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Gender Differences in Knee Joint Congruity Quantified from MRI: A Validation Study with Data from Center for Clinical and Basic Research and Osteoarthritis Initiative

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Abstract

Objective. Gender is a risk factor in the onset of osteoarthritis (OA). The aim of the study was to investigate gender differences in contact area (CA) and congruity index (CI) in the medial tibiofemoral (MTF) joint in 2 different cohorts, quantified automatically from magnetic resonance imaging (MRI). *Design*. The CA and CI markers were validated on 2 different data sets from Center for Clinical and Basic Research (CCBR) and Osteoarthritis Initiative (OAI). The CCBR cohort consisted of 159 subjects and the OAI subcohort consisted of 1,436 subjects. From the MTF joint, the contact area was located and quantified using Euclidean distance transform. Furthermore, the CI was quantified over the contact area by assessing agreement of the first- and second-order general surface features. Then, the gender differences between CA and CI values were evaluated at different stages of radiographic OA. *Results*. Female CAs were significantly higher than male CAs after normalization, male CIs were significantly higher than female CIs after correcting with age and body mass index ($P < 0.05$), consistent across the 2 data sets. For the OAI data set, the gender differences were present at all stages of radiographic OA. *Conclusions*. This study demonstrated the gender differences in CA and CI in MTF joints. The higher normalized CA and lower CI values in female knees may be linked with the increased risk of incidence of radiographic OA in females. These differences may help further understand the gender differences and/or to establish gender specific treatment strategies.

Keywords

knee, radiographic osteoarthritis, gender, congruity index, osteoarthritis initiative, MRI

Introduction

Osteoarthritis (OA) is a major health concern worldwide causing pain and limited range of motion in load-bearing joints, particularly for the elderly.[1] There exist several systemic and nonsystemic risk factors that contribute toward the development and progression of the OA.[2,3] Gender is one of the systemic risk factors during the onset of OA.[4,5] The various factors that contribute to the predisposition of OA in men and/or women could be cartilage structure, hormonal imbalance, biomechanics, malalignment, age, and exercise. Biomechanical factors in general play a significant role in the onset of OA[6] and previous research showed that there existed gender differences in the biomechanics of the OA knees.[7] Age also plays a critical role making women more susceptible to OA than men, generally from the onset of menopause.[8]

The contact area (CA) in the medial tibiofemoral (MTF) joint is the region where the articular cartilage surfaces covering the bone ends are in close proximity. In the CA, the 2 surfaces interact and transfer the local stresses, ideally causing no or insignificant degeneration to the cartilage in a joint with no radiographic OA. The "congruity" could physically be defined as how well any 2 surfaces fit together when superimposed one on another. In an MTF joint with no radiographic OA, the smooth femoral cartilage surface articulates well with the smooth tibial cartilage surface and is congruent in association with the meniscus.

Several studies assessed the gender differences from the longitudinal volume change, gait analysis, pain, and correlation of clinical OA with Kellgren and Lawrence (KL) score.[9] Starting with non-invasive studies from cadavers, the gender differences

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Table 1. Number of Subjects (N_1) and Knees (N_2), Age (Years), and BMI (kg/m^2) for Male and Female Subjects for CCBR and OAI Data Sets with Respect to KL Index.[a]

	CCBR						OAI					
	Male			Female			Male			Female		
	N_1/N_2	Age (Mean)	BMI (Mean)	N_1/N_2	Age (Mean)	BMI (Mean)	N_1/N_2	Age (Mean)	BMI (Mean)	N_1/N_2	Age (Mean)	BMI (Mean)
All KL	74/148	23-77 (57)	20-38 (27)	70/140	21-81 (56)	18-37 (26)*	580/580	45-79 (61)	20-42 (29)	856/856	45-79 (61)	18-49 (29)
KL 0	48/79	23-77 (49)	20-38 (25)	46/66	21-78 (47)	18-36 (24)	106/106	45-78 (59)	21-37 (28)	127/127	45-77 (57)	18-38 (25)**
KL 1	35/40	46- 77 (64)	20-34 (27)	33/48	37-81 (61)	19-37 (26)	62/62	45-78 (62)	22-37 (29)	85/85	45-79 (61)	18-41 (28)
KL 2	10/16	56-70 (65)	24-37 (31)	13/15	47-78 (67)	22-34 (28)*	187/187	45-79 (61)	20-41 (30)	379/379	45-79 (61)	19-47 (30)
KL 3/4	9/13	61-72 (68)	23-34 (29)	10/11	58-78 (67)	23-34 (28)	225/225	45-79 (62)	22-42 (30)	265/265	45-79 (64)	18-49 (31)*

