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The Association Between Quadriceps Strength and Synovitis in Knee Osteoarthritis: An Exploratory Study From the Osteoarthritis Initiative

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ABSTRACT. ***Objective.*** The aim of this study was to explore the association between quadriceps strength and synovitis in knee osteoarthritis (KOA).

Methods. This study was derived from the Osteoarthritis Initiative (OAI), which recruited adults from the OAI cohort with or at risk of KOA. Knees with complete records of isometric quadriceps strength and effusion-synovitis and Hoffa-synovitis assessments were included. Quadriceps strength was measured isometrically at baseline. Effusion-synovitis and Hoffa-synovitis were measured using the Magnetic Resonance Imaging Osteoarthritis Knee Score at baseline and at 1-year and 2-year follow-ups. Generalized estimating equations were used to analyze the associations of baseline quadriceps strength with changes in effusion-synovitis and Hoffa-synovitis in multivariable analyses. Additionally, analyses were stratified by synovitis-driven inflammatory phenotypes.

Results. A total of 1513 knees were included in this study. In total, 61% of the subjects were female; subjects had an average age of 61.9 (SD 8.8) years and a mean BMI of 29.4 (SD 4.7). Regarding the whole population, baseline quadriceps strength was negatively associated with baseline effusion-synovitis and follow-up changes in effusion-synovitis (odds ratio [OR] 0.77-0.86), but no significant association was observed in terms of Hoffa-synovitis. Stratified by synovitis-driven inflammatory phenotype, baseline quadriceps strength was significantly associated with follow-up changes in effusion-synovitis—but not in Hoffa-synovitis—in the population with existing effusion-synovitis (OR 0.75-0.79).

Conclusion. Higher baseline quadriceps strength was negatively associated with changes in effusion-synovitis—but not in Hoffa-synovitis—especially in the population with existing effusion-synovitis. Our findings suggested a potential protective role of the quadriceps in effusion-synovitis.

Key Indexing Terms: effusion-synovitis, Hoffa-synovitis, osteoarthritis, quadriceps

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Knee osteoarthritis (KOA) is one of the most prevalent types of chronic musculoskeletal diseases[1,2] and a leading cause of functional limitation in older adults.[3] As the population ages and the obesity epidemic grows, KOA has become an urgent clinical issue, with increasing healthcare costs.[4,5] However, there have been no disease-modifying osteoarthritis (OA) drugs that can modify both structural damage and symptomatic progression in KOA.[6]

The etiology of KOA is complex, involving multiple biomechanical and biochemical risk factors. Quadriceps weakness has been long recognized as an important risk factor for the development of KOA,[7,8] and strength training has been suggested as the first-line treatment by important guidelines.[9-12] In recent years though, a series of high-quality clinical trials reported that strength training did not result in a significant protective effect against the progression of KOA, raising a particular challenge for its status as standard therapy.[13,14] There is an urgent need for further studies to determine the protective effect of the quadriceps.

In recent years, a growing body of studies focused on the exploration of KOA phenotypes, including aging-driven phenotype, metabolic-driven phenotype, traumatic injury–driven phenotype, cartilage-driven phenotype, subchondral-driven phenotype, and synovitis-driven inflammatory phenotype.[15] With regard to high heterogeneity in KOA, it seems that the key to further improve the efficacy of KOA therapy is individualized treatment for patients with different phenotypes. Traditionally, it has been suggested that the quadriceps dissipate detrimental loads and maintain dynamic stability.[16] In addition, an increasing number of studies have focused on the inflammation-regulating function of the quadriceps. In-depth studies have suggested that myokines (eg, irisin, tumor necrosis factor [TNF], and interleukin 6 [IL-6]) secreted from skeletal muscle (eg, quadriceps) are essential regulatory factors that are likely to affect the KOA through regulating intraarticular inflammation.[17-19] However, the association between the quadriceps and the synovitis-driven inflammatory phenotype of KOA is still unclear.

As more evidence supports the involvement of local inflammatory mediators in KOA pathogenesis,[20] inflammatory phenotype, particularly synovitis-driven inflammatory phenotype, has attracted substantial attention. Synovitis is no longer recognized as an innocent bystander in KOA. Clinically, effusion-synovitis or Hoffa-synovitis are the surrogates used to identify synovial inflammation on noncontrast-enhanced magnetic resonance imaging (MRI).[21] The existence of a fluid equivalent signal in the joint cavity and the degree of hyperintensity in the infrapatellar fat pad was applied to define effusion-synovitis and Hoffa-synovitis, respectively.[22] Nevertheless, the cause for synovitis is not well established; presumably, biomechanical and biochemical factors might be involved. Biomechanically, the synovium, which serves as a membranous organ lining the joint cavity,[23] is susceptible to mechanical pressure applied to the knee joint, and an abnormal biomechanical environment might result in the occurrence of synovitis. Biochemically, the synovium within the knee, containing synovial fibroblasts and macrophages, produces various cytokines,[24] which might interact with surrounding knee structures through cytokine signaling pathways. Additionally, the synovium within the knee, which is rich in blood vessels,[25] is adjacent to the quadriceps. Various myokines released from the quadriceps might crosstalk with synovial tissue at a molecular level.[26] Quadriceps strength serves as an important indicator of quadriceps fitness in the clinic. Once quadriceps fitness is impaired, quadriceps strength tends to decrease and is accompanied by fluctuating myokines. Thus, quadriceps strength could serve as an important indicator of quadriceps status, which might regulate synovitis.

