32.92–33.94]	0.147
Mean variance*	203.49 [196.80–210.18]	215.78 [208.40–223.37]	**0. 001**
LF variance	191.60 [184.13–199.07]	200.39 [192.07–208.70]	0.051
LT variance	144.51 [137.87–151.17]	161.55 [152.75–170.34]	**0.001**
MF variance	257.22 [246.56–267.88]	281.09 [269.41–292.77]	**<0.001**
MT variance	197.92 [187.84–208.01]	205.21 [195.03–215.39]	0.259
PAT variance	226.21 [214.91–237.50]	230.65 [219.74–241.57]	0.533

LF Lateral Femur; LT Lateral Tibia; MF Medial Tibia; MT Medial Tibia; PAT Patella.
P-values <0.05 are in bold.
Data are given as means and [95% confidence intervals].
* Global knee joint.

features – contrast, variance and entropy – showed lower values in the whole joint cartilage and in all five compartments of the African-American group, except the patella, but did not always reach statistical significance. In African-American women pixel pairs appeared more regular, and therefore less entrop, in particular in the medial tibia ($P = 0.009$) and in the lateral tibia ($P = 0.035$). In addition, mean variance and contrast of the total joint cartilage in African-American women were also significantly lower (variance: $P = 0.001$, contrast: $P = 0.018$). This was in agreement with the compartimental analysis, which revealed for both features differences that were most pronounced in the medial femur (variance MF: $P < 0.001$; contrast MF: $P < 0.001$), and the lateral tibia (variance LT $P = 0.001$; contrast LT: $P = 0.038$).

Discussion

In this study we investigated the biochemical composition of knee cartilage in African-American women and Caucasian-American women using 3 T MRI T2 relaxation time measurements. Both groups were closely matched and exhibited either no or a very low and similar prevalence and severity of cartilage lesion on 3 T MRI evaluation.

Our most important finding was that African-American women had significantly lower and more homogeneous mean T2 values in all compartments and the whole joint cartilage except for the patella compared to the matched Caucasian-American women. At first glance, this is somewhat surprising. We would have expected their

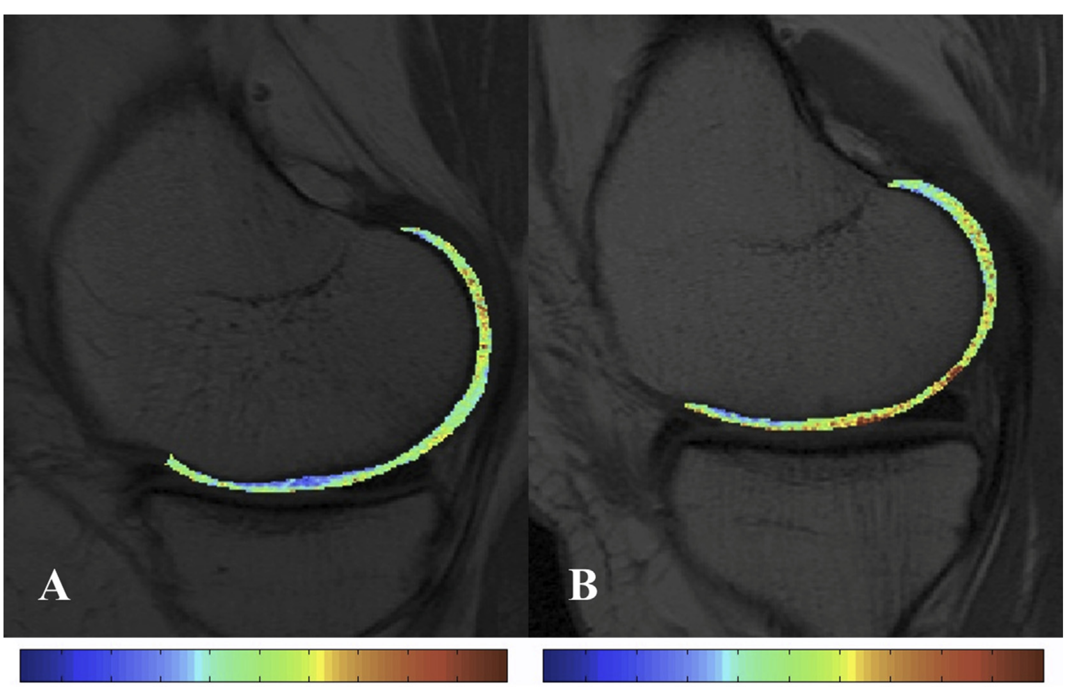

Fig. 3. Representative color-coded sagittal T2 maps showing the segmented medial femur of an African-American subject (A) and a matched Caucasian-American subject (B). Cartilage of the African-American subject (A) shows lower T2 values.