BMI = body mass index; CCBR = Center for Clinical and Basic Research; KL = Kellgren and Lawrence; OAI = Osteoarthritis Initiative.
[a]Subject that has different KL between the knees was added to the both KL groups that the knees belong. Asterisks indicate the significance of difference between the genders for age and BMI for that specific KL index. The significance of difference between genders was given at the female demographic.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

in patellofemoral joint biomechanics were explored[10] and concluded that women had less contact areas and greater contact pressures. In Atheshian *et al.*,[11] the gender differences in congruity for thumb carpometacarpal (CMC) were explored and concluded that male joints were more congruent than female joints; and the lower congruity may be a risk factor for development of CMC joint OA in females more frequently.

Magnetic resonance imaging (MRI) has become a major imaging modality in OA research[12,13] since it allows noninvasive visualization of all the tissues present in the joint, especially the cartilage.[14,15] In the literature,[16-18] knee cartilage volume and bone mineral density differences from MRI were validated and it was observed that men have significantly more cartilage than women after adjustment for confounding factors such as age and body mass index (BMI). Women had smaller joint surfaces and thinner cartilage as compared with men after adjusting for height and weight;[19] however, there were no differences in tibial and patellar surface pressures. With gender differences in morphometric and biological measurements from radiographs, MRI, and biochemical markers; there is a need for research characterizing the gender differences in articular measurements and mechanics. Such differences may have implications for the development of gender based treatment options.[20,21]

Here we investigated the gender differences in CA and congruity index (CI) in the MTF joint stratified according to KL index using the data sets from the Center for Clinical and Basic Research (CCBR), and the Osteoarthritis Initiative (OAI). We hypothesized that male joints show lower normalized CA values and higher CI values compared with females at all stages of the KL index, indicating a significant role of gender in altering the biomechanical properties in the MTF joint.

Methods

Study Population

The CCBR study population consisted of 82 male and 77 female subjects recruited from the greater Copenhagen area. The OAI subjects consisted of 580 male and 856 female subjects selected from publicly available OAI dataset at baseline (https://oai.epi-ucsf.org). The population consisted of individuals with no radiographic OA as well as individuals with varying degrees of radiographic OA. Refer to **Table 1** for detailed characterization of the study population. Subjects with a history of previous knee injury or trauma or contradiction to image acquisition were excluded from both the studies. More details on the CCBR study population are also described elsewhere.[22]

Image Acquisition

The CCBR study had 318 knees. Five out of 318 knees were excluded due to insufficient image quality in either MRI or radiograph. Another 25 knees used for training of classifier for automatic cartilage segmentation were excluded from the evaluation. The radiographs of both the knees for each subject were taken using an X-ray scanner in anterior-posterior load bearing position. The film distance and tube angulation for the scanner were 1.0 m and 10°, respectively. The radiographs were used to grade the severity of OA from the KL index and also to measure the joint space width (JSW) by an experienced radiologist (P. C. Pettersen, who has 5 years of experience in semiquantitative grading).[23] Furthermore, the MRI scans for all the subjects were acquired in a non-load-bearing supine position using a sagittal Turbo 3D T1 sequence at 0.18 T from an Esaote C-span scanner dedicated to scan the lower extremities. The parameters of the scanner were 40° flip angle, 50 ms repetition time (RT), and 16 ms echo time (ET) with scan time of approximately 10 minutes. The in-plane resolution was 0.7 mm × 0.7 mm with slice thickness ranging from 0.7 mm to 0.9 mm.