Thus, the primary aim of this study was to explore the association of quadriceps strength with synovitis. The secondary aim was to investigate whether this association was consistent in the population with or without synovitis-driven inflammatory phenotypes. We hypothesized that higher baseline quadriceps strength would be negatively associated with both effusion-synovitis and Hoffa-synovitis longitudinally, and that the association would be specific in the population with synovitis-driven inflammatory phenotypes.

METHODS

Participants. Participants for this study were drawn from the Osteoarthritis Initiative (OAI) database. The OAI is a multicenter, longitudinal, prospective observational study (ClinicalTrials.gov: NCT00080171) containing 4796 adults aged 45 to 79 years with or at risk of KOA. Specific inclusion and exclusion criteria of the OAI have been described previously.[27] Participants were recruited at 4 clinical centers in the United States.

In the current study, we included 1513 knees with or at risk of KOA that had complete records of quadriceps strength and effusion-synovitis and Hoffa-synovitis assessments at baseline; 1361 knees and 1179 knees remained at the 1-year and 2-year follow-ups, respectively. Notably, some subject knees were derived from the same adult, and all subject knees underwent 3.0-T MRI, both at baseline and follow-ups. The study flowchart is shown in the Figure.

Several potential sources of bias were recorded and evaluated. Demographic data on sex, age, race, and BMI were recorded at the enrollment visit. Considering differences in the radiographic OA (ROA) levels, ROA determined by the Kellgren-Lawrence (KL) classification system (KL grade ≥ 2) was included as the adjustment variable. As previous studies have reported that knee alignment might mediate the effects of quadriceps strength, knee alignment degree based on the femorotibial angle (FTA) was also included in our statistical models.[28,29] FTA was assessed during a clinical exam with a goniometer instead of measurement on radiographs. All these data, along with quadriceps strength and effusion-synovitis and Hoffa-synovitis assessment, are available at the OAI public database (https://nda.nih.gov/oai). Measurements collected at the baseline OAI visit, including quadriceps strength, sex, race, age, BMI, and alignment, are publicly available at the OAI database (files: AllClinical00_SAS, version 0.2.3; and Enrollees, version 25). MRI assessment data were derived from centrally performed semiquantitative readings and are available at the OAI database (files: kMRI_SQ_MOAKS_BICL00, version 0.2; kMRI_SQ_MOAKS_BICL01, version 1.2; and kMRI_SQ_MOAKS_BICL03, version 3.2). All MRI assessments in this study were performed during project 22 (Foundation for the National Institutes of Health [FNIH])[30] and project 65 (Pivotal OAI MRI Analyses [POMA]),[31,32] derived from the OAI (https://www.niams.nih.gov/funding/Funded_Research/Osteoarthritis_Initiative). Additionally, specific datasets for central readings of the KL grade included kXR SQ reading (BU), version 0.8 (projects 15 and 37), from the OAI.

Measurement of quadriceps strength. As part of the OAI protocol, maximum isometric quadriceps strength was assessed at baseline using the Good

