Quadriceps Weakness and Risk of Knee Cartilage Loss Seen on Magnetic Resonance Imaging in a Population-based Cohort with Knee Pain

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ABSTRACT. Objective. To determine whether baseline quadriceps weakness predicts cartilage loss assessed on magnetic resonance imaging (MRI).

Methods. Subjects aged 40–79 with knee pain (n = 163) were recruited from a random population sample and examined for quadriceps weakness with manual isometric strength testing, using a 3-point scoring system (0 = poor resistance, 1 = moderate resistance, 2 = full resistance), which was dichotomized as normal (grade 2) versus weak (grade 0/1). MRI of the more symptomatic knee was obtained at baseline and at mean of 3.3 years. Cartilage was graded 0–4 on MRI. Exponential regression analysis was used to evaluate whether quadriceps weakness was associated with whole knee cartilage loss, and in secondary analyses with compartment-specific cartilage loss, adjusted for age, sex, body mass index, Western Ontario and McMaster Universities Osteoarthritis Arthritis Index pain score, and baseline MRI cartilage score.

Results. Of 163 subjects, 54% were female, with a mean age of 57.7 years. Quadriceps weakness was seen in 11.9% of the subjects. Weakness was a predictor of whole knee cartilage loss (HR 3.48, 95% CI 1.30–9.35). Quadriceps weakness was associated with cartilage loss in the medial tibiofemoral (TF) compartment (HR 4.60, 95% CI 1.25–17.02), while no significant association was found with lateral TF (HR 1.53, 95% CI 0.24–9.78) or patellofemoral compartment (HR 2.76, 95% CI 0.46–16.44).

Conclusion. In this symptomatic, population-based cohort, quadriceps weakness predicted whole knee and medial TF cartilage loss after 3 years. To our knowledge, this is the first study to show that a simple clinical examination of quadriceps strength can predict the risk of knee cartilage loss. (J Rheumatol First Release October 1 2018; doi:10.3899/jrheum.170875)

Key Indexing Terms:
OSTEOARTHRITIS CARTILAGE MAGNETIC RESONANCE IMAGING
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Osteoarthritis (OA) is one of the leading causes of disability worldwide[1,2,3]. Quadriceps muscle weakness is one potentially modifiable risk factor for knee OA because it is consistently found in patients with knee OA[4,5]. The quadriceps muscle acts as a natural knee brace and is known to have effects on knee joint stability and loading[6]. With walking, the quadriceps muscle is activated to counteract the ground reaction forces and affects load distribution in the tibiofemoral (TF) joint[6,7,8]. Weak quadriceps are also quicker to fatigue, leading to poor muscle control[9,10,11,12] that may accelerate knee cartilage loss. Most of the previous studies evaluating strength and knee OA have focused on radiographic changes, which is an indirect method for

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assessing knee cartilage. Several cohort studies that included patients with early disease have found that baseline weakness was a risk factor for developing incident radiographic knee OA[13,14,15,16]. In contrast, conflicting results are reported for quadriceps weakness as a risk factor for progression of established knee OA[17,18,19]. A recent metaanalysis evaluating subjects with radiographic knee OA found that knee extensor weakness was associated with functional and symptomatic decline but no clear association with radiographic TF narrowing and inconclusive evidence for the patellofemoral (PF) compartment[20].

Magnetic resonance imaging (MRI) is superior at assessing cartilage loss directly. There have only been 2 longitudinal studies evaluating quadriceps strength and cartilage loss on MRI, with conflicting results for the PF compartment[21,22]. The first study, using dynamometers to measure strength, reported that increased strength was protective for PF cartilage loss[21], while the second study, using thigh muscle cross-sectional area (CSA) to assess strength indirectly, reported an increased risk of PF cartilage loss[22]. Neither of these 2 studies reported an association of quadriceps weakness with TF cartilage loss. There have been no previous studies evaluating the association of quadriceps strength assessed by physical examination with MRI cartilage loss. The advantage of using a bedside assessment of strength is that it can be easily applied in clinical practice. Given the conflicting evidence for quadriceps strength and cartilage loss, and the lack of studies evaluating strength clinically, more studies are needed.

