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Disease severity and knee extensor force in knee osteoarthritis: Data from the Osteoarthritis Initiative

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Abstract

Objective—To determine whether the method of disease severity measurement influences the magnitude of knee extensor force deficits in knee osteoarthritis (OA).

Methods—Data from the Osteoarthritis Initiative (n = 659) were analyzed. Knee extensor force was assessed with isometric contractions. Clinical severity was measured with the Western Ontario and McMaster Osteoarthritis Index (WOMAC). Patients were stratified into tertiles of severity (i.e. moderate, mild and severe OA), based on lowest, middle and highest WOMAC scores. Kellgren-Lawrence grading (KLG) was used to assess radiographic severity of the tibiofemoral compartment and patients were again stratified into mild (KLG<2), moderate (KLG = 2) and severe (KLG>2) knee OA.

Results—When stratifying with WOMAC, force was significantly lower in severe compared to mild (~18% lower, p<0.001) and moderate (~9% lower, p = 0.03) groups and in moderate compared to mild group (~10% lower, p = 0.03). When stratifying with KLG, small, non-significant differences were observed in the severe (~7% lower, p = 0.19) and moderate (~8% lower, p = 0.08) compared to mild group. Large intra-group variability was observed when comparing WOMAC score across radiographic severity (coefficients of variation were 79.3%, 74.6% and 61.6% for KLG<2, KLG = 2 and KLG>2, respectively).

Conclusion—The method of disease severity stratification influences the magnitude of knee extensor force deficits as no difference in force between disease subgroups was observed when stratifying with KLG. Furthermore, there was large variability in WOMAC score within each radiographic subgroup, highlighting the limitations in using radiographic measures to reflect symptom severity.

The relationship between radiographic and clinical features of knee osteoarthritis (OA) is equivocal with some studies reporting a discordance between radiographic and clinical severity (1, 2), and others observing modest-to-strong associations (3–5). The continued examination of the relationship between clinical and radiographic knee OA is necessary because 1) the definition of disease severity status using a composite index of pain,

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Conflict of Interest
None

structural and functional features has been identified as a means of developing valid outcome measures for clinical trials (6), 2) stratification of patients in descriptive and randomized studies is commonly performed using radiographic criteria in isolation or combined with clinical criteria (7) and 3) X-rays are perceived to be helpful in making management decisions by clinicians (8, 9).

Discordance between clinical and radiographic severity has potential consequences including adding undesirable heterogeneity to study groups (e.g. severe clinical but mild radiographic disease) and serving as a confounding influence when considering patient care. Duncan et al. (4) reported a moderate association between radiographic disease severity defined by Kellgren-Lawrence grade (KLG) and clinical severity measured with the Western Ontario and McMaster Osteoarthritis Index (WOMAC). This suggests that the use of either tool to define disease severity should affect an outcome measure similarly (i.e. the value of an outcome measure should be similar regardless of disease definition), although this type of investigation has yet to be undertaken. Others have reported that KLG is a poor predictor of clinically relevant outcomes, including WOMAC (10, 11). Therefore, it remains unclear how the method of disease severity stratification (i.e. radiographic vs. clinical) affects common outcomes in knee OA research.

Knee extensor force is a clinically relevant outcome measure, which is correlated with pain and function (12, 13). Knee extensor muscles are weaker in knee OA compared to healthy-contralateral limbs or age-matched controls (14). Recently, knee extensor weakness was observed across a radiographic spectrum of knee OA, however no difference in force was noted between those with KLG = 2 and those with KLG >2, suggesting that this method provides limited information about how muscle strength is affected across a spectrum of OA (15). The magnitude of muscle weakness across a clinical spectrum of knee OA has yet to be assessed. The purpose of this study was to determine whether the method of disease severity measurement (i.e. clinical versus radiographic) influences the magnitude of knee extensor force deficits in participants with knee OA. A secondary purpose was to further examine the relationship between WOMAC and KLG as they are two commonly used severity measures in the OA literature.