The OAI study consisted of 1436 scans. The data set was from 0.E.1. We selected this subcohort for this study since the MTF cartilage segmentations were available only for it from Dam *et.al.*[13] The KL index was graded using the radiograph acquired in anterior-posterior loadbearing position. The MRI images of OAI sub-cohort were acquired using

3.0 T 3D dual-echo steady-state water excitation Siemens Trio scanner with 25° flip angle, 16 ms RT, 4.7 ms ET, in-plane resolution of 0.36 mm × 0.36 mm, slice thickness of 0.7 mm, and scanning time of approximately 10 minutes.

The CCBR study protocol was approved by the local ethical committee and was carried out in accordance with the principles of the Helsinki Declaration II and European Guidelines for good Clinical Practice. Also, the OAI study protocol was approved by local ethics committees at all the participating sites. All participants signed and approved the written information consent prior to the study.

The MTF cartilage compartments of the scans from both studies were segmented fully automatically using a voxel classification in a supervised learning approach described elsewhere.[13,24]

Contact Area Quantification

The CA in a knee was defined as the region where the tibial superior surface and the femoral inferior surface were less than a voxel width apart. We refer to the CA as the cartilage-cartilage contact area (**Fig. 1**) but not the cartilage-meniscus contact area. First, the tibial surface that was less than a voxel width from femoral surface was estimated and called *TibProx*. Second, the femoral surface that was less than a voxel width from the tibial surface was computed and denoted as *FemProx*. The areas of *TibProx* and *FemProx* were quantified by converting the estimated region into a triangulated surface. The *CA* was defined as the mean of the area of *TibProx* and the area of *FemProx* since the cartilage surfaces were not symmetric. Then to account for differences in knee sizes, the *CA* values were normalized. For OAI scans, The *CA* values were normalized using tibial bone surface area (tAB) (CA = CA/tAB × 100). Since we do not have tAB measures for CCBR scans, we normalized the *CA* values for these scans by dividing with square of the corresponding tibial bone width (following the methodology from Dam *et al*.[25]). Below, CA refers to normalized CA.

Congruity Index Quantification

Using the estimated tibial and femoral proximity surfaces, the point-by-point CI in the MTF joint was quantified by assessing and combining the first- and second-order general surface features in *TibProx* and *FemProx* (**Fig. 1**). We proposed that the MTF joint was locally congruent if the distance between the local surface normal vectors (first-order features) scaled by local surface normal curvatures (second-order features) was small. Since the number of points in *TibProx* most likely was not equal to the number of points in *FemProx*, we computed the CI from *TibProx* to *FemProx* and vice versa. The methods to compute the CA and point-by-point CI were detailed and validated previously.[26]

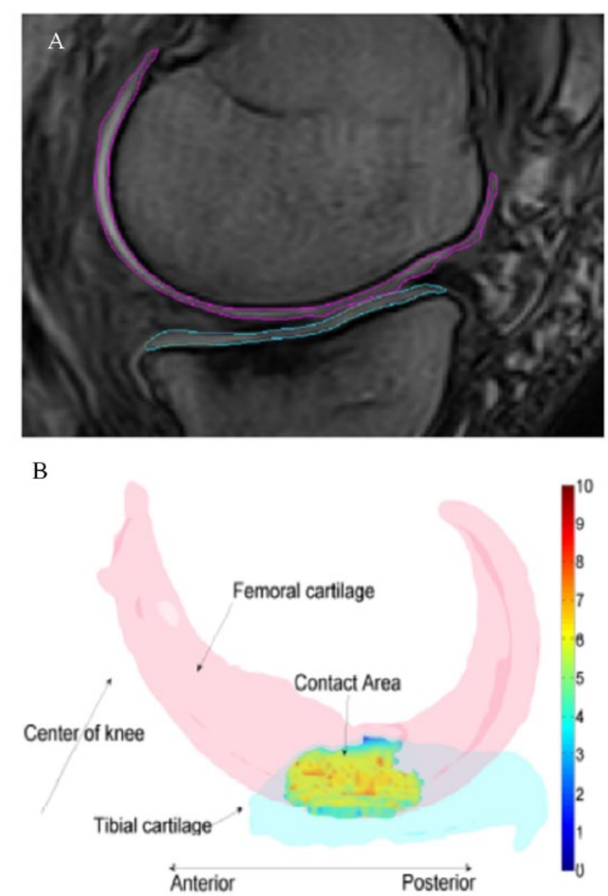

Figure 1. (**A**) Illustration of medial tibial and femoral cartilage tracings on a slice of MRI. (**B**) Illustration of location of contact region where the CI was quantified in the medial tibiofemoral joint. Color bar indicates values of CI.
MRI= magnetic resonance imaging; CI= congruity index.

