



Tibial tuberosity to trochlear groove distance and its association with patellofemoral osteoarthritis-related structural damage worsening: data from the osteoarthritis initiative

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Abstract

Objectives To determine whether the tibial tuberosity-to-trochlear groove (TT-TG) distance is associated with concurrent patellofemoral joint osteoarthritis (OA)-related structural damage and its worsening on 24-month follow-up magnetic resonance imaging (MRI) in participants in the Osteoarthritis Initiative (OAI).

Methods Six hundred subjects (one index knee per participant) were assessed. To evaluate patellofemoral OA-related structural damage, baseline and 24-month semiquantitative MRI Osteoarthritis Knee Score (MOAKS) variables for cartilage defects, bone marrow lesions (BMLs), osteophytes, effusion, and synovitis were extracted from available readings. The TT-TG distance was measured in all subjects using baseline MRIs by two musculoskeletal radiologists. The associations between baseline TT-TG distance and concurrent baseline MOAKS variables and their worsening in follow-up MRI were investigated using regression analysis adjusted for variables associated with tibiofemoral and patellofemoral OA.

Results At baseline, increased TT-TG distance was associated with concurrent lateral patellar and trochlear cartilage damages, BML, osteophytes, and knee joint effusion [cross-sectional evaluations; overall odds ratio 95% confidence interval (OR 95% CI): 1.098 (1.045–1.154), $p < 0.001$]. In the longitudinal analysis, increased TT-TG distance was significantly related to lateral patellar and trochlear cartilage, BML, and joint effusion worsening (overall OR 95% CI: 1.111 (1.056–1.170), $p < 0.001$).

Conclusions TT-TG distance was associated with simultaneous lateral patellofemoral OA-related structural damage and its worsening over 24 months. Abnormally lateralized tibial tuberosity may be considered as a risk factor for future patellofemoral OA worsening.

Key Points

- Excessive TT-TG distance on MRI is an indicator/predictor of lateral-patellofemoral-OA.
- TT-TG is associated with simultaneous lateral-patellofemoral-OA (6–17% chance-increase for each millimeter increase).
- TT-TG is associated with longitudinal (24-months) lateral-patellofemoral-OA (5–15% chance-increase for each millimeter).

Keywords Osteoarthritis · Knee · Patella · Magnetic resonance imaging

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Abbreviations

2D	Two-dimensional
ACL	Anterior cruciate ligament
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
BML	Bone marrow lesion
CI	Confidence interval
CT	Computed tomography
DESS	Dual echo at steady state
FNIH	Foundation for the National Institute of Health
IW	Intermediate weighted
JSL	Joint space loss
KL	Kellgren-Lawrence
MOAKS	Magnetic resonance imaging osteoarthritis knee score
MPR	Multiplanar reconstruction
MRI	Magnetic resonance imaging
OA	Osteoarthritis
OAI	Osteoarthritis initiative
OR	Odds ratio
PASE	Physical activity scale for elderly
ROC	Receiver-operating characteristic
SD	Standard deviation
TSE	Turbo spin echo
TTM	Tibial tuberosity medialization (TTM)
TT-TG	Tibial tuberosity trochlear groove
WE	Water excitation
WOMAC	Western Ontario & McMaster Universities osteoarthritis index

Introduction

Patellofemoral osteoarthritis (OA) is a common debilitating disease with a prevalence of 28%–52% in the adult population based on knee radiography [1]. Compared with tibiofemoral OA, fewer data are available in the literature regarding the risk factors for patellofemoral OA development and progression. Previous studies have suggested that abnormal patellofemoral morphology and associated patellofemoral maltracking may lead to the alteration in the joint contact area and pressure distribution as well as the mechanical load [2–5]. Such malalignment may impose increasing contact pressure on the lateral patellofemoral articular surface during flexion-extension motion and therefore may predispose subjects to the development and possible worsening of patellofemoral OA [2, 3]. It has also been previously suggested that simultaneous patellofemoral OA is seen in association with underlying patellofemoral malalignment such as abnormal lateralization of the tibial tuberosity [2–7].

The position of the tibial tuberosity, as an indicator of patellofemoral alignment, can contribute to the lateral force vector acting on the patella [8, 9]. The tibial tuberosity-to-trochlear groove (TT-TG) distance, as a widely used metric for determination of tibial tuberosity lateralization, measures the distance between the central midpoint of the tibial tuberosity and the deepest point of the trochlea using axial magnetic resonance imaging (MRI) or computed tomography (CT) images [10, 11]. It has been suggested that an increased TT-TG distance increases the lateral patella contact pressure and predisposes the patellofemoral joint to cartilage damage [7, 12]. Although this assumption has been primarily investigated in a limited number of cross-sectional studies, the results were not consistent [3, 4, 12, 13]. Additionally, these results only included cross-sectional analysis, and the association between the TT-TG distance and longitudinal patellofemoral OA worsening has not been previously investigated. Therefore, the clinical importance of TT-TG distance measurement as a patellofemoral OA predictor remains to be determined.

Besides the lateralization of the tibial tuberosity, there are several other patellofemoral morphological abnormalities including patella alta, trochlear dysplasia, and patellar tilt, many of which have already been shown to be associated with patellofemoral OA [5, 13, 14]. An abnormally lateralized tibial tuberosity (excessive TT-TG distance) can be corrected by surgical methods including tibial tuberosity medialization (TTM), which is currently used in the setting of patellar instability [15–18]. Additionally, surgical correction of an abnormally lateralized tibial tuberosity along with cartilage repair procedures resulted in improvements in symptoms and function in subjects with isolated patellofemoral OA [19, 20].