Table V
Cartilage T2 values (in ms) of laminar analysis and mean GLCM parameters

Parameter	Subjects		P − value
	African American	Caucasian American	
	n = 100	n = 100	
Laminar analysis			
Mean superficial layer T2*	34.67 [34.27–35.06]	35.91 [35.46–36.35]	**<0.001**
LF superficial layer T2	35.62 [35.09–36.14]	36.94 [36.38–37.50]	**<0.001**
LT superficial T2	31.08 [30.50–31.66]	32.35 [31.67–33.03]	**0.003**
MF superficial T2	38.42 [37.89–38.94]	39.93 [39.32–40.54]	**<0.001**
MT superficial T2	31.51 [30.96–32.05]	33.48 [32.90–34.07]	**<0.001**
PAT superficial T2	36.71 [36.08–37.34]	36.82 [36.23–37.42]	0.776
Mean deep layer T2*	29.53 [29.23–29.82]	29.93 [29.61–30.26]	**0.031**
LF deep layer T2	31.51 [31.07–31.95]	32.16 [31.73–32.59]	**0.019**
LT deep layer T2	24.49 [24.13–24.85]	24.63 [24.20–25.07]	0.579
MF deep layer T2	35.54 [35.00–36.07]	36.22 [35.65–36.78]	**0.038**
MT deep layer T2	26.73 [26.41–27.06]	26.41 [26.04–26.78]	0.160
PAT deep layer T2	29.37 [28.90–29.85]	30.22 [29.72–30.73]	**0.018**
Texture analysis			
Mean contrast*	281.83 [271.31–292.35]	295.01 [283.40–306.84]	**0.018**
LF contrast	265.62 [254.67–276.58]	274.60 [262.48–286.72]	0.202
LT contrast	184.02 [174.75–193.28]	197.93 [185.18–210.69]	**0.038**
MF contrast	372.66 [354.97–390.35]	405.57 [385.91–425.23]	**<0.001**
MT contrast	291.95 [275.44–308.45]	296.02 [279.19–312.84]	0.703
PAT contrast	294.90 [278.83–310.97]	300.95 [284.16–317.73]	0.536
Mean entropy*	6.20 [6.17–6.23]	6.24 [6.20–6.28]	0.090
LF entropy	6.59 [6.54–6.65]	6.65 [6.60–6.70]	0.119
LT entropy	5.68 [5.63–5.74]	5.77 [5.71–5.83]	**0.035**
MF entropy	6.83 [6.79–6.88]	6.88 [6.83–6.93]	0.113
MT entropy	5.83 [5.79–5.88]	5.91 [5.87–5.96]	**0.009**
PAT entropy	6.06 [6.00–6.12]	6.00 [5.93–6.06]	0.157

LF Lateral Femur; LT Lateral Tibia; MF Medial Tibia; MT Medial Tibia; PAT Patella.
P values <0.05 are in bold.
Data are given as mean values [95% confidence intervals].
* Global knee joint.

T2 values to be higher and more heterogeneous relative to Caucasian-American women since African-American women are at increased risk for OA and previous studies have reported that elevations in the mean and heterogeneity of cartilage T2 values are indicative of early cartilage degeneration[20,37,40,41].

Why T2 values in African-American women are lower and more homogenous and how these findings relate to a higher prevalence of OA in African-American women remains to be determined. Knee cartilage consists of a relatively small amount of chondrocytes that are embedded in an extracellular matrix (ECM) composed primarily of water (about 70%), collagen type II (about 25%) and proteoglycans and underlies a regular turnover[42]. T2 relaxation time measures in the contrary are known to correlate strongly with cartilage water content[17] and to show inverse correlations with cartilage collagen content[18]. Based on these facts, lower mean T2 values in standard and laminar analysis may be the result of a higher cartilage collagen content, a lower cartilage water content or a combination of both. Supporting evidence for a higher collagen content in African-American women knee cartilage comes from the Johnston County study in which higher serum levels of cartilage-oligomeric matrix protein (COMP) were reported for African-Americans women than Caucasians[13]. As COMP is a glycoprotein that accelerates type 2 collagen fibril formation and stabilizes the collagen network[43], higher COMP serum levels in AA might therefore be reflective of higher cartilage collagen content. In this context it seems noteworthy that African-Americans have in general a higher tendency towards excessive scarring and keloid formation than Caucasians, which is mainly ascribed to an excessive collagen deposition in the dermis[44]. Further histological studies are needed to verify if collagen content in African-American knee cartilage is indeed shifted towards higher levels relative to Caucasians.