Statistical Methods

The computations and statistics were performed in MATLAB (Mathworks Inc). Whether the measures on any 2 groups were different was evaluated using the independent-sample *t* tests. When the data was normally distributed, the Student *t* test was used otherwise we used Mann-Whitney *U* tests. The differences between groups were corrected for age and BMI, whenever appropriate. A *P* value of less than 0.05 was used to establish statistical significance.

Since the study contained data from both knees, we explicitly modeled the interknee correlations within subjects for CA and CI values using generalized estimation equations (GEE). The GEEQBOX package implemented in MATLAB was used to compute the GEE *P* values (P_{GEE}).[27]

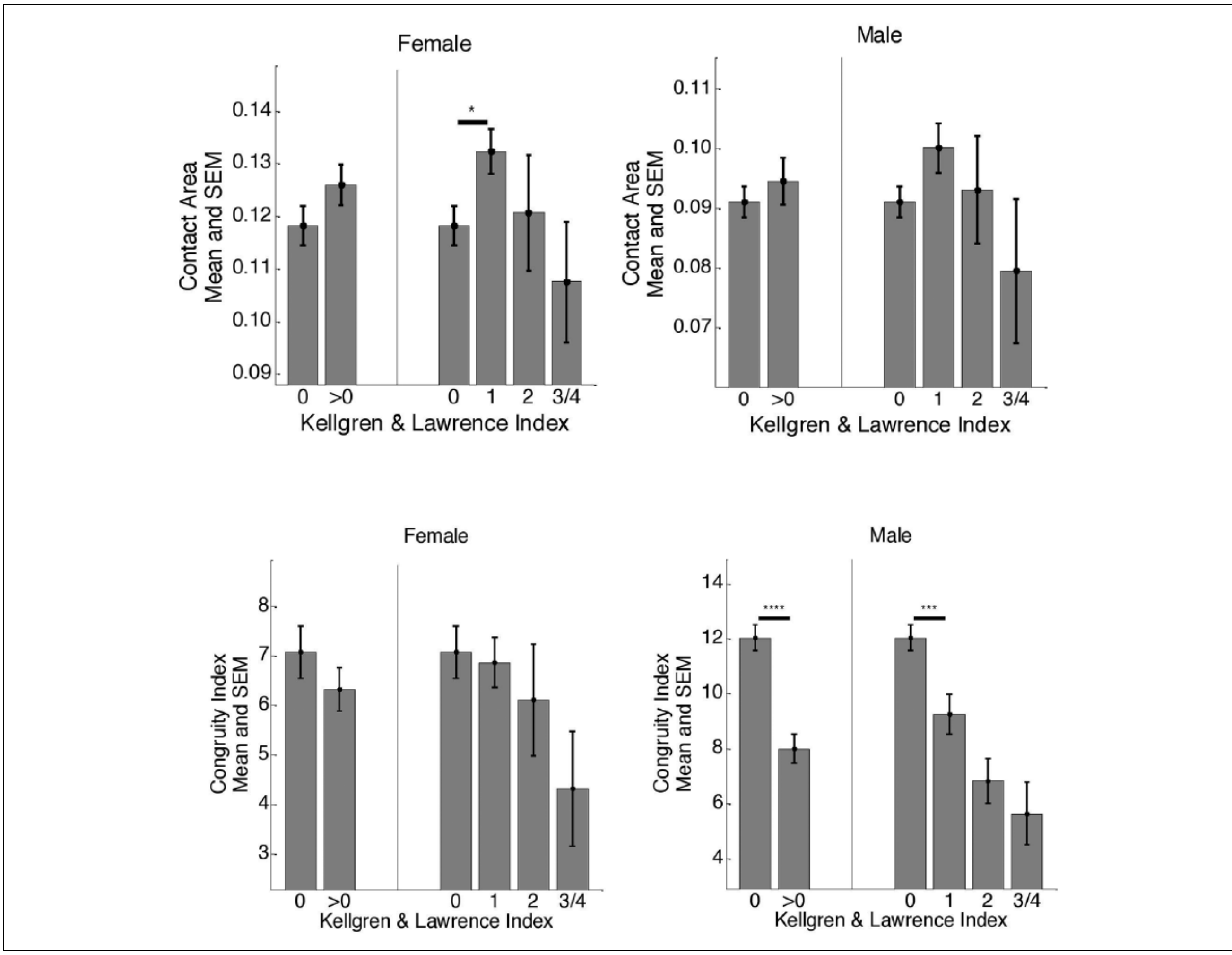

Figure 2. Cross-sectional separation across different KL grades for male and female subjects based on CA and CI for CCBR scans. The asterisks indicate the statistical significance computed from appropriate *t* test. *P <0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. KL= Kellgren and Lawrence; CA= contact area; CI= congruity index; CCBR= Center for Clinical and Basic Research; SEM= standard error mean.

Results

The age and BMI of the populations were evenly distributed for both the data sets (**Table 1**). We arranged the populations according to gender and further stratified with respect to KL index.

Gender Differences in CA

Stratification of CA according to KL index for the male and female subjects is shown in **Figures 2** and **3**. For the CCBR scans, the CA values for male subjects were not significantly different with respect to KL index whereas for female joints, the CA values were significantly different between no radiographic OA (KL 0) and presence of radiographic OA (KL 1) subjects ($P < 0.05$). However, for OAI scans, significant increases in CA values were observed at mild/moderate radiographic OA (KL 0 to KL2/KL3) in both genders. In general, for both studies, the CA values of the female subjects were larger than the male subjects from no radiographic OA to all stages of radiographic OA (**Table 2**). Also, radiographic OA knees demonstrated higher CA values for both genders, which was also consistent across the 2 studies.

For both studies, the gender differences were retained at all stages of KL after intrasubject adjustment using GEE (e.g., for KL 0 in CCBR, $P_{GEE} = 4 \times e^{-9}$).

Gender Differences in CI

For both male and female, similar trends were observed for cross-sectional separation of CI according to KL index (**Figs. 2** and **3**) across both studies. In the CCBR study, the CIs for male joints were significantly different between KL 0 and KL 1 ($P <$ 0.0001). In both studies, we also found that male joints with no radiographic OA were more congruent than male joints with definite radiographic OA ($P < 0.0001$). The CIs of the female