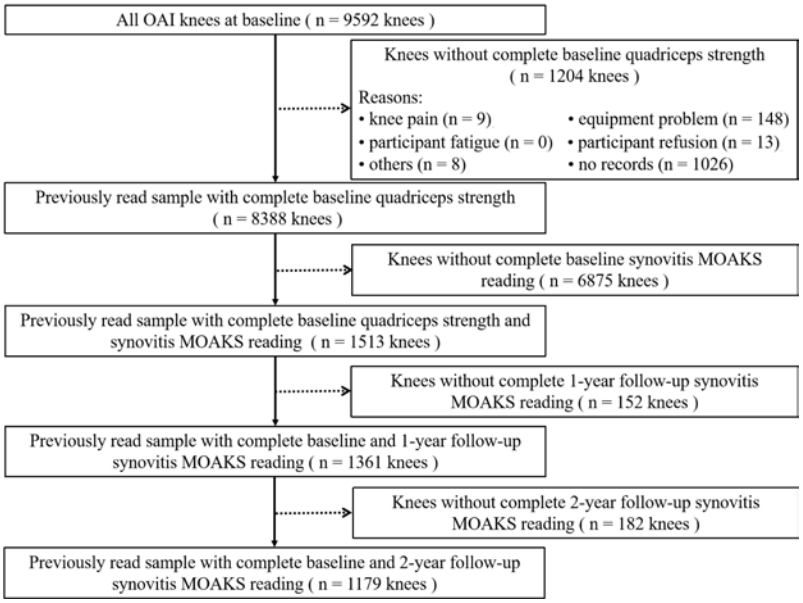

Figure. Flowchart showing participant selection from the OAI cohort. MOAKS: Magnetic Resonance Imaging Osteoarthritis Knee Score; OAI: Osteoarthritis Initiative.

Strength Chair (Metitur Oy).[33] These measurements were performed using the OAI protocol with test-retest reliability (r = 0.88-0.92) by trained OAI personnel. Participants were seated upright, with pelvis and thigh fixated with straps and with the knee in 60° flexion. The transducer was attached 2 cm proximal to the calcaneus. After 2 warm-up trials with 50% effort, 3 repetitions at maximum effort were recorded, and the highest record (N·m) was regarded as the maximum strength. Considering differences in body weight, we normalized maximum strength to body mass (N·m/kg).

Effusion-synovitis and Hoffa-synovitis assessment. MRIs of index knees were performed on the 3T Trio MRI system (Siemens) at the 4 OAI clinical centers. The OAI pulse sequence protocol and the sequence parameters have been previously published in detail.[34]

Two experienced musculoskeletal radiologists (A. Guermazi and F.W. Roemer), who were blinded to the clinical data, read the MRIs according to the Magnetic Resonance Imaging Osteoarthritis Knee Score (MOAKS) system.[22] Effusion-synovitis assessed in the intercondylar region (on axial image) was graded as follows: 0 = normal, 1 = small, 2 = medium, and 3 = large.[22] Hoffa-synovitis assessed in the infrapatellar region (on sagittal image) was graded as follows: 0 = normal, 1 = mild, 2 = moderate, and 3 = severe. The synovitis-driven inflammatory phenotype was defined as effusion-synovitis or Hoffa-synovitis > 0 at baseline. We used the effusion-synovitis and Hoffa-synovitis assessments from the target knee at each visit; change in synovitis was calculated as follows: follow-up score − baseline score. A change < 0 in synovitis was defined as synovitis improvement, a change of 0 in synovitis was defined as synovitis stabilization, and a change > 0 in synovitis was defined as synovitis deterioration. According to previous studies, interrater reliability for Hoffa-synovitis and effusion-synovitis showed good (weighted κ 0.68, 95% CI 0.38-0.99) and near-perfect (weighted κ 0.95, 95% CI 0.61-1.00) agreement, respectively.[35]

Statistical analysis. Subject knee characteristics were summarized with means and frequencies. In primary analyses, the cross-sectional and longitudinal associations of baseline quadriceps strength with effusion-synovitis and Hoffa-synovitis in the whole population were evaluated by univariable and multivariable logistic regression analyses, before and after adjustment for race, age, sex, BMI, ROA, alignment, and baseline synovitis (only for longitudinal analyses). As baseline quadriceps strength might have a different effect on participants with or without the synovitis-driven inflammatory phenotype, inflammation-stratified analyses were performed in this study. The independent-sample t test was used to compare the baseline quadriceps strength between groups with and without the synovitis-driven inflammatory phenotype. Further, multivariable ordinal logistic regressions were used to estimate the associations between baseline quadriceps strength and changes in effusion-synovitis or Hoffa-synovitis, before and after adjustment for race, age, sex, BMI, ROA, and alignment. The linearity in the logistic regression was verified through the linear relationship of quadriceps strength with logits of synovitis changes over 1-year and 2-year follow-ups. Parallel line tests combined with the logit function were performed to examine the proportional odds assumption of ordinal logistic regression. Odds ratios (ORs) and P values were estimated for regression analyses. The generalized estimating equation approach with a robust sandwich estimator was used to account for correlations between 2 knees within an individual. All analyses were performed with SPSS (IBM Corp). Statistical significance was accepted at $P < 0.05$.

Ethical approval. Institutional review boards at all OAI clinical sites and the OAI coordinating center (University of California, San Francisco) approved the OAI study (10–00532); all participants gave written informed consent.