Patients and Methods

Data for the analysis of tibiofemoral (TF) knee OA was obtained from the public use datasets (version 0.2.2 clinical dataset) of the Osteoarthritis Initiative (OAI; online at www.oai.ucsf.edu), a multicentre, longitudinal cohort study designed to identify biomarkers for the development and progression of symptomatic knee OA. The OAI dataset comprises demographic, clinical and imaging data on 4796 patients (age 45–79) from four centres. Only baseline data from tibiofemoral (TF) compartment of native (i.e. non-replaced) right knees of the progression sub-cohort were analyzed in this study. Eligibility for the progression sub-cohort was based on the presence of pain, aching or stiffness in or around the knee for at least one month during the last 12 months and the presence of TF osteophytes (Osteoarthritis Research Society International atlas, grade ≥ 1) (16), on a posterio-anterior fixed-flexion knee X-ray. A description of the rationale for these criteria and a full list of exclusion criteria can be found on the OAI website (www.oai.ucsf.edu/datarelease/OperationsManuals.asp). Other inclusion criteria were the availability of baseline KLG and completion of three trials of isometric knee extension testing. After excluding patients failing to meet the inclusion criteria, the analysis was conducted on 659 participants. Institutional review board approval was obtained at the participating sites (Baltimore, MD; Columbus, OH; Pittsburgh, PA, and Pawtucket, RI) and written informed consent was obtained from each participating subject.

Measurement of clinical severity

WOMAC is a cross-culturally validated and reliable instrument encompassing three domains of disease status (pain, stiffness and function), which is used as an outcome measure in interventional trials (17). Self-reported scales such as WOMAC have been used previously to establish absolute cutoff scores to be used to predict clinically meaningful endpoints such as suitability for total knee arthroplasty (18). Accordingly, we employed WOMAC as an independent variable to stratify subjects into study groups based on clinical disease severity. The WOMAC Likert version 3.1 has 24 items and is divided into pain, stiffness and function domains. Each item has 5 response options (none, mild, moderate, severe, extreme) corresponding to scores 0–4, with higher scores indicating increasing severity. In order to compare knee extensor force across a clinical spectrum of OA, WOMAC was used as an independent variable whereby total score (24 items, total score 0–96) was used to stratify study participants into tertiles with the lowest, middle and highest groups representing mild, moderate and severe knee OA, respectively. In order to compare the relationship between WOMAC and KLG, WOMAC total score and pain and function subscale scores (pain: 5 items, total score 0–20, function: 17 items, total score 0–68) were used as dependent variables across a radiographic spectrum of knee OA.

Measurement of radiographic disease severity

KLG was used to assess radiographic severity semi-quantitatively (19). KLG is performed using a 5 point scale where 0 = no changes, 1 = doubtful narrowing of joint space and possible osteophytic lipping, 2 = definite osteophytes, definite joint space narrowing, 3 = moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour and 4 = large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour (20). KLG<2 was designated mild OA, KLG = 2 as moderate OA and KLG>2 as severe OA (21). It should be noted that it is common in the literature to classify participants with KLG<2 as healthy controls (i.e. OA is absent, (12, 13, 15). However, in order to be included in the progression sub-cohort of the OAI dataset criteria that reflect the disease process more comprehensively were used (i.e. pain and radiographic findings), thus even participants with KLG<2 had evidence of knee OA and were considered to be “mild”. Standing posterio-anterior radiographs were acquired using the fixed-flexion protocol, described previously.(22) Briefly, bilateral X-rays were acquired with the patient standing with knees flexed 20–30 degrees and feet internally rotated 10 degrees. Patient positioning was fixed using a plexiglass positioning frame (SyanFlexer, Synarc). Further details can be downloaded at www.oai.ucsf.edu/datarelease/OperationsManuals.asp. Reliability of KLG was assessed (2 blinded readers) on a subset of the progression cohort with a weighted kappa = 0.88 (95%CI 0.82–0.94).