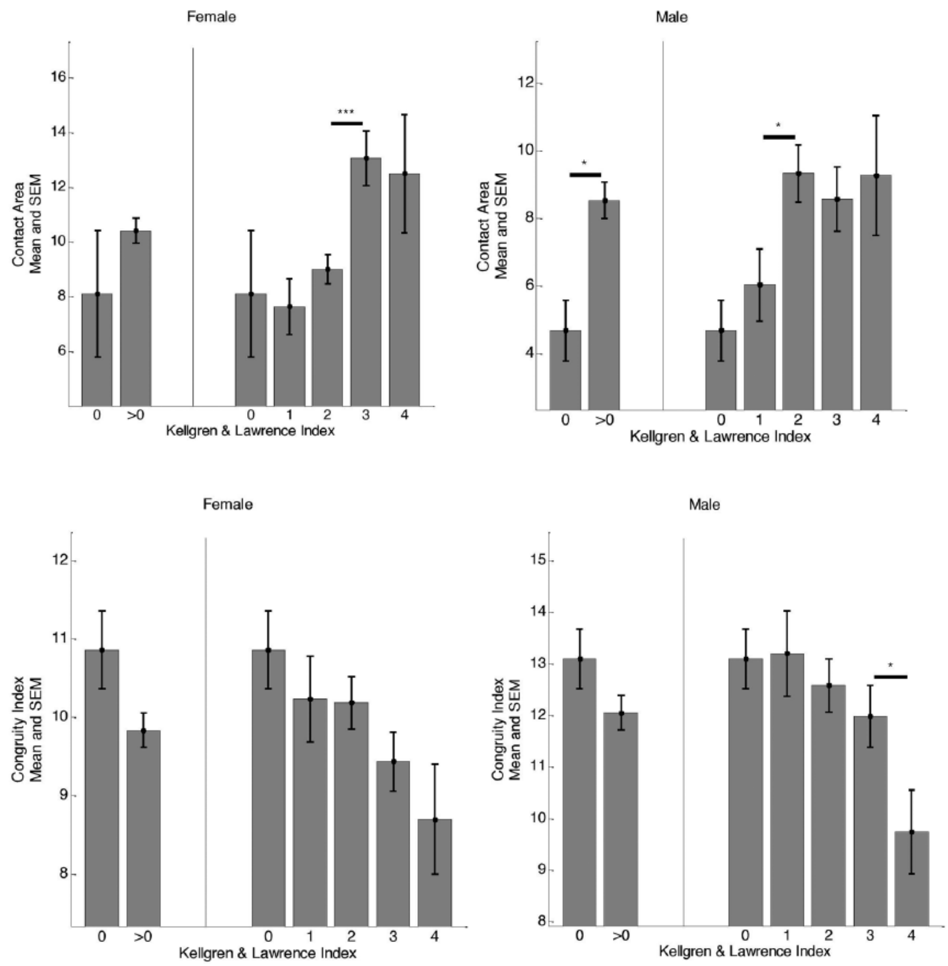

Figure 3. Cross-sectional separation across different KL grades for male and female subjects based on CA and CI for OAI scans. The asterisks indicate the statistical significance computed from appropriate *t* test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.
KL= Kellgren and Lawrence; CA= contact area; CI= congruity index; OAI= Osteoarthritis Initiative; SEM= standard error mean.

joints were generally lower, but not different between no radiographic OA and definite OA ($P = 0.40$). See **Figures 2** and **3** for comparison of mean CI values for male and female subjects with respect to KL index. The male joints were more congruent than female joints at no radiographic OA and at possible presence of radiographic OA ($P < 0.01$) for both OAI and CCBR populations. However, at moderate to advanced stages of radiographic OA, the differences were significant only in the OAI population ($P < 0.0001$, see **Table 3** for more details).

Also, for both studies, the gender differences in CI were retained at all stages of KL after intrasubject adjustment using GEE (e.g., for KL 0 for CCBR, $P_{\text{GEE}} = 4 \times e^{-6}$).

Discussion

We investigated the gender difference in MTF joint CA and CI by focusing on their ability to separate subjects with no radiographic OA from definite radiographic OA. These results were from 2 independent cohorts and supported that there may be gender differences in the onset of radiographic OA from a biomechanical point of view. For proper biomechanics of synovial joints, there are different tissues (cartilage, meniscus) involved in transmitting the load effectively during all daily activities. The normalized CA values representing the cartilage-cartilage CA were higher in radiographic OA compared with no radiographic OA. This trend is consistent between genders and across the 2 studies. In the CCBR scans, there was an increase in cartilage-cartilage CA from no radiographic OA to early radiographic OA in both male and female joints suggesting that the meniscus likely plays a role in the onset of biomechanical instability in the joint. However, for the OAI cohort, this trend was observed between no radiographic OA and mild/moderate radiographic OA. Therefore, we speculate that these differences may be due to usage of different normalization procedures in scaling out the knee size differences. The higher

Table 2. CA Values of Male and Female Subjects for Both Data Sets.[a]

	CCBR		OAI	
	CA Male	CA Female	CA Male	CA Female
No radiographic OA (KL 0)	0.091 ± 0.02	0.118 ± 0.03****	4.7 ± 5.0	8.1 ± 11.6*
Possible radiographic OA (KL 1)	0.101 ± 0.03	0.132 ± 0.03****	6.1 ± 7.5	7.6 ± 7.1*
Definite radiographic OA (KL 2 and above)	0.087 ± 0.04	0.114 ± 0.04**	9.0 ± 9.8	10.8 ± 10.4***

CA = contact area; CCBR = Center for Clinical and Basic Research; KL = Kellgren and Lawrence; OA = osteoarthritis; OAI = Osteoarthritis Initiative.
[a]The significance of difference between genders computed as P value from a statistical test is given in terms of asterisks.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

Table 3. CI Values of Male and Female Subjects from Both Data Sets.[a]