RESULTS

Demographic and clinical characteristics of the subjects studied. A total of 1513 knees from subjects aged between 45 and 79 years were included in this study. Characteristics of the study sample are shown in Table 1. A total of 55% of knees had ROA. Regarding the whole population, the mean alignment was −0.4 (SD 3.9) degrees and the mean quadriceps strength was 1.2 (SD 0.5) N·m/kg. Stratified by presence or absence of synovitis, there was no significant difference in quadriceps strength between the 2 groups. The distribution across MOAKS grades 0, 1, 2, and 3 was 43%, 36.8%, 15%, and 5.2%, respectively, for baseline effusion-synovitis. The distribution across MOAKS grades 0, 1, 2, and 3 was 41.1%, 47.9%, 10.2%, and 0.9%, respectively, for baseline Hoffa-synovitis.

Greater baseline prevalence of ROA was observed in the eligible sample compared with the overall OAI cohort (44% vs 55%). A total of 334 subjects were lost to follow-up because of

Table 1. Baseline characteristics of participants.

	Value
White, %	83.6
Female, %	61
BMI[a]	29.4 (4.7)
Age, yrs	61.9 (8.8)
ROA, %	55
Alignment[b], degrees	–0.4 (3.9)
Effusion-synovitis[c], %	
Grade 0	43
Grade 1	36.8
Grade 2	15
Grade 3	5.2
Hoffa-synovitis[c], %	
Grade 0	41.1
Grade 1	47.9
Grade 2	10.2
Grade 3	0.9
Quadriceps strength, N·m/kg	
Total	1.2 (0.5)
With effusion-synovitis[d]	1.2 (0.5)
Without effusion-synovitis[d]	1.3 (0.5)
With Hoffa-synovitis[e]	1.2 (0.5)
Without Hoffa-synovitis[e]	1.3 (0.5)

Values are mean (SD) unless otherwise specified. [a] BMI is calculated as weight in kilograms divided by height in meters squared. [b] Alignment is measured in degrees (negative values indicate degrees of valgus alignment). [c] Effusion-synovitis and Hoffa-synovitis are graded according to the MOAKS system. [d] Comparison between participants with and without effusion-synovitis. [e] Comparison between participants with and without Hoffa-synovitis. MOAKS: Magnetic Resonance Imaging Osteoarthritis Knee Score; ROA: radiological osteoarthritis.

the lack of MRI. There were no significant differences in demographic factors (ie, sex, BMI, ROA, and alignment) among those with and without follow-up MRI, except for age and race (data not shown).

Associations of quadriceps strength with synovitis in the whole population. Table 2 presents the associations of baseline quadriceps strength with baseline and changes in effusion-synovitis and Hoffa-synovitis in the whole population. In univariable and multivariable analyses, baseline quadriceps strength was negatively associated with baseline effusion-synovitis and follow-up changes in effusion-synovitis (OR 0.77-0.86). For Hoffa-synovitis, baseline quadriceps strength was cross-sectionally associated with baseline Hoffa-synovitis (OR 0.80, 95% CI 0.68-0.93; $P = 0.004$) after adjustment for race, age, sex, BMI, ROA, and alignment. However, this association did not remain significant in the longitudinal analysis.

Associations of quadriceps strength with effusion-synovitis in 2 subpopulations. Table 3 presents associations of baseline quadriceps strength with baseline and changes in effusion-synovitis in the populations with and without existing effusion-synovitis. There was no significant difference in baseline quadriceps strength between the populations with and without existing effusion-synovitis. At baseline, multivariable regression analyses suggested that quadriceps strength was negatively associated with effusion-synovitis in the population with existing effusion-synovitis (OR 0.75, 95% CI 0.61-0.94; $P = 0.01$). Longitudinally, baseline quadriceps strength was significantly associated with effusion-synovitis changes in the population with existing effusion-synovitis at 1-year and 2-year follow-ups, having adjusted for race, age, sex, BMI, ROA, and alignment (1-year follow-up: OR 0.79, 95% CI 0.64-0.97; $P = 0.03$; 2-year follow-up: OR 0.79, 95% CI 0.62-0.99; $P = 0.049$). These significant associations were not observed in the population without existing effusion-synovitis.

Associations of quadriceps strength with Hoffa-synovitis in 2 subpopulations. Table 4 presents associations of baseline quadriceps strength with Hoffa-synovitis in the populations with and without existing Hoffa-synovitis. No significant associations of baseline quadriceps strength with baseline Hoffa-synovitis or with follow-up changes in Hoffa-synovitis were detected in the populations with or without existing Hoffa-synovitis.

DISCUSSION

To our knowledge, this is the first study to explore the cross-sectional and longitudinal association between quadriceps strength and synovitis. We found that higher baseline

Table 2. Associations of baseline quadriceps strength (N·m/kg) with baseline and changes in synovitis in the whole population.