Thus, we aimed to determine whether the TT-TG distance is associated with concurrent patellofemoral joint OA-related structural damage and its worsening on 24-month follow-up MRI in participants in the Osteoarthritis Initiative (OAI).

Materials and methods

Study population

We used data and images from the open access data sets of the OAI cohort, which is an ongoing multicenter study of 4,796 subjects with or at risk of knee OA, who were followed for OA outcomes (for additional details refer to <https://oai.epi-ucsf.org>). Our study used data of the OA biomarkers consortium Foundation for the National Institute of Health (FNIH) project, which is a nested case-control study within the OAI and constitutes a group of 600 participants.

The FNIH study was designed for assessing the role of MRI-based measures over 24 months as biomarkers of tibiofemoral OA structural and symptom progression during

the 24–48 months. Eligible participants had at least one knee with tibiofemoral Kellgren-Lawrence (KL) grade of 1 (12.5%), 2 (51%), or 3 (36.5%) at baseline and had an available knee radiograph and 3-T MRI at baseline and 24-month follow-up. Subjects with total knee/hip replacement or metal implants were excluded. Knees with advanced radiographic OA or severe symptoms at baseline were also excluded (minimum medial joint space width < 1.0 mm and/or Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index pain score of > 91). Index knees were selected based on radiographic and pain progression outcomes in each subject (for details: <https://oai.epi-ucsf.org/datarelease/docs/FNIH>).

This available database also contains robust patellofemoral structural damage determination using the semiquantitative MRI-based MOAKS (MRI Osteoarthritis Knee Score) method. With proper adjustment of statistical models for radiographic tibiofemoral OA status at baseline and follow-up, this available data set provides an opportunity to evaluate the potential risk factors of patellofemoral OA. All subjects (one index knee per participant) from the FNIH project were included in this study. Enrolled subjects underwent MRI at baseline and 24 months. Relevant existing data, MRIs, and MRI-based measurements were extracted and analyzed. A schematic diagram of our study is presented in Fig. 1.

MRI protocol

Details of the full OAI pulse sequence protocol and parameters have been previously reported ([supplementary text](#)) [21, 22].

Semiquantitative assessment of patellofemoral joint

To evaluate patellofemoral joint structural damages, available measurements of the validated semiquantitative MOAKS method were used ([supplementary text](#)) [21]. Cartilage damage, BML, and osteophyte scores were evaluated for both the medial and lateral sides of the patellar and trochlear subregions.

Cartilage lesions were scored on a 4-point scale based on the percentage of surface and full-thickness of patellar/trochlear cartilage affected by the injury (0: none, 1: < 10% of region is involved, 2: 10–75%, 3: > 75%). BML size scores ranged from 0 to 3 (0: none, 1: < 33% is involved, 2: 33–66%, 3–4: > 66%). BML numbers were also counted in each subregion. The size of osteophytes was scored using a 4-point scale (0 = none, 1 = small, 2 = medium, 3 = large). Synovitis (defined as the signal abnormalities in Hoffa's fat pad) and effusion were evaluated using a 4-point scale based on the grade of Hoffa-synovitis and the size of effusion, without contrast enhancement [23]. The presence of baseline anterior cruciate ligament (ACL) tear was also assessed on a 3-point scale (0 = none, 1 = partial tear, and 2 = complete tear).

The reliability of the MOAKS method has been previously demonstrated, with the intra- and interobserver reliability of near perfect (0.71–1.0) and moderate-strong (0.64–0.93) for all patellar measures, respectively (using the kappa method) [21].

TT-TG distance measurement

Two fellowship-trained musculoskeletal radiologists (CS and MH) with three years of clinical experience in interpreting musculoskeletal MRI assessed the baseline TT-TG distance in all 600 knees in consensus. TT-TG distance (mm) was calculated on axial MRI using a previously described method [13; 14]. In brief, the TT-TG was measured as the distance between the midpoint of the patellar tendon attachment site to the tibial tuberosity and the mid-sulcal plane at the deepest point of the trochlea (Fig. 2). The reliability of the MRI-derived TT-TG distance has been previously demonstrated, with the very good intra- and interobserver reliability in measurements [24].

Statistical analysis

Baseline characteristics and factors related to patellofemoral/tibiofemoral OA including the gender, age, body mass index (BMI), WOMAC pain score, baseline tibiofemoral KL grade, knee alignment (varus/valgus/normal; based on physical examinations), ACL injury (using MOAKS), history of knee injury, kneeling activity, PASE (Physical Activity Scale for Elderly) score, and muscle strength score were evaluated [25, 26]. All further analyses were adjusted for the possible confounding effect of these variables. In this regard, all analyses were adjusted for baseline tibiofemoral KL grade, and all longitudinal analyses were also adjusted for the presence of an interval radiographic tibiofemoral joint space width loss > 0.7 mm in the 48-month follow-up (joint space loss or JSL progression) to account for the primary outcome determination in the FNIH study design for tibiofemoral radiographic progression.

In the cross-sectional part, the association between baseline TT-TG distance and baseline MOAKS variables and overall baseline patellofemoral OA disease (presence vs. absence) was assessed using the logistic regression model. Presence of patellofemoral OA was defined as subjects who had both patellar/trochlear cartilage damage and patellar/trochlear osteophytes using MOAKS [1, 27].