	CCBR		OAI	
	CI Male	CI Female	CI Male	CI Female
No radiographic OA (KL 0)	12.0 ± 4.1	7.1 ± 4.3****	13.1 ± 5.3	10.9 ± 5.0**
Possible radiographic OA (KL 1)	9.3 ± 4.6	6.9 ± 3.5***	13.2 ± 6.3	10.2 ± 4.5**
Definite radiographic OA (KL 2 and above)	6.3 ± 3.7	5.3 ± 3.9	11.8 ± 6.1	9.8 ± 5.1****

CCBR = Center for Clinical and Basic Research; CI = congruity index; KL = Kellgren and Lawrence; OA = osteoarthritis; OAI = Osteoarthritis Initiative.
[a]The significance of difference between genders computed as P value from a t test is given in terms of asterisks.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

CA values of the female subjects after adjusting for knee sizes suggests that more cartilage-cartilage CA may be involved in load transmission for them compared with male joints at all stages of radiographic OA. The lower CA values at advanced stages of radiographic OA for both genders and even across the studies may be due to loss of cartilage.

Similar to CA, significant differences in CI values were evident between the genders from both the studies at all stages of KL index. Malalignment (Q-angle) may be one of the determining factors responsible for variation of local congruency in the joint. However, it was also hypothesized that local incongruity plays a role in determining the alignment.[28] Male joints demonstrated higher local congruence compared with female joints at no radiographic OA and definite OA indicating higher risk of females to develop radiographic OA. The differences between genders were not significant for CCBR scans at moderate to advanced stages of radiographic OA; we feel that it may be due to low sample size of the scans. Therefore, since male joints with no radiographic OA were more locally congruent, this may be responsible for higher malalignment in females compared with males. In this study, we computed the CI values only in the cartilage-cartilage CA, and by including the cartilage-meniscus region in the analysis, we would possibly be able to draw more concrete conclusions.

The quantification of CA and CI values was based on fully automatic segmentations from 2 different data sets. This supports that the observed gender differences were likely due to actual differences in CA and CI values and not due to algorithmic or acquisition artifacts. Female MTF joint CI values were significantly lower than the male joint CI values irrespective of source of data. The CI values were also comparable between the datasets at no radiographic OA stage and early stages of radiographic OA. The CA values of the female joints were greater than male joints after normalization. On the other hand, interestingly from CCBR study, we found that females who were older and have higher BMI have more CA. Young male and female joints were also more congruent than older individuals. However, these differences were corrected while doing the KL index comparison between the genders.

There were some limitations in this study. The quantifications of CA and CI values heavily depend on the knee angle, and with the available data, we were not able to validate the gender differences on other flexion angles. However, for consistency across knees with varying degrees of radiographic OA, we feel that the non-loadbearing supine position was a good posture. Therefore, we were also not able to optimize the knee angle at which the maximum gender differences in CA and CI could be extracted. Also, we did not include the cartilage-meniscus contact region in the analysis, even if this is a vital region that could be included along with cartilage-cartilage contact region. Even though we may be able to extract this from the OAI scans, we want to leave it to a future study. Moreover, we could not validate our methods with an *ex vivo* model, which is a further limitation.

In conclusion, we conducted a validation study to explore the gender differences in the MTF joint CA and CI values from both low- and high-field MRI. Similar results were found between the datasets with significant gender differences found in CA and CI values at all stages of radiographic OA. The existing differences may be helpful to understand the gender dissimilarities in subjects with no radiographic OA and those with definite radiographic OA. Further, the results may provide implications for making gender specific interventions or treatment strategies to treat radiographic OA.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Sudhakar Tummala has received a PhD scholarship partly funded by Biomediq A/S. Dieuwke Schiphof was a PhD student at Erasmus MC, Rotterdam. Inger Byrjalsen is an employee of Nordic Bioscience A/S. Erik Dam is an employee and shareholder of Biomediq A/S. The intellectual and commercial property rights to the investigated MRI markers belong to Biomediq A/S.

Ethical Approval

The CCBR study protocol was approved by the local ethical committee and was carried out in accordance with the principles of the Helsinki Declaration II and European Guidelines for good Clinical Practice. Also, the OAI study protocol was approved by local ethics committees at all the participating sites.

Informed Consent

All participants signed and approved the written information consent prior to the study.

Trial Registration

Not applicable.

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