	Changes in Synovitis[a], %			Univariable Regression[b]		Multivariable Regression[b]	
	Deterioration	Stabilization	Improvement	OR (95% CI)	*P*	OR (95% CI)	*P*
Effusion-synovitis							
Baseline	–	–	–	0.86 (0.76-0.97)	0.01	0.85 (0.73-0.90)[c]	0.04
1-year follow-up	17.4	69.7	12.7	0.82 (0.72-0.94)	0.005	0.77 (0.64-0.91)[d]	0.003
2-year follow-up	23.9	63.4	12.6	0.86 (0.75-0.99)	0.047	0.86 (0.71-1.04)[d]	0.12
Hoffa-synovitis							
Baseline	–	–	–	0.97 (0.86-1.09)	0.60	0.80 (0.68-0.93)[c]	0.004
1-year follow-up	4.9	92.8	2.2	0.77 (0.62-0.95)	0.02	0.87 (0.68-1.12)[d]	0.29
2-year follow-up	8.3	88.9	2.8	0.91 (0.76-1.09)	0.30	1.02 (0.81-1.27)[d]	0.90

[a] Changes in synovitis (%) are graded as deterioration, stabilization, and improvement according to the MOAKS system. [b] Generalized estimating equation models were applied. [c] Adjusted for age, sex, race, BMI, ROA, and alignment at baseline for synovitis at baseline. [d] Adjusted for age, sex, race, BMI, ROA, alignment, and synovitis score at baseline for synovitis changes at follow-ups. MOAKS: Magnetic Resonance Imaging Osteoarthritis Knee Score; OR: odds ratio; ROA: radiological osteoarthritis.

Table 3. Associations of baseline quadriceps strength (N·m/kg) with baseline and changes in effusion-synovitis in the 2 subpopulations.

	Changes in Effusion-Synovitis[a], %			OR (95% CI)[b,c]	*P*
	Deterioration	Stabilization	Improvement		
With effusion-synovitis					
Baseline, n = 862	–	–	–	0.75 (0.61-0.94)	0.01
1-year follow-up, n = 762	12.9	64.1	22.8	0.79 (0.64-0.97)	0.03
2-year follow-up, n = 678	18.4	59.5	21.9	0.79 (0.62-0.99)	0.049
Without effusion-synovitis					
Baseline, n = 651	–	–	–	–	–
1-year follow-up, n = 599	23.2	76.7	0.0	0.86 (0.63-1.19)	0.36
2-year follow-up, n = 501	31.3	68.6	0.0	1.27 (0.91-1.76)	0.16

[a] Changes in effusion-synovitis (%) are graded as deterioration, stabilization, and improvement according to the MOAKS system. [b] Generalized estimating equation models were applied. [c] Adjusted for age, sex, race, BMI, ROA, and alignment at baseline. MOAKS: Magnetic Resonance Imaging Osteoarthritis Knee Score; OR: odds ratio; ROA: radiological osteoarthritis.

Table 4. Associations of baseline quadriceps strength (N·m/kg) with baseline and changes in Hoffa-synovitis.

	Changes in Hoffa-Synovitis[a], %			OR (95% CI)[b,c]	*P*
	Deterioration	Stabilization	Improvement		
Hoffa-synovitis					
Baseline, n = 891	–	–	–	0.81 (0.63-1.04)	0.10
1-year follow-up, n = 796	4.7	91.7	3.7	0.78 (0.58-1.05)	0.11
2-year follow-up, n = 701	6.6	88.7	4.7	0.89 (0.67-1.20)	0.45
Without Hoffa-synovitis					
Baseline, n = 622	–	–	–	–	–
1-year follow-up, n = 621	5.3	94.7	0.0	1.12 (0.69-1.83)	0.65
2-year follow-up, n = 479	10.9	89.1	0.0	1.25 (0.83-1.86)	0.29

[a] Changes in Hoffa-synovitis (%) are graded as deterioration, stabilization, and improvement according to the MOAKS system. [b] Generalized estimating equation models were applied. [c] Adjusted for age, sex, race, BMI, ROA, and alignment at baseline. MOAKS: Magnetic Resonance Imaging Osteoarthritis Knee Score; OR: odds ratio; ROA: radiological osteoarthritis.

quadriceps strength was negatively associated with baseline effusion-synovitis and follow-up changes in effusion-synovitis, but no significant association was observed in terms of Hoffa-synovitis. Stratified by the synovitis-driven inflammatory phenotype, there exists cross-sectional and longitudinal associations between baseline quadriceps strength and effusion-synovitis in the population with existing effusion-synovitis. However, we did not find similar associations in the population with existing Hoffa-synovitis. Our findings suggest that baseline quadriceps strength may play an essential role in regulating effusion-synovitis, especially in the population with existing effusion-synovitis.