In the longitudinal part, we investigated whether the TT-TG distance was associated with future worsening of patellofemoral MOAKS variables using logistic regression. In this regard, subjects were dichotomized into worsening versus non-worsening groups. Worsening of MOAKS variables was defined based on the previously published method ([Supplementary text](#)) [28]. The overall relationship between TT-TG distance and worsening of patellofemoral OA was also

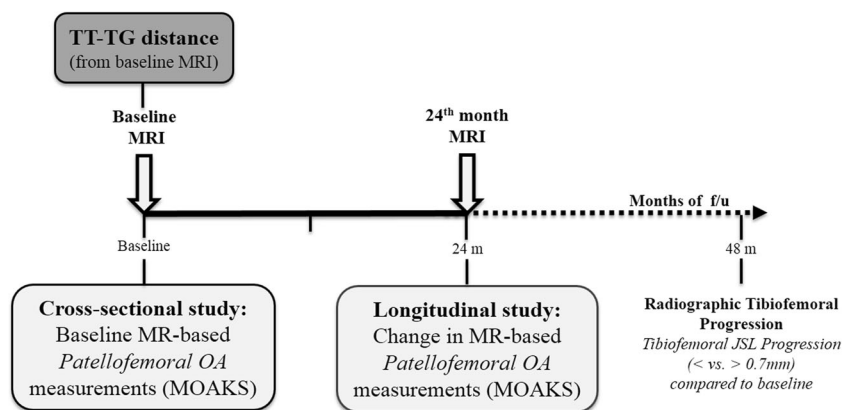


Fig. 1 Timeline of the study. *Baseline*: tibial tuberosity-to-trochlear groove (TT-TG) distance measurement; baseline MRI assessments for patellofemoral osteoarthritis (OA) including MRI Osteoarthritis Knee Score (MOAKS). *24 months*: Follow-up MRI assessments of patellofemoral OA. *48 months*: Primary FNIH outcome for tibiofemoral

OA progression. Follow-up radiographic assessment of tibiofemoral joint space loss (JSL). All analyses were adjusted for 48-month JSL progression. JSL: joint space loss; f/u: follow-up; MRI: magnetic resonance imaging

explored. Subjects with any worsening change in patellar or trochlear cartilage, BML, or osteophyte MOAKS measurements were considered as worsening. Besides the regression analysis, the TT-TG distance measure was also compared between the study groups using the t-test or analysis of variance (ANOVA) method in each part of the analysis.

The areas under the receiver-operating characteristic (ROC) curve (AUCs) were evaluated to investigate predictive value of TT-TG distance for patellofemoral OA, and the optimal cutoff values of TT-TG distance with the highest Youden's Index and the best predictive ability were calculated ([supplementary results](#)).

A two-tailed p value $< 5\%$ was considered significant. Analyses were performed using SPSS (v.24, Chicago, IL, USA), STATA (v.14, College Station, TX, USA), and the R platform (v.3.2.5).

Results

Table 1 demonstrates the baseline characteristics of the study population. Six hundred participants (female: 58.8%; age: 61.5 ± 8.9 years; BMI: 30.7 ± 4.78) were included.

Table 2 shows the results of the cross-sectional study; regression analyses showed significant associations between baseline TT-TG distance and concurrent patellar and trochlear lateral surface [odds ratio (OR) 95% confidence interval (CI): 1.127(1.078–1.178)] [OR 95% CI: 1.132 (1.079–1.186)], lateral full-thickness [OR 95% CI: 1.179 (1.117–1.245)] [OR 95% CI: 1.156 (1.094–1.220)] cartilage damage, and lateral BML size [OR 95% CI: 1.158 (1.104–1.215)] [OR 95% CI: 1.150 (1.093–1.209)], and number [OR 95% CI: 1.132 (1.079–1.186)] [OR 95% CI: 1.129 (1.074–1.186)] scores, respectively. There were also significant associations between the TT-TG distance and baseline patellar and trochlear medial [OR 95% CI: 1.053 (1.008–1.101)] [OR 95% CI: 1.087(1.040–1.135)] and lateral [OR 95% CI: 1.119 (1.069–1.169)] [OR 95% CI: 1.151 (1.099–1.206)] osteophyte scores as well as the baseline knee effusion [OR 95% CI: 1.066 (1.022–1.112)]. On the other hand, there was a significant inverse association between the TT-TG distance and medial trochlear score [OR 95% CI: 0.941 (0.890–0.995)].

Results of the longitudinal study (Table 3) demonstrated a significant association between the baseline TT-TG distance and subsequent worsening of the lateral patellar cartilage [OR 95% CI: 1.078 (1.001–1.160)], medial and lateral trochlear

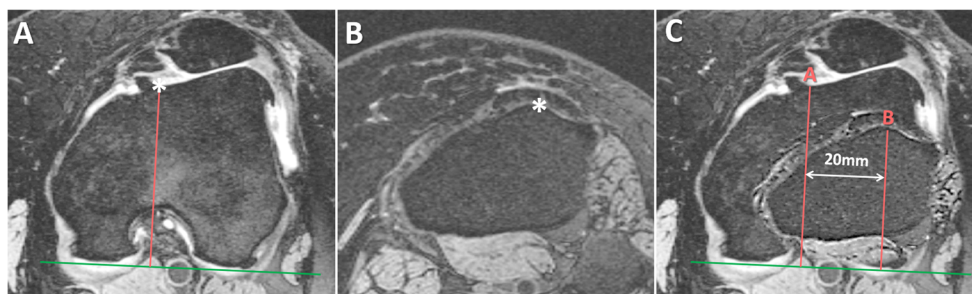


Fig. 2 TT-TG distance, the measurement was defined as the distance between the mid sulcal plane (A) and the mid tuberosity plane (B). Both lines were drawn perpendicular to baseline, joining the most

posterior point of the two femoral condyles (C). Measurement is demonstrated on axial multiplanar reformations (MPRs) of the 3D dual-echo steady-state (DESS) MRI sequence