The goal of our study was to determine whether quadriceps weakness was associated with MRI cartilage loss at 3 years in a population-based cohort with predominantly preradiographic disease [Kellgren-Lawrence (KL) grade < 2]. Unlike previous studies, we used a bedside examination, previously shown to be reliable, to measure quadriceps muscle strength. The primary outcome was whole knee cartilage loss, and secondary analyses evaluated compartment-specific cartilage loss in the medial TF, lateral TF, and PF compartments.

MATERIALS AND METHODS

Study participants. The population for this cohort was recruited between 2002 and 2005 and has been described in detail previously[23,24,25]. Briefly, subjects 40–79 years old with knee pain were recruited as a random population sample in the Greater Vancouver area in British Columbia, Canada. Recruitment was conducted using stratified sampling to achieve equal representation within age decades (40–49 yrs, 50–59 yrs, etc.) and sex. Subjects were excluded at baseline if they had inflammatory arthritis or fibromyalgia, previous knee arthroplasty, knee injury or surgery within the previous 6 months, knee pain referred from hips or back, or were unable to undergo MRI.

All participants were invited for followup at 3 years. Exclusion criteria at followup were the following: (1) inflammatory arthritis; (2) knee arthroplasty; (3) inability to perform MRI; and (4) inability to attend the study center[25]. Of the 255 subjects at baseline, 1 (0.4%) had died, 25 (9.8%) were lost to followup with unknown status, and 35 (13.7%) were not interested in participating. Of the remaining 194 subjects, 28 (14.4%) were not eligible (8 total knee replacement, 3 inflammatory arthritis, 3 unable to undergo MRI, 9 comorbidities, and 5 unable to visit study center) and 3 subjects (1.5%) did not complete their MRI[25]. A total of 163 subjects completed all study assessments and were included in the analysis. All subjects provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Board, University of British Columbia (REB# H05-70403).

Clinical evaluation. A physician examiner assessed subjects using a routine standardized knee examination, including quadriceps strength, as previously described[26]. In subjects with bilateral knee pain, the more symptomatic knee was selected. Quadriceps strength was assessed in the sitting position with the knee at 90° and legs dangling over the examination table. The examiner placed his/her hand anteriorly just above the ankle joint. The subject was asked to slowly push the leg out toward the examiner and to push with full force against the examiner's resistance but to avoid any movement of the leg, so that testing was performed isometrically. The subject's degree of resistance was then rated. The strength scoring system was adapted from the widely used Medical Research Council (MRC) manual muscle testing, which grades strength from 0 to 5[27]. In our study, muscle strength was scored using a 3-point scoring system from 0 to 2, corresponding to grades 3–5 on the MRC scale, which are the only scores applicable to ambulatory subjects. Specifically, full strength (5/5 on the MRC scale) was equivalent to a score of 2 in our study (full resistance); moderate strength (4/5 on MRC scale) was equivalent to a score of 1 (moderate resistance); and poor strength (3/5 on MRC scale) was equivalent to a score 0 in our study (poor resistance). We have previously shown a high interrater reliability for quadriceps muscle strength testing with a reliability coefficient of 0.86[26]. Since grade 0 (poor resistance) was infrequent, we dichotomized the patients into those with full strength (grade 2) and those with any quadriceps weakness (grades 1 or 0). Subjects completed the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index, version VA3.1, a validated instrument to assess knee OA, which includes subscales for pain, stiffness, and physical function[28]. Scores were normalized to a 0–100 scale.

Plain radiographic assessment. Weight-bearing baseline radiographs were obtained, using a fixed-flexion technique with the SynaFlexer positioning frame, and a skyline view was obtained with the subject in the supine position[29]. Radiographs were scored independently by a radiologist (SN) with 17 years of musculoskeletal radiology experience and a rheumatologist (JC) with 12 years of experience reading knee radiographs; both were blinded to clinical and MRI information, using KL 0–4 grading[30]. The interrater reliability was good, with an intraclass correlation coefficient of 0.79[24].