Besides from a potential higher collagen content, lower T2 values could also arise from a diminished cartilage water content. Potential mechanisms involve either a decreased water binding capacity of African-American cartilage or an increased cartilage water loss or a reduced water entry into the cartilage due to more compact collagen bundles. To date, no studies exist on the hydration status of cartilage by race. So far, lower cartilage water content has been regarded as beneficial, as increased water content and increased water mobility were linked to OA[21]. However, as cartilage is an avascular and alympathic tissue, in which nutrition and elimination of waste products are diffusion-dependent[42], one might speculate that a too dense and too water-impermeable cartilage matrix might hamper proper nutrition of chondrocytes and promote accelerated cartilage degeneration. This could potentially explain the apparent paradoxon between low and homogeneous T2 values and a high prevalence of OA in African-American women.

Besides its sensitivity to hydration and collagen content, T2 relaxation time measurements have been also attributed a strong dependence of collagen fiber orientation[16]. Unfortunately our current texture analysis generates spatially invariant results and therefore is not suited to interprete our findings in correspondence to the natural collagen fibril organization of cartilage. However, taking into account that cartilage in African-American women has lower T2 and less heterogeneity suggests the possibility that their collagen structure is more organized. In the future, more advanced texture techniques including cartilage flattening algorithms[45] should be applied to compare directional differences in texture GLCM parameters between races.

In summary, our observed differences in T2 relaxations time measurements and in texture could be explained by a higher concentration of collagen type 2 in African-American cartilage, a lower water content or differences in collagen fiber orientation. So far, it has been difficult to demonstrate differences in biochemical knee cartilage composition using histopathological studies. In fact, when we performed a literature research, we did not find any histologic study nor any other study looking at cartilage composition or cartilage collagen content in different races. To the best of our knowledge this is the first study that indicates racial differences in biochemical knee cartilage composition.

Although novel for cartilage, racial differences have been recently described for the skin as well as for musculoskeletal tissues such as bone. Girardeau and coworkers found that skin types differed morphologically and functionally in their dermal component between Caucasian and African-American individuals[46]. Also, differences in bone microarchitecture and bone mineral density were observed in African-American women compared to Caucasian women[47]. Those studies indirectly provide support for our results of T2 relaxation time measurement of knee cartilage.

While all other compartments showed significant results, differences at the patella were not demonstrated in this study. These might have been eliminated by the presence of advanced focal patellar osteoarthritic damage as demonstrated by a mean cartilage lesion score of higher than two in this compartment for both groups. A previous study showed an inverse correlation of longitudinal T2 changes versus baseline T2 values and morphological cartilage abnormalities, which suggests that once morphological cartilage defects occur, T2 values may be limited for evaluating further cartilage degradation[28]. This could have impacted the patella T2 values in our study.

Because compartmental T2 values do not account for the spatial distribution of T2 values within the compartments, our study also investigated laminar and texture pattern of cartilage spatial distribution of T2 values within the cartilage. When separating the cartilage into a superficial layer adjacent to the joint space and a deep layer adjacent to the bone-cartilage interface, we found in agreement with our global T2 measurements results, that superficial cartilage layer T2 values in African-American women were significantly lower than T2 values in Caucasian-Americans in each compartment and the whole knee joint cartilage except for the patella. In keeping with our global T2 findings, we also observed significantly lower T2 values in African-American women than in Caucasian-Americans in the deep layers of medial and lateral femur, patella, and whole joint cartilage, but not in the tibia. The lack of deep layer T2 differences among races in the tibia is most likely attributable to the impact of chemical shift artifacts from the bone/cartilage interface. These artifacts are most pronounced in the tibia, in particular in the T2 sequence that was analyzed here, which used a frequency encoding direction from head to foot.