Table 1 Baseline characteristics of study subjects

Baseline	Mean ± SD or number (%)
Number	600
Gender (female)	353 (58.8%)
Age (years)	61.5 ± 8.9
BMI (kg/m ²)	30.7 ± 4.78
WOMAC pain score (range: 0-16)	2.4 ± 3.12
KL grade (range: 0-4)	
1	75 (12.5%)
2	306 (51%)
3	219 (36.5%)
Knee alignment (based on physical examination)	
Normal	165 (27.5%)
Varus	187 (31.2%)
Valgus	244 (40.7%)
ACL injury (positive MOAKS)	38 (6.4%)
Knee injury (positive)	213 (35.5%)
Kneeling (30 min per week)	0.46 ± 0.95
PASE score (range: 2-445)	164.4 ± 82.7
Muscle strength score (hours per week)	0.90 ± 1.46
MOAKS patellar scores	
Cartilage morphology scores (0/1/2/3)	
Medial	
Surface score	168 (28%)/63 (10.5%)/352 (58.7%)/17 (2.8%)
Thickness score	403 (67.2%)/64 (10.7%)/129 (21.5%)/4 (0.7%)
Lateral	
Surface score	282 (47%)/26 (4.3%)/209 (34.8%)/83 (13.8%)
Thickness score	444 (74%)/27 (4.5%)/101 (16.8%)/28 (4.7%)
BML scores (0/1/2/3-4)	
Medial	
Size score	389 (64.8%)/138 (23%)/60 (10%)/13 (2.2%)
Number score	389 (64.8%)/155 (25.8%)/54 (9%)/2 (0.3%)
Lateral	
Size score	384 (64%)/108 (18%)/84 (14%)/24 (4%)
Number score	384 (64%)/162 (27%)/41 (6.8%)/13 (2.2%)
Osteophyte score (0/1/2/3)	
Medial	252 (42%)/279 (46.5%)/68 (11.3%)/1 (0.2%)
Lateral	285 (47.5%)/ 242 (40.3%)/ 58 (9.7%)/ 15 (2.5%)
MOAKS trochlear scores	
Cartilage morphology scores (0/1/2/3)	
Medial	
Surface score	271 (45.2%)/68 (11.3%)/254 (42.3%)/7 (1.2%)
Thickness score	507 (84.5%)/29 (4.8%)/63 (10.5%)/1 (0.2%)
Lateral	
Surface score	374 (62.3%)/26 (4.3%)/172 (28.7%)/28 (4.7%)
Thickness score	454 (75.7%)/24 (4%)/115 (19.2%)/7 (1.2%)
BML scores (0/1/2/3-4)	
Medial	
Size score	441 (73.5%)/137 (22.8%)/15 (2.5%)/7 (1.2%)
Number score	445 (74.2%)/138 (23%)/14 (2.3%)/3 (0.5%)
Lateral	

Table 1 (continued)

Baseline	Mean ± SD or number (%)
Size score	426 (71%)/74 (12.3%)/75 (12.5%)/25 (4.2%)
Number score	428 (71.3%)/131 (21.8%)/30 (5%)/11 (1.8%)
Osteophyte score (0/1/2/3)	
Medial	262 (43.7%)/254 (42.3%)/72 (12%)/12 (2%)
Lateral	346 (57.7%)/155 (25.8%)/76 (12.7%)/23 (3.8%)

Data are presented as mean ± standard deviation or number (percentage %). Missing data were considered in percentage calculations. SD: standard deviation; BMI: body mass index; WOMAC: Western Ontario & McMaster Universities osteoarthritis index; KL: radiographic Kellgren and Lawrence; ACL: anterior cruciate ligament; PASE: Physical Activity Scale for the Elderly; MOAKS: MRI Osteoarthritis Knee Score; BML: bone marrow lesion

cartilage [OR 95% CI: 1.208 (1.093–1.334)] [OR 95% CI: 1.119 (1.033–1.211)], lateral patella and trochlea BML [OR 95% CI: 1.060 (1.001–1.122)] [OR 95% CI: 1.108 (1.041–1.179)], and knee effusion [OR 95% CI: 1.073 (1.018–1.131)] scores. There was a significant inverse association between the TT-TG distance and worsening of the medial trochlear BML score [OR 95% CI: 0.889 (0.817–0.967)].

Table 4 demonstrates the overall association between the presence/worsening of medial and lateral patellofemoral OA-related structural damage and baseline TT-TG distance. Analyses revealed that subjects with greater TT-TG distance had higher odds of concurrent [OR 95% CI: 1.098 (1.045–1.154)] and future worsening [OR 95% CI: 1.111 (1.056–1.170)] of lateral, but not medial, patellofemoral joint damage.