MRI grading. MRI was performed using a GE 1.5T magnet (GE Healthcare) and has been described in detail previously[23]. Six joint areas of the knee were assessed, including the medial and lateral tibial plateau, medial and lateral femoral condyles, and patella and trochlear groove. Baseline and followup MR images were read side-by-side by an experienced musculoskeletal radiologist (AG) with 15 years of experience with semiquantitative MRI analysis of knee OA, blinded to time sequence, radiographic, and clinical information. Cartilage damage was graded using a semiquantitative scale of 0–4 based on the following definitions previously described by Disler, *et al*[31]: 0 = normal, 1 = abnormal signal without a cartilage contour defect, 2 = contour defect ≤ 50% cartilage thickness, 3 = contour defect > 50% but < 100% cartilage thickness, and 4 = 100% cartilage contour defect with subjacent bone signal abnormality[23,25]. If multiple defects were present within a given site, the most severe score was assigned. Intrarater reliability ranged for different joint regions from 0.84 to 1.00 for cartilage[24].

Outcome measures. Cartilage loss was defined as worsening of cartilage score of ≥ 2 grades in at least 1 site or worsening of ≥ 1 grade in at least 2 sites[25]. This definition of cartilage loss only accounted for changes in the lesion depth, not changes in the lesion area. Thus, within-grade cartilage change was not included in our definition. For the medial TF compartment, cartilage loss was defined as worsening of cartilage score ≥ 2 in the medial tibia or medial femur or worsening ≥ 1 at both sites; for the lateral TF compartment, worsening of cartilage score ≥ 2 in the lateral tibia or lateral femur or worsening ≥ 1 at both sites; and for the PF compartment, worsening of the cartilage score ≥ 2 in the patella or trochlear groove or worsening ≥ 1

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at both sites. Subjects who were logically unable to meet the definition of cartilage loss owing to high baseline MRI cartilage scores were excluded from the respective analyses.

Statistical analysis. To obtain population-based results, a sample weight was developed as previously described[32]. The weight was scaled to sum to the baseline sample size (n = 255). The longitudinal subset analyzed in our present study consisted of 163 subjects. A sample weight was developed as the ratio of baseline sample proportion in a given age-sex cell over the longitudinal sample proportion in that cell, multiplied by the baseline weight. The sample weight was scaled to sum to the followup sample size (n = 163). All the analyses in the present study were weighted with the longitudinal sample weight[32].

Data were analyzed descriptively using means (SD). Baseline variables were compared between those with quadriceps weakness and those without, using chi-square test for categorical variables or a 2-sample t test for continuous variables. Exponential regression analysis was used to assess whether quadriceps weakness was a risk factor for cartilage loss for the knee as a whole (primary analysis) or for cartilage loss in the medial TF, lateral TF, and PF compartments (secondary analyses). Results are reported as crude and adjusted HR and 95% CI. Analyses were adjusted for age, sex, body mass index (BMI), WOMAC pain score, and baseline MRI cartilage score. In additional sensitivity analyses, we included varus and valgus knee malalignment, compared to normal, as a potential confounder. Malalignment was evaluated by visual inspection using a standardized methodology previously shown to be reliable (reliability coefficient of 0.94)[26]. Further, because previous MRI studies had reported either on radiographic OA (ROA) or preradiographic disease, we ran an additional sensitivity analysis on KL < 2 and KL ≥ 2 subgroups. Suitability of exponential models was assessed using likelihood ratio tests versus Weibull models. Analyses were performed using SAS, version 9.4 (SAS Institute).

RESULTS

There were 163 subjects seen at a mean followup time of 3.3 years. Participants seen in followup, compared to those lost to followup, did not differ statistically on any variable. Numerically, those seen were older (57.7 vs 55.2 yrs), less frequently female (54.0% vs 60.3%), had more frequently normal quadriceps strength (88.1% vs 83.2%), and lower BMI (weighted 26.1 vs 27.2). KL grade and cartilage scores were also similar.

At baseline, mean age was 57.7 years, 54% were female, KL grades 0–4 were seen in 39.9%, 20.7%, 21.2%, 10%, and 8.2%, respectively, and MRI cartilage grade ≥ 2 was seen in 75.9% (Table 1). Those with quadriceps weakness, compared to those without, were older (64.1 vs 56.8 yrs, p = 0.003), were more frequently female (79.4% vs 50.6%, p = 0.017), and had higher WOMAC pain score (32.4 vs 17.9, p = 0.009), but had similar frequencies of KL grade ≥ 2 and cartilage score ≥ 2 (Table 1). Baseline quadriceps weakness was seen in 11.9% of all subjects and of those, the majority were women (79.4%). Cartilage loss was seen in 15.5% of subjects overall and was more frequent in those with quadriceps weakness compared to those without (44.0% vs 11.7%), with similar results for compartment-specific cartilage loss (Table 2).