Of note, African-American women experienced a greater percentage of knee symptoms compared to Caucasian-American women. This seems at first glance unexpected, as the cartilage was in both cohorts predominantly and in similar percentages lesion free and both cohorts consisted merely of fairly young and healthy subjects with no or doubtful signs of OA (KL grade ≤ 1). However, previous studies have demonstrated in line with our finding that African-Americans seem to exhibit in general a greater sensitivity to pain, a lower pain threshold and also a lower tolerance for pain compared to Caucasians[48–50]. This racial disparity in pain sensitivity was lately confirmed even in racial cohorts with present OA[51] and might be due to genetic variants in the pain μ-opioid receptor in African Americans, which alter the function and change responsiveness to known μ-opioid receptor ligands[52].

Although African-Americans are known to have a higher prevalence of OA, we surprisingly observed similar rates of total knee replacements (TKR) in the family histories of African-American and Caucasian-American women. A decreased propensity of African-Americans to undergo TKR has long been described[53] and is still persistent[54]. Explanations include their belief systems[12], less structural and functional social support[55], and higher postoperative infection and complication rates[56]. Due to these reasons, the OA-ridden African-American ancestors of our study subjects might not have undergone TKR as frequently as ancestors from their Caucasian-American counterparts.

Our study has several limitations: First, to investigate the effect of race on knee cartilage composition, study subjects from a normal cohort are the best choice, however, the OAI normal cohort does not contain any African-American women. Second, although our rigorous matching policy allowed us to control for most of the OA-related confounders, we could not account for all factors that have been linked to the development of OA. Particularly, we lacked information on medication intake[57], bone mineral density[58], occupational history[9] or the degree of muscle weakness[59]. Third, the differences in mean T2 that we detected between the two races, appear quite subtle, but are indeed meaningful. Lastly, due to the study design it was not feasible to obtain histological correlation to prove our results. However, the detected disparities in cartilage mean T2 values between groups that were paralleled by a lack of differences in WORMS macrostructural cartilage scores make it seem worthwhile to assess the biochemical properties of cartilage *in vitro*. In addition, other quantitative MRI techniques such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T1rho have been shown to be associated with the biomechanical properties of cartilage *in vivo* and proteoglycan content[60–64] and could be used in future studies to collect more information on racial differences in cartilage composition. Also, longitudinal studies may provide further insight on the effect of race on changes in knee cartilage composition. Correlation of elevated knee cartilage T2 measurements with clinical findings should be investigated and interpreted further.

In conclusion, using MRI T2 relaxation time measurements we found significant racial differences in biochemical knee cartilage composition between strictly matched African-American and Caucasian women with a similar degree of degeneration as well as in matched pairs that had no cartilage lesions. Our findings may imply the need to conduct separate analyses by race when studying prediction of outcomes by T2 relaxation time measurements and should spur further research on the evolution of OA by race over time. Moreover, once histologically confirmed, our results may have potential implications in later patient care: African-American women might need special OA therapies and also special preventive strategies that are tailored to their specific cartilage needs.

Authors' contributions

AY and UH are the primary authors and contributed equally. AY contributed to the manuscript in the following ways: conception and design, patient selection, cartilage segmentation, analysis and interpretation of data, statistical modeling, manuscript drafting and revision. UH contributed to the manuscript in the conception and design, analysis and interpretation of data, statistical modeling, manuscript drafting and revision. The following authors contributed as described: MK (patient selection, cartilage segmentation, statistical analysis, interpretation of data, and revision), GBJ (statistical analysis and revision), FL and HL (patient selection), CM and MN (statistical expertise and revision), NEL (revision) and TML (study supervisor, conception and design, data analysis and interpretation, manuscript revision).

Role of funding source

The study was supported by the Osteoarthritis Initiative, a public–private partnership comprising five NIH contracts (National

Institute of Arthritis and Musculoskeletal and Skin Diseases contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) with research conducted by the Osteoarthritis Initiative Study Investigators. Private funding partners include Merck Research, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer; the private sector funding for the Osteoarthritis Initiative is managed by the Foundation for the National Institutes of Health.

The analyses in this study were funded through the National Institute of Arthritis and Musculoskeletal and Skin Diseases grants U01-AR059507 and P50-AR060752.

The study was also funded by a Grant from Beijing High Levels of Health Technical Talent Team of Construction Project (no. 2013-3-033).

This manuscript has received the approval of the OAI Publication Committee based on a review of its scientific content and data interpretation.

Conflict of interest

The authors declare that they have no conflict of interest.

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