In the sub-analysis (Supplementary Fig. 1), the TT-TG distance demonstrated AUCs of 0.599 (standard error: 0.024; $p < 0.001$) for indicating future lateral patellofemoral OA-related structural damage. Based on the ROC curve analysis, the optimal cutoff values with the highest Youden Index score for the predictive value of TT-TG distance in future lateral patellofemoral OA structural damage worsening was 10.5 mm (sensitivity 55.6 %; specificity 58.4 %). Finally, the association between the TT-TG distance (categorized based on the previous 15-mm and newly suggested 10.5-mm cutoff value) and worsening of lateral patellofemoral OA-related structural damage was evaluated (Supplementary Table 1).

Discussion

In our study, we found that the TT-TG distance could be considered a marker for simultaneous lateral patellofemoral OA-related structural damage and a predictor of future worsening using the baseline and 24-month follow-up MRI data.

In 1978, Goutallier et al. initially defined the TT-TG distance using plain radiographs [29]; this has been primarily used as a metric for abnormal patellofemoral morphology in subjects with patellofemoral instability. After that, CT scans

permitted its measurement in extension, and in 1992 Dejour et al. introduced the CT-derived TT-TG distance as a particular factor in patellar instability [30]. It has been suggested that the CT scan is a gold standard method for TT-TG distance determination [31, 32]. Several studies have evaluated whether TT-TG distances on CT and MRI were identical; based on these reports, it has been demonstrated that both MRI and CT can be used to measure the TT-TG distance with excellent reliability and accuracy [10, 24, 33], although these measurements may not be identical and the TT-TG distance on MRI was up to 3 mm smaller than measurements using CT scans [10, 33, 34]. In addition to TT-TG measurement, MRI can accurately demonstrate early stages and subtle features of patellofemoral OA including soft tissue and osseous structural damages [35].

It has been hypothesized that excessive TT-TG distance can lead to increased lateral patellofemoral joint contact pressure and theoretically predispose subjects to lateral patellofemoral OA and in extreme cases to lateral patellar dislocation [36, 37]. A few cross-sectional studies have investigated the relationship between the TT-TG and patellofemoral OA, but the results were controversial [3, 7, 12]. In the first investigation performed on 85 subjects with patellofemoral OA associated with varus deformity, it was reported that the CT-derived TT-TG distance was associated with the severity of lateral patellofemoral OA [12]. Thakkar et al. also found a significant association between increased TT-TG distance (using MRI) and lateral patellofemoral cartilage abnormality and knee effusion in their cross-sectional study on 32 subjects [7]. A larger cross-sectional MRI examination of 622 subjects revealed no significant difference in TT-TG distance (based on MRI) between normal knees and those with patellofemoral OA [3]. In that study, enrolled subjects were dichotomized into patellofemoral OA-positive and -negative groups (based on cartilage lesions), and detailed analysis on OA-related structural damages such as BML was not performed [3]. It has also been suggested that excessive TT-TG distance was related to knee joint effusion and superolateral Hoffa's fat pad (SHFP) edema, which have been considered prognostic factors for patellofemoral OA [7, 38–40]. Taken together, it

Table 2 Baseline cross-sectional study: association between patellofemoral joint structural damage (patellar and trochlear MOAKS variables: cartilage, BML, osteophyte, synovitis, and effusion) and baseline TT-TG distance