Measurement of isometric knee extensor force

Participants completed brief isometric knee extension maximal voluntary contractions (MVC) to measure maximal knee extensor force. The individual trial with the highest force output was used to represent maximal force. Knee extensor force in the OAI dataset was assessed with the Good Strength apparatus (Metitur, Jyväskylä, Finland). Briefly, patients were positioned upright in a chair. The back of the chair was moved forward to support the participant's back, The force transducer was secured behind the participant's right ankle with a velcro strap (2 cm above the calcaneus) and a goniometer was used to position the leg at 60 degrees from full extension, using the lateral joint line as the axis. Straps were positioned around the participants' hips and across the test leg. Two submaximal practice trials were completed, followed by 3 MVCs (~3 s in duration), each separated by 30 s. A complete description of the protocol and data collection process can be downloaded at www.oai.ucsf.edu/datarelease/OperationsManuals.asp. It should be noted that isometric

knee extensor force, WOMAC score and KLG were all measured in the same knee for each participant.

Statistical analysis

The relationship between the dependent variable (force) and possible covariates was determined with Pearson correlation coefficient (except for sex, where the Spearman rank correlation coefficient was used). Two one-way randomized ANCOVAs were performed to rule out the possibility that observed differences in force between disease severity states were due to covariate effects; one for WOMAC stratification and one for KLG stratification. Post-hoc differences between disease subgroups were evaluated with the Tukey's honestly significant difference test for both clinical and radiographic disease stratification methods. The Kruskal-Wallis test with post-hoc Dunn's multiple comparisons test was used to determine between group differences for WOMAC total and subscale scores (excluding stiffness subscale) for radiographic severity. Level of significance was set at $p<0.05$. All descriptive data are reported using means ± standard deviation. Statistics were performed using SPSS Version 17.0 (Chicago, IL).

Results

Basic demographic information for all participants is listed in Table 1. Mean force values for WOMAC and KLG stratification are listed in Table 2. When comparing knee extensor force across WOMAC groups, a significant difference was observed ($p<0.001$). With post hoc testing, a significant difference was observed for: moderate versus mild groups (~ 9% lower in moderate, $p = 0.03$, 95% confidence interval 4 – 63 N), severe versus mild groups (~18% lower in severe, $p<0.001$, 95% confidence interval 38 – 96 N) and severe versus moderate groups (~10% lower in severe, $p = 0.03$, 95% confidence interval 4 – 64 N). In order to determine whether these differences were due to covariate effects, study parameters significantly correlated with knee extensor strength were included in an ANCOVA. Age ($r = −0.29$), height ($r = 0.51$), body mass ($r = 0.37$) and sex ($r = 0.60$) were all significantly correlated with knee extensor force ($p<0.001$). BMI was not significantly correlated with knee extensor force ($p = 0.08$). The significant difference observed for WOMAC groups persisted when controlling for age, height, body mass and sex ($p<0.001$).

For stratification with KLG a significant difference existed for all groups ($p = 0.007$), however this significant difference did not persist when controlling for covariates with ANCOVA ($p = 0.09$). The small differences observed between severe and mild groups (~7% lower force in the severe group, $p = 0.19$, 95% confidence interval −8 – 56 N) and between the moderate and mild groups (~8% lower force in the moderate group, $p = 0.08$, 95% confidence interval −3 – 67 N), were not statistically significant with post hoc testing. Furthermore, the moderate and severe groups had nearly identical forces (Table 2).

The values for pain subscale, function subscale and total WOMAC score across a spectrum of radiographic severity are listed in Table 3. A significant difference for total WOMAC score ($p = 0.0002$), and pain ($p = 0.0007$) and function ($p = 0.0007$) subscale scores was observed. Although differences were significant there was variability in WOMAC score across radiographic severity. Coefficients of variation for total WOMAC scores for mild, moderate and severe OA were 79.3%, 74.6% and 61.6%, respectively.

Discussion

The results of this study suggest that the method of disease severity stratification influences the outcome of studies measuring knee extensor force in knee OA. Furthermore, it appears that using KLG is limited as a severity stratification method, such that differences in force

between radiographically mild, moderate and severe patients were small and not significant. Finally, although participants with worsening radiographic severity tended to have more severe symptoms, there was large variability in clinical severity across radiographically homogeneous subgroups. This suggests that patients with radiographically severe knee OA may have a wide range of symptom severity, making it difficult for clinicians to reconcile clinical and radiographic findings.