An increasing body of evidence supports the mediated role of inflammation in KOA pathogenesis[20]; inflammatory phenotype seems to be an important reference for clinical targeted therapy of KOA. As an important dynamic stabilizer, traditionally, the quadriceps has been found to reduce overloading and maintain intraarticular biomechanical balance.[16] With recent advances in knowledge about the inflammation-regulating function of skeletal muscle, myokines (eg, irisin, TNF, and IL-6) secreted from muscle are thought to be important inflammation-regulating chemicals in KOA.[17-19,26] Wang et al[18] reported that irisin could exert chondroprotective actions through inhibition of the inflammatory pathway. Rainbow et al[36] also reported the role of muscle in cartilage homeostasis through inflammatory pathways at a genetic level. However, it is a pity that knee inflammation has received less attention regarding the quadriceps mechanism. As typical signs of knee inflammation, effusion-synovitis and Hoffa-synovitis, assessed by MRI, are thought to be important imaging markers of KOA.[35] In a cross-sectional analysis of 105 participants, Knoop et al[37] found that quadriceps strength was significantly associated with effusion-synovitis. However, the cross-sectional results could not delineate potentially causal relationships between quadriceps strength and effusion-synovitis. Based on the above evidence, we could conjecture that quadriceps strength could regulate synovitis through antiinflammatory myokines in KOA to some extent.

In order to explore the association of quadriceps strength with synovitis, this study set baseline quadriceps strength as the key exposure, which is the most accessible marker to represent muscle fitness in clinical practice. In addition, both effusion-synovitis and Hoffa-synovitis were included as primary outcomes in the analyses. Our study first demonstrated the significant and negative association between quadriceps strength and changes in effusion-synovitis. This indicates that higher baseline quadriceps strength may have a protective effect on

effusion-synovitis. Quadriceps strength has been suggested to be closely associated with patella trajectory,[38] and quadriceps weakness might lead to abnormal friction and stress within the patellofemoral joint, which consequently influence synovium inflammation. Additionally, the synovium is a richly vascularized tissue[39] that is adjacent to quadriceps. It may be that some myokines secreted from the quadriceps are protective and interact with the synovium in an endocrine manner to exert an antiinflammatory function.[40]

Interestingly, experimental knee effusion has also been reported to impair quadriceps muscle function inversely.[41-43] Palmieri-Smith et al[41,42] reported that both experimental effusion and pain could induce quadriceps dysfunction and alter knee joint mechanics. A further study reported that experimental effusion did not lead to changes in corticomotor excitability, though quadriceps activation decreased.[43] Thus, the underlying mechanism is still unknown. We would like to attribute this contradiction with our findings to the cause of disease. For patients with posttraumatic KOA or experimental effusion, quickly increasing effusion may inhibit quadriceps function in the short term. In the long term, however, our results showed that loss of quadriceps strength preceded increasing effusion-synovitis naturally. In view of this, more strategic rehabilitation plans, such as eccentric contraction strength training and nutritional supplementation, need to be recommended in the early course of KOA before effusion accumulation.

Further, it is likely that higher quadriceps strength played distinct roles in the participants with and without existing effusion-synovitis. In an inflammation-stratified analysis, we found that higher baseline quadriceps strength was negatively associated with effusion-synovitis changes in the population with existing effusion-synovitis compared to the population without existing effusion-synovitis. However, no significant difference in baseline quadriceps strength was observed between these 2 groups. These results suggest that baseline quadriceps strength might not be the trigger but the buffer for existing effusion-synovitis. This might also provide a clue about the insignificant improvements in pain reported in a previous high-quality randomized controlled trial, which compared the effect of high-intensity vs low-intensity strength training on knee pain.[13] Compared with normal knees, the stability of ligaments and joint capsules tends to be impaired among the population with the inflammatory phenotype, which underlines the buffering role of quadriceps strength in KOA. Additionally, myokines released from the quadriceps could be helpful in treating inflammation. Thus, our results indicate that quadriceps strength training was especially warranted for patients with the inflammatory phenotype, whereas it could also be recommended to other populations to increase their strength reserve.

Likewise, we have also explored Hoffa-synovitis, but no significant association between baseline quadriceps strength and follow-up changes in Hoffa-synovitis was observed in the primary or inflammation-stratified analyses. Our results suggest that the effect of quadriceps strength is reflected mainly in effusion-synovitis, which may be related to the anatomically adjacent relationship between the synovium and the surrounding structures. The infrapatellar fat pad is a more independent unit. Compared to the infrapatellar fat pad, the synovium within the suprapatellar bursa seems to be more easily affected by muscle pull, which provides clues concerning the mechanism underlying the effect of the quadriceps on synovitis. Moreover, the OR values were similar between the effusion-synovitis and Hoffa-synovitis analyses, although no statistically significant associations were observed in the latter analyses. This may be due to the low rate of Hoffa-synovitis change in our sample. Therefore, we also acknowledge that the results of our analysis must be interpreted with caution; in addition, more long-term studies are needed that focus on Hoffa-synovitis.