Baseline	Number of subjects in each score	TT-TG distance Mean (SD) for each score	ANOVA F (3,596), P value	OR (95% CI), p value	
				Crude	Adjusted
Cartilage morphology scores (0/1/2/3)					
Surface score					
Medial patella	168/63/352/17	10.8(4.4)/10.2(3.3)/10.3(3.4)/10.8(2.8)	0.853, 0.466	0.975 (0.934 – 1.017), 0.241	0.972 (0.927 – 1.019), 0.239
Medial trochlea	271/68/254/7	10.6(3.5)/9.9(3.7)/10.4(3.9)/10.9(2.3)	0.593, 0.620	0.990 (0.949 – 1.031), 0.618	0.980 (0.938 – 1.024), 0.374
Lateral patella	282/26/209/83	9.8(3.8)/9.1(2.55)/10.75(3.6)/12.2(3.2)	11.15, < 0.001	1.125 (1.077 – 1.176), < 0.001	1.127 (1.078 – 1.178), < 0.001
Lateral trochlea	374/26/172/28	9.8(3.7)/12.0(3.0)/11.1(3.4)/12.6(3.9)	11.01, < 0.001	1.138 (1.087 – 1.192), < 0.001	1.132 (1.079 – 1.186), < 0.001
Thickness score					
Medial patella	403/64/129/4	10.3(3.9)/10.55(3.2)/10.6(3.3)/9.75(1.7)	0.196, 0.899	1.014 (0.969 – 1.061), 0.542	1.026 (0.974 – 1.079), 0.335
Medial trochlea	507/29/63/1	10.4(3.5)/11.1(7.2)/10.0(3.1)/12.0	0.626, 0.598	0.993 (0.935 – 1.054), 0.818	0.998 (0.936 – 1.064), 0.943
Lateral patella	444/27/101/28	9.9(3.7)/11.7(3)/11.5(3.5)/13.3(3.5)	13.21, < 0.001	1.172 (1.112 – 1.236), < 0.001	1.179 (1.117 – 1.245), < 0.001
Lateral trochlea	454/24/115/7	10.0(3.7)/11.4(3.1)/11.8(3.4)/13.1(3.5)	9.90, < 0.001	1.153 (1.095 – 1.213), < 0.001	1.156 (1.094 – 1.220), < 0.001
BML scores (0/1/2/3-4)					
Size score					
Medial patella	389/138/60/13	10.4(3.9)/10.3(3.5)/10.75(3.1)/9.5(2.6)	0.482, 0.695	0.998 (0.955 – 1.044), 0.944	1.002 (0.954 – 1.052), 0.934
Medial trochlea	441/137/15/7	10.7(3.8)/9.8(3.3)/9.7(2.7)/8.6(3.0)	2.50, 0.058	0.931 (0.882 – 0.982), 0.008	0.941 (0.890 – 0.995), 0.034
Lateral patella	384/108/84/24	9.8(3.7)/10.9(3.4)/11.8(3.5)/12.9(3.1)	12.10, < 0.001	1.150 (1.097 – 1.206), < 0.001	1.158 (1.104 – 1.215), < 0.001
Lateral trochlea	426/74/75/25	9.9(3.3)/11.1(3.5)/12.2(5.1)/12.1(3.6)	12.42, < 0.001	1.141 (1.088 – 1.198), < 0.001	1.150 (1.093 – 1.209), < 0.001
Number score					
Medial patella	389/155/54/2	10.4(3.9)/10.4(3.4)/10.4(3.3)/10.5(2.1)	0.007, 0.999	0.998 (0.954 – 1.043), 0.927	1.004 (0.956 – 1.054), 0.880
Medial trochlea	445/138/14/3	10.6(3.8)/9.9(3.3)/9.1(3.1)/8.3(3.1)	2.25, 0.081	0.934 (0.886 – 0.986), 0.013	0.947 (0.895 – 1.002), 0.061
Lateral patella	384/162/41/13	9.8(3.7)/11.6(3.5)/10.9(3.4)/11.6(3)	7.67, < 0.001	1.125 (1.076 – 1.177), < 0.001	1.132 (1.079 – 1.186), < 0.001
Lateral trochlea	428/131/30/11	9.9(3.3)/11.7(4.7)/11.2(2.8)/13.5(2.3)	8.90, < 0.001	1.127 (1.076 – 1.183), < 0.001	1.129 (1.074 – 1.186), < 0.001
Osteophyte score (0/1/2/3)					
Medial patella	252/279/68/1	9.9(3.3)/10.6(4)/11.3(3.5)/7	3.34, 0.019	1.051 (1.009 – 1.096), 0.017	1.053 (1.008 – 1.101), 0.022
Medial trochlea	262/254/72/12	9.9(3.4)/10.6(3.9)/11.6(3.7)/10.8(3.9)	4.51, 0.004	1.064 (1.021 – 1.108), 0.003	1.087 (1.040 – 1.135), < 0.001
Lateral patella	285/242/58/15	9.8(3.7)/10.5(3.4)/12.5(3.6)/11.8(4.8)	9.54, < 0.001	1.114 (1.068 – 1.163), < 0.001	1.119 (1.069 – 1.169), < 0.001
Lateral trochlea	346/155/76/23	9.8(3.6)/10.6(3.6)/11.9(3.3)/13.3(3.9)	12.74, < 0.001	1.145 (1.094 – 1.197), < 0.001	1.151 (1.099 – 1.206), < 0.001

Table 2 (continued)

Baseline	Number of subjects in each score	TT-TG distance Mean (SD) for each score	ANOVA F _(3,596) , p value	OR (95% CI), p value	
				Crude	Adjusted
Synovitis score (0/1/2/3)	246/302/47/5	10.4(3.5)/10.2(3.3)/11.1(3.5)/13.8(17)	2.17, 0.090	1.015 (0.973 – 1.059), 0.474	1.028 (0.989 – 1.030), 0.366
Effusion score (0/1/2/3)	233/250/97/20	9.9(3.2)/10.4(3.5)/11.6(4.9)/10.4(4.2)	4.41, 0.004	1.066 (1.024 – 1.111), 0.002	1.066 (1.022 – 1.112), 0.003

Data are presented as mean (standard deviation) for TT-TG distance. Data were analyzed using an ordinal logistic regression model (for the association between the TT-TG distance and baseline MOAKS scores) and one-way ANOVA analysis. Logistic analysis was adjusted for baseline variables including age, BMI, gender, WOMAC pain, kneeling activity, history of knee injury, ACL tear, varus or valgus, PASE score, muscle strength, and tibiofemoral KL grade. MOAKS: MRI Osteoarthritis Knee Score; BML: bone marrow lesion; TT-TG: tibial tuberosity-trochlear groove; SD: standard deviation; SE: standard error; ANOVA: analysis of variance; BMI: body mass index; WOMAC: Western Ontario & McMaster Universities osteoarthritis index; KL: radiographic Kellgren and Lawrence; ACL: anterior cruciate ligament; PASE: Physical Activity Scale for the Elderly

Bold numbers: p -value <0.05

might be possible that excessive TT-TG distance leads to patellofemoral OA by inducing effusion and SHFP edema. To the best of our knowledge, no prior reports have described the predictive value of the TT-TG distance for longitudinal patellofemoral OA worsening. The results of our study not only reconfirmed the cross-sectional association between TT-TG distance and patellofemoral OA, but also demonstrated that TT-TG could be considered as an important and easily obtainable marker of future lateral patellofemoral OA. Although our results showed significant associations, the obtained ORs were not extensive. The reason was that we evaluated the continuous form of the TT-TG distance variable (not dichotomized); this means that with the OR range from 1.05–1.15 (95% CI), for each millimeter increase in TT-TG distance, there was a 5–15% increase in the odds of overall lateral patellofemoral OA worsening. The more noticeable results were also obtained after excluding subjects who had a maximum score at baseline evaluations, and therefore no subsequent progression could occur. In this study, standard OA-related structural damage including cartilage loss, BML, and formation of osteophytes was utilized for describing the patellofemoral OA using the validated MOAKS method [21, 27, 28, 41].