Table 3 shows the risk of cartilage loss. For the medial TF, lateral TF, and PF compartment-specific analyses, weighted n included 149.4, 151.5, and 156.4 subjects, respectively, who were able to progress and were hence included in the analysis. Quadriceps weakness was significantly associated with whole knee cartilage loss with an adjusted HR 3.48 (95% CI 1.30–9.35, p = 0.013). In compartment-specific analyses, quadriceps weakness was a significant risk factor for cartilage loss in the medial TF compartment (adjusted HR 4.60, 95% CI 1.25–17.02, p = 0.022), while no statistically significant associations were seen in the lateral TF (adjusted HR 1.53, 95% CI 0.24–9.78, p = 0.652) and PF compartments (adjusted HR 2.76, 95% CI 0.46–16.44, p = 0.265). Sensitivity analysis with inclusion of varus and valgus knee malalignment showed similar results (data not shown).

A sensitivity analysis evaluating the association of quadriceps weakness with cartilage loss for those with preradiographic knee OA (KL grade < 2) was performed. The results were similar, compared to the main analysis, for the whole joint (HR 6.03, 95% CI 1.30-28.02, p = 0.022), medial TF (HR 7.95, 95% CI 0.82–77.55, p = 0.075), and lateral TF

Table 1. Characteristics of study population at baseline (n = 163).

Variables	Total Cohort	No Quadriceps Weakness, n = 143.5	Quadriceps Weakness, n = 19.5	p*
Age, yrs, mean (SD)	57.7 (10.1)	56.8 (9.9)	64.1 (9.5)	0.003
Women	88.1 (54.0)	72.6 (50.6)	15.5 (79.4)	0.017
BMI, kg/m^2, mean (SD)	26.1 (4.2)	26.1 (4.3)	25.5 (3.4)	0.543
WOMAC pain (0–100), mean (SD)	19.6 (16.8)	17.9 (15.2)	32.4 (21.5)	0.009
MRI cartilage score ≥ 2	123.6 (75.9)	106.6 (74.3)	17.0 (87.6)	0.196
Medial TF MRI cartilage score ≥ 2	88.4 (54.2)	75.7 (52.7)	12.7 (65.2)	0.299
Lateral TF MRI cartilage score ≥ 2	52.5 (32.2)	46.2 (32.2)	6.3 (32.4)	0.983
PF MRI cartilage score ≥ 2	92.6 (56.8)	77.2 (53.8)	15.3 (78.9)	0.036
KL grade 0	65.0 (39.9)	61.5 (42.8)	3.6 (18.4)	
KL grade 1	33.8 (20.7)	27.2 (19.0)	6.5 (33.6)	
KL grade 2	34.5 (21.2)	31.2 (21.8)	3.3 (16.8)	0.036
KL grade 3	16.3 (10.0)	14.7 (10.2)	1.6 (8.4)	
KL grade 4	13.4 (8.2)	9.0 (6.2)	4.4 (22.7)	
KL grade ≥ 2	64.2 (39.4)	54.9 (38.2)	9.3 (48.0)	0.409

Values are n (%) unless otherwise specified. Stratum-sampling weights were used, hence n = weighted counts which are non-integer. * From a chi-square test (categorical) or a 2-sample t test (continuous). WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; TF: tibiofemoral; PF: patellofemoral; KL: Kellgren-Lawrence; MRI: magnetic resonance imaging; BMI: body mass index.

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Table 2. Frequency of knee cartilage loss.

Variables	Whole Joint, n = 163.0	Medial TF*, n = 149.4	Lateral TF*, n = 151.5	PF*, n = 156.4
No quadriceps weakness	16.7 (11.7)	9.0 (6.9)	4.9 (3.7)	6.3 (4.5)
Quadriceps weakness	8.6 (44.0)	5.0 (28.4)	2.4 (13.7)	2.0 (11.8)
Total cohort	25.3 (15.5)	14.0 (9.4)	7.3 (4.8)	8.3 (5.3)

Values are weighted n (%). * N depends on the number able to progress in the given compartment. TF: tibiofemoral; PF: patellofemoral.