Stratification of a knee OA study sample using WOMAC scores allowed for clinically homogeneous subgroups. Thus, it was apparent that quadriceps muscle weakness occurs across a clinical spectrum of knee OA. While it is well established that quadriceps muscles in knee OA are weaker than healthy controls or contralateral knees (14, 23–26), the progression of quadriceps weakness in knee OA had not previously been examined from a clinical perspective. From our observations, it is clear that weakness occurs across a disease spectrum. Conversely, we observed that force differences between moderate and severe radiographic groups were small and non-significant compared to the mild group. Palmieri-Smith et al. (15) reported that the knee extensors of those with KLG ≥ 2 were approximately 20% weaker than a group with KLG <2, however there was no difference between those with KLG = 2 and KLG >2. Similarly, we observed that knee extensor force was nearly identical in participants with KLG = 2 and KLG>2 (Table 2). Taken together, these results suggest that using KLG to stratify knee OA patients on the basis of radiographic severity does not adequately reflect the magnitude of knee extensor weakness experienced by patients with severe clinical knee OA. Brandt et al. (27) reported no difference in quadriceps strength between those with stable versus progressive radiographic knee OA over 2.5 years, however it is possible that differences were masked because radiographic stratification provides limited information about muscle strength.

The observation that knee extensor force is lowest in those with the highest WOMAC scores (i.e. most severe symptoms) is consistent with our understanding of the mechanisms of knee extensor muscle weakness in knee OA. Knee extensor weakness in knee OA is likely due to a combination of disuse atrophy and reduced voluntary activation due to pain (for a review see reference 28). As WOMAC score is dependent in part on the participant's perceived level of pain, it follows that the mechanism for lower force in this group could be due to joint pain and subsequent decrease in activation of the quadriceps, although this needs to be substantiated. Other factors that could contribute to lower force in this subgroup include joint effusion, laxity or structural damage which can cause reduced strength even in the absence of pain (24, 29, 30). As the degree of muscle impairment may be different across a clinical spectrum of disease, it is possible that the mechanism of weakness is also different. There is some evidence to suggest that muscle weakness in early knee OA may be from disuse atrophy, while deficits in voluntary activation have been reported in more severe disease (31, 32), although this needs to be substantiated.

We also observed that deficits in force were of a higher magnitude when patients were stratified clinically. Specifically force deficits in severe OA compared to mild were twofold higher when stratifying clinically compared to radiographically (~19% difference versus ~7–8% difference). This finding is not surprising considering the tenuous relationship that has been reported between radiographic findings and quadriceps muscle weakness (33–35). Recent reports have illustrated that quadriceps weakness is not associated with isolated patellofemoral and tibiofemoral OA in men (35), does not predict incident radiographic OA (34) and is not a risk factor for cartilage loss measured semi-quantitatively with MRI (33). Therefore, it is clear that disease severity stratification method influences the measurement of knee extensor force deficits in knee OA.

Similar to Duncan et al. we observed WOMAC score (both total and subscale scores) of increasing severity for worsening of KLG (21). An association between these two commonly used measurement tools supports their utility for disease severity stratification in large population studies. However, to our knowledge we are the first to report on the variability of WOMAC scores for individual participants in the KLG groups. The high coefficients of variation for total WOMAC score (>60% variation in total WOMAC score for each group) have implications not only for outcome measurement, but also for individual patient care. Bedson et al. (9) reported that primary care physicians were less likely to refer patients with knee pain to a physiotherapist and more likely to refer to an orthopedic surgeon when X-rays were positive for knee OA, regardless of clinical severity. As the relevance of radiographic findings to the individual patient is variable, this has the potential to impact on patient management.