The non-operative medical management of patellofemoral OA includes weight loss, pharmacological pain control, physical therapies, etc. [42–44]. It has been accepted that additional correction of OA predisposing factors (such as realignment surgery) simultaneous with cartilage restoration surgery induced a significant improvement in long-term clinical results [19, 20]. In this context, Gigante et al. showed improvement of the clinical outcomes after combined distal realignment (in subjects with CT-derived TT-TG distance > 20 mm) and matrix-assisted autologous chondrocyte transplantation [45]. Previous practices have defined the cutoff value of 15 mm (using CT) in the setting of patellofemoral instability, which has primarily aimed at detection of subjects who may benefit from a realignment procedure [36, 37]. Our results showed that a TT-TG distance of 10.5 mm (based on MRI) was the optimal cutoff for predicting future patellofemoral damage worsening. Although a TT-TG distance > 15mm using CT examinations has been considered abnormal in the setting of patellofemoral instability, this value was not an optimal cutoff for indicating and predicting patellofemoral OA, which may be due to the difference in modality (CT versus MRI) or outcome of interest (patellofemoral instability versus MRI-based patellofemoral OA). The patellofemoral OA-related MRI-based structural damage worsening was not significantly different between the subjects who had a TT-TG distance of > 15 mm versus ≤ 15 mm in previous reports and our ancillary analyses [3].

Abnormally lateralized tibial tuberosity can only be corrected using surgical methods such as TTM, which is currently primarily used in the setting of patellar instability [15–18]. However,

Table 3 Follow-up study: association between patellofemoral joint structural worsening (worsening change in patellar and trochlear MOAKS variables: cartilage, BML, osteophyte, synovitis, and effusion) and baseline TT-TG distance

Change	TT-TG distance Mean (SD), number of subjects		t-test <i>p</i> value	OR (95% CI), <i>p</i> value	
	Worsening	Non-worsening		Crude	Adjusted
Cartilage morphology scores (surface/thickness change)					
Medial patella	10.4(2.6), 65	10.4(3.8), 534	0.975	1.001 (0.934 – 1.073), 0.975	1.006 (0.935 - 1.083), 0.873
Medial trochlea	13.3(8.5), 21	10.3(3.4), 579	< 0.001	1.158 (1.050 – 1.277), 0.003	1.208 (1.093 - 1.334), < 0.001
Lateral patella	11.4(3.5), 51	10.3(3.7), 548	0.045	1.070 (1.000 – 1.146), 0.050	1.078 (1.001 - 1.160), 0.047
Lateral trochlea	12.0(3.3), 37	10.3(3.7), 563	0.007	1.102 (1.021 – 1.188), 0.012	1.119 (1.033 - 1.211), 0.006
BML scores (size/number change)					
Medial patella	10.8(3.1), 82	10.35(3.8), 517	0.357	1.029 (0.969 – 1.092), 0.357	1.023 (0.961 - 1.088), 0.475
Medial trochlea	9.2(3.1), 64	10.6(3.8), 535	0.005	0.891 (0.823 – 0.964), 0.004	0.889 (0.817 - 0.967), 0.006
Lateral patella	11.1(3.4), 104	10.3(3.7), 495	0.039	1.058 (1.002 – 1.117), 0.044	1.060 (1.001 - 1.122), 0.046
Lateral trochlea	11.6(4.6), 89	10.2(3.5), 510	0.001	1.100 (1.036 – 1.168), 0.002	1.108 (1.041 - 1.179), 0.001
Osteophyte score (size change)					
Medial patella	10.0(5.0), 8	10.4(3.7), 592	0.752	0.968 (0.793 – 1.182), 0.750	0.979 (0.785 - 1.222), 0.852
Medial trochlea	8.6(2.4), 8	10.5(3.7), 592	0.169	0.854 (0.688 – 1.060), 0.152	0.810 (0.626 - 1.047), 0.108
Lateral patella	8.3(2.9), 3	10.4(3.7), 597	0.330	0.832 (0.584 – 1.185), 0.307	0.697 (0.397 - 1.224), 0.209
Lateral trochlea	12.5(4.2), 6	10.4(3.7), 594	0.165	1.099 (0.965 – 1.252), 0.153	1.138 (0.944 - 1.373), 0.176
Synovitis score					
	10.1(3), 58	10.5(3.8), 542	0.436	0.970 (0.898 – 1.047), 0.434	0.963 (0.883 - 1.050), 0.390
Effusion score					
	10.9(4.2), 154	10.2(3.5), 446	0.044	1.051 (1.000 – 1.103), 0.048	1.073 (1.018 - 1.131), 0.008

Data are presented as mean (standard deviation) for TT-TG distance. Data were analyzed using logistic regression model (for the association between TT-TG distance and worsening of the MOAKS scores) and t-test analysis. Logistic analysis was adjusted for baseline variables including age, BMI, gender, WOMAC pain, kneeling activity, history of knee injury, ACL tear, varus or valgus, PASE score, muscle strength, and tibiofemoral KL grade as well as radiographic tibiofemoral JSL progression. MOAKS: MRI Osteoarthritis Knee Score; BML: bone marrow lesion; TT-TG: tibial tuberosity-trochlear groove; SD: standard deviation; SE: standard error; OR: odds ratio; CI: confidence intervals; BMI: body mass index; WOMAC: Western Ontario & McMaster Universities osteoarthritis index; KL: radiographic Kellgren and Lawrence; ACL: anterior cruciate ligament; PASE: Physical Activity Scale for the Elderly; JSL: joint space loss