The strength of this study is that we explored the longitudinal associations between quadriceps strength and synovitis using a large sample. There are also some limitations that need to be addressed in this study. First, we were unable to measure quadriceps fitness directly in our study. However, we used isometric quadriceps strength as a functional indicator for quadriceps fitness, which is the most accessible measure in the clinic. More indicators reflecting quadriceps fitness should be included in future investigations. Second, we did not measure quantitative effusion-synovitis, which could be more sensitive to change. Although we did not adopted quantitative methods to assess synovitis, we used the MOAKS system, a widely accepted semiquantitative scoring system, to evaluate synovitis and improve the generalizability of this study. Third, selection bias may exist in this study in terms of disease severity, since the eligible sample was derived from FNIH and POMA projects, which used nested case-control design, potentially increasing the ratio of cases. Given the exploratory nature of this study, further studies are needed to evaluate our results in other cohorts, though a variety of factors (ie, age, sex, BMI, race, ROA, and alignment) have been adjusted for in the analyses. Further, in our study, we only included participants with complete research data. As a result of limited records, there were a large number of subjects excluded without specific reasons. Therefore, the findings should be generalized with caution. Finally, all of our analyses were limited in terms of the 2-year follow-ups, and future studies should assess the effect of quadriceps strength in the longer term.

In conclusion, higher baseline quadriceps strength was negatively associated with changes in effusion-synovitis but not in Hoffa-synovitis, especially in the population with existing effusion-synovitis. Although the associations were not fully consistent, quadriceps strength appears to have a buffering role for effusion-synovitis among the population with the effusion-synovitis–driven inflammatory phenotype.

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REFERENCES

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393:1745-59.
2. Li J, Zhu Z, Li Y, et al. Qualitative and quantitative measures of prefemoral and quadriceps fat pads are associated with incident