Table 3. Association of quadriceps weakness with cartilage loss for the whole knee, and compartment-specific analyses.

Analysis	Whole Joint	Medial TF	Lateral TF	PF
Crude	5.02 (2.19–11.54); < 0.001	5.00 (1.67–15.00); 0.004	4.22 (0.91–19.67); 0.067	2.94 (0.60–14.42); 0.184
Adjusted*	3.48 (1.30–9.35); 0.013	4.60 (1.25–17.02); 0.022	1.53 (0.24–9.78); 0.652	2.76 (0.46–16.44); 0.265

Values are HR (95% CI); p value. *Adjusted for age, sex, body mass index, Western Ontario and McMaster Universities Osteoarthritis Index pain score, and baseline cartilage score. TF: tibiofemoral; PF: patellofemoral.

compartment (HR 11.34, 95% CI 0.24–526.42, p = 0.215), although in the medial TF compartment the association was no longer statistically significant, likely owing to limited power. The model for the PF compartment did not converge on this restricted subcohort. Because of small sample size and limited power, the sensitivity analysis for the KL ≥ 2 subgroup was not feasible.

DISCUSSION

In this population-based cohort with knee pain and predominantly preradiographic disease, bedside clinical examination of quadriceps weakness was a significant predictor for whole knee MRI cartilage loss with a 3-fold increased risk in those with quadriceps weakness, compared to those without. In secondary analyses, quadriceps weakness was associated with medial TF cartilage loss while no statistically significant association was found in the lateral TF or PF compartment.

To our knowledge, there have been only 2 previous longitudinal MRI studies evaluating quadriceps strength and risk of knee cartilage loss. The 2 studies reached different conclusions. The study by Amin, *et al*[21] found that subjects with radiographic knee OA and quadriceps weakness had increased risk of lateral PF cartilage loss after 30 months. In contrast, Goldman, *et al*[22] evaluated subjects with risk factors for knee OA (but no ROA) and showed that greater quadriceps strength increased the risk of PF cartilage loss after 48 months. In that study, they quantified muscle strength with both measured extensor strength and muscle CSA on MRI, and found that an increased ratio of extensor to flexor muscle CSA (which correlated with measured muscle strength), was significantly associated with accelerated PF cartilage loss[22]. Although we found that the risk of patellar cartilage loss was increased in those with quadriceps weakness, in keeping with the findings by Amin, *et al*[21], this did not reach statistical significance. In contrast to these 2 studies, we found that quadriceps weakness was significantly associated with whole knee and medial TF cartilage loss, a novel finding that requires confirmation with future studies.

The differing conclusions from our present study in comparison to the previous MRI studies may be partially explained by differences in study design and patient population. Amin, *et al*[21] included subjects with ROA (KL grade ≥ 2), thus evaluating for progression of knee OA. In contrast, Goldman, *et al*[22] included subjects with risk factors for knee OA and KL grade 0 and 1 who had low mean baseline cartilage scores, thus evaluating for both incidence and progression of cartilage damage. In our study, we had a random sample of the population with knee pain, including a mix of subjects with (75.9%) and without (24.1%) baseline MRI cartilage damage. It is possible that the risk factors for the initiation and progression of knee OA are distinct, and the role of quadriceps strength may differ in the various stages of knee OA. In those with preradiographic disease, quadriceps weakness may be a risk factor for the development of knee OA, while weakness seen in later stages of knee OA may be related to pain and disuse atrophy. In our study, we had 28.4% of subjects with medial TF cartilage loss, slightly higher compared to 21.6% in the Amin study[21], and we had slightly lower frequency of PF cartilage loss compared to Amin, *et al*[21]. Frequencies of progression were not provided in the Goldman, *et al* study[22]. Therefore, in addition to different populations being studied, varying event frequencies may have contributed to different results. Further, given that the quadriceps muscle consists of 4 distinct muscles, the relative strength of individual muscle groups and co-contraction of muscles may play an important role in load distribution and rotational stability of the knee. Our method of assessing quadriceps strength did not allow for detailed evaluation of the different quadriceps muscle groups, but this may be an area of future research. Finally, MRI cartilage scoring also differed, as the 2 other studies used the semiquantitative whole-organ MRI score, which takes into