Bold numbers: *p*-value <0.05

the biomechanical abnormalities associated with abnormal TT-TG distance can be addressed using readily accessible and feasible nonsurgical treatments [15, 46]. One study demonstrated that while the patellar brace was being worn there was a significant improvement in tracking vector and biomechanical abnormalities [15]. Also, it has been suggested that physical therapy focusing on extensor muscle strength can be considered the initial management of biomechanical abnormalities and patellar instability caused by an excessive TT-TG distance [15, 46, 47]. According to the variety of available interventions, biomechanical abnormalities associated with the excessive TT-TG distance

might be considered a potential modifiable risk factor for patellofemoral OA.

Several limitations existed in our study. First, the FNIH study outcomes were primarily designed based on tibiofemoral OA. All inclusion/exclusion criteria were related to the baseline features of the tibiofemoral joint (e.g., 12.5% of enrolled subjects had tibiofemoral KL grade < 2 when evaluating isolated patellofemoral OA) as well as the radiographic progression of the tibiofemoral joint. Also, the study groups were not matched for several characteristics related to patellofemoral OA. To address this limitation and any potential selection bias, we

Table 4 Overall associations: association between the presence and worsening of medial/lateral patellofemoral OA-related structural damages with baseline TT-TG

	TT-TG distance		t-test <i>p</i> value	OR (95% CI), <i>p</i> value	
	Mean (SD), number of subjects			Crude	Adjusted
	Positive	Negative			
Baseline overall patellofemoral structural damage					
Medial	10.49(3.8), 384	10.46(3.5), 216	0.492	1.015 (0.969 - 1.063), 0.528	1.013 (0.965 - 1.063), 0.604
Lateral	11.08(3.6), 269	9.87(3.7), 331	< 0.001	1.098 (1.046 - 1.152), < 0.001	1.098 (1.045 - 1.154), < 0.001
Worsening in overall patellofemoral structural damages					
Medial	10.36(4.0), 200	10.44(3.5), 398	0.792	0.992 (0.946 - 1.039), 0.721	0.993 (0.946 - 1.042), 0.778
Lateral	11.28(4.1), 207	9.95(3.4), 392	< 0.001	1.106 (1.052 - 1.163), < 0.001	1.111 (1.056 - 1.170), < 0.001

Data are presented as mean (standard deviation) for TT-TG distance. Data were analyzed using logistic regression model (for the association between the TT-TG distance and patellofemoral OA-related damage presence or worsening) and t-test. Logistic analysis was adjusted for baseline variables including age, BMI, gender, WOMAC pain, kneeling activity, history of knee injury, ACL tear, varus or valgus, PASE score, muscle strength, and KL grade as well as radiographic JSL progression (for worsening change analyses). MOAKS: MRI Osteoarthritis Knee Score; OA: osteoarthritis; BML: bone marrow lesion; TT-TG: tibial tuberosity-trochlear groove; SD: standard deviation; SE: standard error; OR: odds ratio; CI: confidence intervals; BMI: body mass index; WOMAC: Western Ontario & McMaster Universities osteoarthritis index; KL: Radiographic Kellgren and Lawrence; ACL: anterior cruciate ligament; PASE: Physical Activity Scale for the Elderly; JSL: joint space loss

Bold numbers: *p*-value <0.05

assessed all possible risk/protective factors related to baseline and follow-up patellofemoral/tibiofemoral OA; all results were adjusted for the possible effect of these confounding variables such as baseline (KL grade) and follow-up (JSL progression). Second, the sample size and follow-up duration period may not be adequate, and the association between TT-TG distance and long-term OA degeneration needs to be further explored in future cohort studies. Third, there was an absence of patellofemoral joint radiographic and symptom outcome. Although knee pain measurements are available in OAI, all these evaluations could be contributed by tibiofemoral OA, and a pain-grading system specific for the patellofemoral joint was not available. Also, only posteroanterior, not lateral or axial, knee radiographs are available in OAI, which were not optimal for radiographic grading of patellofemoral OA. Fourth, the association between patellofemoral OA and other patellar morphological abnormalities including patella alta, trochlear dysplasia, and patellar tilt were not evaluated in our study as these other measurements have been previously demonstrated to be associated to patellofemoral OA [5, 13, 14]. Besides all other patellar morphological abnormalities, excessive TT-TG distance is a modifiable abnormality that can be corrected using surgical treatments, especially in patients with high-risk of OA. Finally, despite the possible relationship between the lateralized tibial tuberosity and SHFP edema, which is associated with patellofemoral OA, the role of this factor in mediating the effect of excessive TT-TG distance on OA progression was not assessed in our study [7, 38–40].

In conclusion, we showed that excessive TT-TG distance can predict the longitudinal worsening of patellofemoral OA besides its role as an indicator of patellofemoral instability

syndrome. Thus, biomechanical abnormalities associated with the increased TT-TG distance can be considered a risk factor for lateral patellofemoral OA.

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Ethical approval Institutional Review Board approval was not required because we used the open access OAI database.

The OAI study has received ethics board approval by the institutional review board at the University of California, San Francisco (OAI Coordinating Center; Approval Number: 10-00532).

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported in the OAI database and OAI-related articles.

Methodology

- prospective
- observational
- multicenter study

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