radiographic osteoarthritis: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2020;28:453-61.
3. Neogi T. The epidemiology and impact of pain in osteoarthritis. Osteoarthritis Cartilage 2013;21:1145-53.
4. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172-80.
5. Hunter DJ, Schofield D, Callander E. The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol 2014;10:437-41.
6. Culvenor AG, Ruhdorfer A, Juhl C, Eckstein F, Øiestad BE. Knee extensor strength and risk of structural, symptomatic, and functional decline in knee osteoarthritis: a systematic review and meta-analysis. Arthritis Care Res 2017;69:649-58.
7. Øiestad BE, Juhl CB, Eitzen I, Thorlund JB. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. Osteoarthritis Cartilage 2015;23:171-7.
8. Kemnitz J, Wirth W, Eckstein F, Ruhdorfer A, Culvenor AG. Longitudinal change in thigh muscle strength prior to and concurrent with symptomatic and radiographic knee osteoarthritis progression: data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2017;25:1633-40.
9. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2020;72:149-62.
10. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. JAMA 2021;325:568-78.
11. Fernandes L, Hagen KB, Bijlsma JWJ, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis 2013;72:1125-35.
12. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363-88.
13. Messier SP, Mihalko SL, Beavers DP, et al. Effect of high-intensity strength training on knee pain and knee joint compressive forces among adults with knee osteoarthritis: the START randomized clinical trial. JAMA 2021;325:646-57.
14. Holm PM, Schrøder HM, Wernbom M, Skou ST. Low-dose strength training in addition to neuromuscular exercise and education in patients with knee osteoarthritis in secondary care - a randomized controlled trial. Osteoarthritis Cartilage 2020;28:744-54.
15. Mobasheri A, Rayman MP, Gualillo O, Sellam J, van der Kraan P, Fearon U. The role of metabolism in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2017;13:302-11.
16. Segal NA, Glass NA, Felson DT, et al. Effect of quadriceps strength and proprioception on risk for knee osteoarthritis. Med Sci Sports Exerc 2010;42:2081-8.
17. Chen W, Wang L, You W, Shan T. Myokines mediate the cross talk between skeletal muscle and other organs. J Cell Physiol 2021;236:2393-412.
18. Wang FS, Kuo CW, Ko JY, et al. Irisin mitigates oxidative stress, chondrocyte dysfunction and osteoarthritis development through regulating mitochondrial integrity and autophagy. Antioxidants 2020;9:810.
19. He Z, Li H, Han X, et al. Irisin inhibits osteocyte apoptosis by activating the Erk signaling pathway in vitro and attenuates ALCT-induced osteoarthritis in mice. Bone 2020;141:115573.
20. Pelletier JP, Martel-Pelletier J, Abramson SB. Osteoarthritis, an inflammatory disease: potential implication for the selection of new therapeutic targets. Arthritis Rheum 2001;44:1237-47.
21. Hayashi D, Roemer FW, Katur A, et al. Imaging of synovitis in osteoarthritis: current status and outlook. Semin Arthritis Rheum 2011;41:116-30.
22. Hunter DJ, Guermazi A, Lo GH, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011; 19:990-1002.
23. Yoshitomi H. Regulation of immune responses and chronic inflammation by fibroblast-like synoviocytes. Front Immunol 2019;10:1395.
24. Yang Y, Wang Y, Kong Y, et al. Carnosine prevents type 2 diabetes-induced osteoarthritis through the ROS/NF-κB pathway. Front Pharmacol 2018;9:598.
25. Rocha FAC, Silva Jr FS, Leite ACRM, et al. Tadalafil analgesia in experimental arthritis involves suppression of intra-articular TNF release. Br J Pharmacol 2011;164:828-35.
26. Krishnasamy P, Hall M, Robbins SR. The role of skeletal muscle in the pathophysiology and management of knee osteoarthritis. Rheumatology 2018;57:iv22-33.
27. Ruhdorfer A, Wirth W, Eckstein F. Relationship between isometric thigh muscle strength and minimum clinically important differences in knee function in osteoarthritis: data from the Osteoarthritis Initiative. Arthritis Care Res 2015;67:509-18.
28. Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. Arthritis Rheum 2008;59:943-51.
29. Sharma L, Dunlop DD, Cahue S, Song J, Hayes KW. Quadriceps strength and osteoarthritis progression in malaligned and lax knees. Ann Intern Med 2003;138:613-9.
30. Hunter DJ, Nevitt M, Losina E, Kraus V. Biomarkers for osteoarthritis: current position and steps towards further validation. Best Pract Res Clin Rheumatol 2014;28:61-71.
31. Roemer FW, Kwoh CK, Hannon MJ, et al. What comes first? Multitissue involvement leading to radiographic osteoarthritis: magnetic resonance imaging-based trajectory analysis over four years in the osteoarthritis initiative. Arthritis Rheumatol 2015; 67:2085-96.
32. Roemer FW, Kwoh CK, Hannon MJ, et al. Can structural joint damage measured with MR imaging be used to predict knee replacement in the following year? Radiology 2015;274:810-20.
33. Ruhdorfer A, Wirth W, Hitzl W, Nevitt M, Eckstein F. Association of thigh muscle strength with knee symptoms and radiographic disease stage of osteoarthritis: data from the Osteoarthritis Initiative. Arthritis Care Res 2014;66:1344-53.
34. Peterfy CG, Schneider E, Nevitt M. The Osteoarthritis Initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008;16:1433-41.
35. Atukorala I, Kwoh CK, Guermazi A, et al. Synovitis in knee osteoarthritis: a precursor of disease? Ann Rheum Dis 2016; 75:390-5.
36. Rainbow RS, Kwon H, Foote AT, Preda RC, Kaplan DL, Zeng L. Muscle cell-derived factors inhibit inflammatory stimuli-induced damage in hMSC-derived chondrocytes. Osteoarthritis Cartilage 2013;21:990-8.
37. Knoop J, Dekker J, Klein JP, et al. Biomechanical factors and physical examination findings in osteoarthritis of the knee: associations with tissue abnormalities assessed by conventional radiography and high-resolution 3.0 Tesla magnetic resonance imaging. Arthritis Res Ther 2012;14:R212.
38. Lin F, Wilson NA, Makhsous M, et al. In vivo patellar tracking induced by individual quadriceps components in individuals with patellofemoral pain. J Biomech 2010;43:235-41.

39. Roemer FW, Guermazi A, Felson DT, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis 2011;70:1804-9.
40. Huh JY. The role of exercise-induced myokines in regulating metabolism. Arch Pharm Res 2018;41:14-29.
41. Palmieri-Smith RM, Kreinbrink J, Ashton-Miller JA, Wojtys EM. Quadriceps inhibition induced by an experimental knee joint effusion affects knee joint mechanics during a single-legged drop landing. Am J Sports Med 2007;35:1269-75.
42. Palmieri-Smith RM, Villwock M, Downie B, Hecht G, Zernicke R. Pain and effusion and quadriceps activation and strength. J Athl Train 2013;48:186-91.
43. Lepley AS, Bahhur NO, Murray AM, Pietrosimone BG. Quadriceps corticomotor excitability following an experimental knee joint effusion. Knee Surg Sports Traumatol Arthrosc 2015;23:1010-7.