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account cartilage lesion depth and area, compared to our study, in which cartilage scores were based on changes to cartilage depth alone. Our definition of cartilage loss was more stringent, requiring a change of ≥ 2 grades in 1 joint surface or worsening of ≥ 1 grade on 2 joint surfaces, compared to only requiring change of ≥ 1 grade in the other 2 studies. Because of the more stringent definition and because we did not take into account lesion area, we may have underestimated the effect of quadriceps weakness on knee cartilage loss, strengthening our conclusion.

In addition to differences in study populations and MRI scoring, the 2 previous MRI studies used dynamometers to assess muscle strength and/or MRI muscle CSA, whereas we used a standardized clinical examination. A previous study found that manual knee extensor strength testing was highly correlated with hand-held dynamometers[33]. Although small differences in strength may not be recorded with the bedside examination, the assessment can be applied easily in clinical practice. Using this method of quadriceps strength assessment, we are the first study, to our knowledge, to demonstrate that a bedside evaluation of strength can be used to assess risk of knee cartilage loss, offering a potential window of opportunity for intervention. However, the effect of strength training on structural outcomes is unclear. Previous studies have shown that quadriceps strengthening may not affect gait patterns and knee loading[34], although the magnitude of knee loading is estimated from the knee adduction moment (KAM), which gives information only about the distribution of the knee loads and not the actual contact forces[35]. Bennell, *et al*[34] showed that an exercise intervention did not alter the KAM but also postulated that if a more demanding task for measuring KAM was used (i.e., single leg squat vs walking), perhaps a difference would be noted. Nevertheless, although quadriceps strengthening intervention may not affect gait biomechanics, there is good evidence that it improves knee pain, function, and quality of life[36] and is recommended by current OA guidelines[37,38,39].

Limitations of our study include the small number of subjects (12%) with quadriceps weakness. It is possible that subjects with poor quadriceps muscle resistance did not have true muscle weakness but were limited by underlying pain, as those with quadriceps weakness had significantly higher WOMAC pain scores. We attempted to limit the effect of knee pain by assessing strength isometrically, which avoids any movement of the knee. Although knee pain, or periarticular pain, may still prevent subjects from exerting full resistance, this problem would apply equally to all studies including those using a dynamometer. Quadriceps weakness may also be the result of reduced physical activity owing to knee pain and OA stage. Therefore, OA severity at baseline, in addition to pain, may be confounding the relationship of quadriceps weakness with cartilage loss. Accordingly, we have adjusted for these potential confounders. Another limitation was that our definition of knee OA cartilage loss was based on worsening of cartilage loss at multiple sites or worsening by a substantial amount at a single site, which leads to a more conservative estimate of cartilage loss and hence a lower frequency of cartilage loss. Nevertheless, we found statistically significant associations with cartilage loss over 3 years. Another potential limitation is our mix of subjects with normal cartilage and those with prevalent cartilage lesions, because the effect of quadriceps strength on the initiation and the progression of knee OA may be different. As a result of the small sample size, we were unable to evaluate incidence of cartilage loss separately from progression.

The strengths of our study include the use of a symptomatic population-based cohort, with the inclusion of a mixture of subjects with both preradiographic and radiographic knee OA. This allows for generalizability of the results to the symptomatic population, including those with preradiographic disease, which is important, because targeted interventions may be more effective in early disease. Another major strength of the study was the use of the physical examination to detect weakness, which can be performed easily, quickly, and inexpensively at the bedside.

In our population-based cohort of symptomatic subjects with predominantly preradiographic knee OA, quadriceps weakness was associated with a statistically significantly increased risk of cartilage loss in the whole joint and in the medial TF compartment independent of age, sex, BMI, baseline pain severity, or ROA severity. To our knowledge, this is the first study to show that a simple bedside physical examination of quadriceps strength can assist clinicians in identifying patients at increased risk of knee cartilage loss.

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