Interpretation of this data is limited by several factors. First, the cross-sectional design employed herein does not allow for determination of temporality of the relationship between muscle weakness and disease severity. Therefore, it is unclear if muscle weakness precedes or is a result of worsening symptoms. Another limitation of this study was the use of ordinal measurement tools for clinical and radiographic disease severity. In particular, KLG has been criticized because the magnitude of difference between the grades may not be equal (19). Furthermore, Schipof et al. (7, 36) reported that there is a discrepancy between studies on how KLG is implemented (e.g. 5/11 studies reviewed in their article defined KLG = 2 as having definite osteophytes), making inter-study comparison difficult. The use of novel quantitative and semi-quantitative scoring systems based on MRI of the knee joint is becoming increasingly popular and is more sensitive to structural progression than plain films (37). It is possible that WOMAC is better correlated with MRI measures of disease incidence and progression, although some studies have reported weak or no associations (38, 39). Moreover, many of these measurement tools have yet to be validated in clinical studies, and the use of radiographs for disease stratification and as an outcome measure is still widespread.

A further limitation is that data in this study are limited to the TF compartment. Associations have also been observed between KLG for the patellofemoral (PF) compartment and WOMAC (21) and it is possible that knee extensor force is affected to a greater degree in PF disease. Large population studies have observed significant associations between quadriceps muscle weakness and progression of PF OA, particularly of the lateral PF compartment (33, 40). A potential mechanism has also been postulated whereby weak quadriceps (particularly the vastus medialis) allows for lateral tracking of the patella during activity (40). The relationships between clinical and radiographic measures observed in our study may have been stronger and less variable if PF OA was incorporated into the analysis.

In conclusion, we observed that clinical as opposed to radiographic measures for disease severity stratification may provide more robust information when measuring knee extensor force in patients with knee OA. Additionally, the variability in clinical severity in those with mild, moderate and severe radiographic knee OA suggests that patients with radiographically severe knee OA may have a wide range of symptom severity. Thus, it may be difficult to reconcile clinical and radiographic findings in individual patients.

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Significance and Innovations

- The criteria used to stratify disease severity (i.e. clinical versus radiographic) in studies of knee osteoarthritis influence the magnitude of reported knee extensor force deficits.
- Stratification for disease severity using Kellgren-Lawrence grading is of limited utility when describing the relationship between disease severity and knee OA, as no difference in force between subgroups was observed.
- Although participants with greater radiographic severity tended to have more severe symptoms, there was large variability in clinical severity across radiographically homogeneous subgroups. This suggests that patients with radiographically severe knee OA may have a wide range of symptom severity.

Table 1

Patient characteristics.

n	659
Age	61.4±9.0 (45:79)
Height (m)	1.69±0.09 (1.48:1.90)
Weight (kg)	85.5±16.4 (48.8:131.4)
Body Mass Index (kg/m^2)	29.9±5.0 (19.5:48.7)
Sex (male/female)	289/370

Data are presented as mean ± standard deviation. Data in parentheses indicate minimum: maximum.

Table 2

Isometric knee extensor force across clinical and radiographic spectra of tibiofemoral knee OA. Values for force are in N.

Classification Variable	Mild	Moderate	Severe	p-value
WOMAC	374±140	341±137 *	307±135 *†	<0.0001
KLG	363±147	331±140	338±1.34	>0.007

WOMAC: Western Ontario and McMaster Osteoarthritis Index; KLG: Kellgren-Lawrence grading of the tibiofemoral joint. For the WOMAC classification variable, participants were stratified into severity groups based on tertiles of WOMAC score. For KLG classification variables KLG<2, KLG=2 and KLG>2 represented mild, moderate and severe radiographic disease respectively. Data are presented as mean ± standard deviation.

* Significantly different than mild OA with post hoc testing ($p<0.05$).

† Significantly different than moderate OA with post hoc testing ($p<0.05$).

Table 3

WOMAC scores across tibiofemoral osteoarthritis disease severity measured by KLG.

Classification Variable	KLG<2	KLG = 2	KLG>2	p-value
Pain	3.97±3.47	4.70±3.87	5.20±3.56 *	0.0007
Function	12.25±10.87	15.50±12.76	16.40±11.20 *	0.0007
Total	18.4±14.6	23.1±17.2 *	24.7±15.2 *	0.0002

WOMAC: Western Ontario and McMaster Osteoarthritis Index; KLG: Kellgren-Lawrence grade. Data are presented as mean±standard deviation.

* Significantly different than KLG<2