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Defining and Evaluating a Novel Outcome Measure Representing End-Stage Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Abstract

Objective—We described a definition of end-stage knee osteoarthritis (esKOA) and evaluated its association with health outcomes and osteoarthritis risk factors.

Method—We included Osteoarthritis Initiative participants with or at-risk for knee osteoarthritis who had complete baseline data. We defined esKOA by adapting a validated appropriateness algorithm for total knee replacement based on data from baseline and the first 4 follow-up visits. We performed person-based analyses, including both knees from all participants. Participants met the definition of esKOA at the visit at which ≥1 knees reached the esKOA criteria. We assessed differences in individual characteristics between groups at baseline and over time; and tested if

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ETHICAL STANDARDS

Institutional review boards at each OAI clinical site and the OAI coordinating center (University of California, San Francisco) approved the OAI study and all participants provided informed consent prior to participating in the OAI.

CONFLICT OF INTEREST

The authors declare they have no conflicts of interest with regard to this work.

incident esKOA (outcome) was associated with osteoarthritis risk factors (e.g. age, maximum adult weight, quadriceps strength).

Results—The cohort consisted of 3916 participants with mean age of 61 (SD=9) years, and mean body mass index of 28.4 (4.7) kg/m^2; 59% were female, and 9.7% developed incident esKOA. Those with incident esKOA had poorer health outcomes at baseline and greater declines in health outcomes, with the exception of SF-12 mental health score. Five out of 9 tested risk factors were associated with incident esKOA in unadjusted analyses, with older age (≥65 years; odds ratio=1.44, 95% confidence interval=1.19 to 1.83) and quadriceps weakness (odds ratio=0.78, 95% confidence interval=0.71 to 0.86) remaining significant in adjusted models.

Conclusions—Older age and quadriceps weakness predicted esKOA. esKOA is also characterized by poor health-related outcomes. This definition of esKOA could be a new clinically relevant outcome measure for osteoarthritis research.

Key Indexing Terms

knee; osteoarthritis; musculoskeletal pain; disease severity

INTRODUCTION

Knee osteoarthritis is a common and disabling musculoskeletal disorder [1,2] that has a substantial public health impact due to morbidity and healthcare utilization, including arthroplasty, at an estimated cost of $30 billion per year [3]. There is, therefore, a major unmet need to develop interventions that mitigate the symptomatic and structural progression of knee osteoarthritis, especially to a level of severity that predicates costly and burdensome interventions, such as joint replacement. The testing of such interventions has been obfuscated by the absence of a useful and reliable definition or proxy indicator of severe knee osteoarthritis. Ideally, it would be helpful if receipt of a total knee replacement could be used to define this clinical status; however, its highly variable relationship with biological measures of knee osteoarthritis severity and strong dependence on a range of non-medical sociological influences (e.g., expectations, mental and physical readiness for surgery, comorbidities) [4], renders it unreliable as a consistent indicator of disease severity [5,6]. Also, the low frequency of its occurrence in cohorts demands sample sizes that are impractical for most research settings [7].

Thus, we propose that a definition of end-stage knee osteoarthritis (esKOA), which focuses on patient-reported outcomes and osteoarthritis structural severity measures can eliminate the influence of non-osteoarthritis related factors in the designation of this disease status. As a starting point for this effort, we have adapted an algorithm originally designed based on an instrument devised by Escobar and colleagues to indicate appropriateness for knee arthroplasty [8] and further developed and validated by Riddle et al [5]. In the setting of a consensus panel of experts, we then modified that algorithm to make it applicable in an effort to define severe knee osteoarthritis in a consistent fashion, and to enhance its utility for deployment in epidemiologic studies and clinical trials. We viewed esKOA as present in a knee with considerable pain and functional limitations, structural damage, and/or other

clinical complications (e.g., joint laxity, flexion contractures) that prohibit the normal use of a joint.

Our objectives were to detail the definition of esKOA and to evaluate its utility of in a large knee osteoarthritis cohort study by evaluating its incidence and to evaluate its construct validity by testing its association with health outcomes and known knee osteoarthritis risk factors. We hypothesized that risk factors for incident knee osteoarthritis would be associated with esKOA, and that individuals with incident esKOA would have poorer health outcomes than those without.

MATERIALS AND METHODS

To characterize individuals with esKOA we conducted person-based analyses using data from the first 48 months of observation from the Osteoarthritis Initiative (OAI). The OAI is a longitudinal observational study of individuals with or at risk for knee osteoarthritis that occurred at four clinical sites in the United States: Memorial Hospital of Rhode Island, The Ohio State University, University of Maryland and John Hopkins University, and the University of Pittsburgh. The staff at the clinical sites enrolled 4,796 men and women between February 2004 and May 2006. The OAI protocol, including a detailed description of the eligibility criteria for each subcohort, is publicly available on the OAI website [9]. Institutional review boards at each OAI clinical site and the OAI coordinating center (University of California, San Francisco) approved the study. All participants provided informed consent.

These analyses included both knees from all participants with complete baseline data in the OAI. The study sample represented the full spectrum of disease from no disease to asymptomatic knees with risk factors to severe radiographic disease, pain, and disability. Knees that already had esKOA or a total knee replacement at baseline were excluded. We censored knees after receiving a total knee replacement or death. We address challenges with missing data in the sections below.

Radiographic Assessments

Weight-bearing, bilateral, fixed-flexion, posterior-anterior knee radiographs were obtained at the OAI baseline and each subsequent visit. Central readers read the images blinded to the order of follow-up images and scored the knees for Kellgren-Lawrence [KL] grades (0 to 4) and OARSI joint space narrowing score (JSN; medial and lateral tibiofemoral compartments). 9.9% (4,240/42,800) of knee-visits had a missing KL grade. When possible we imputed missing KL grades. If a knee had a missing KL grade between two visits when a knee received the same KL grade (e.g., visit 1: KL=1, visit 2: missing, visit 3: KL=1) we replaced the missing value with the same KL grade as identified at the adjacent time points. Since knee osteoarthritis is typically characterized by a gradual radiographic progression we replaced any other missing KL grade or JSN score with the KL grade or OARSI JSN score from the prior visit. Knees were read for KL grade with follow-up radiographs blinded to order, and as a result, KL grades sometimes decreased at a later visit compared to an earlier visit. If a knee had an improved KL grade at a visit, we replaced the improved grade with the KL grade from the previous visit (e.g., if a knee had consecutive visits with KL=1, KL=2,

KL=1, the final visit was re-assigned a KL score of 2). The agreement for these readings (read-reread) was good (weighted kappa (intra-rater reliability)=0.70 to 0.78). The KL grades and OARSI JSN scores are publicly available (File: kXR_SQ_BU; version 0.6, 1.6, 3.5, 5.5, 6.3) [10].

Magnetic Resonance Imaging Readings for Patellofemoral Osteoarthritis

Because radiographs within the OAI did not include a skyline view, we used magnetic resonance (MR) images to score patellofemoral osteoarthritis when it was called for by the algorithm. Two of the 16 nodes used to define esKOA required this disease status assessment, n=82 (0.2%) knee-visits. These nodes included individuals under 55 years of age with KL=4 and intense or severe symptoms. The patellofemoral assessment was used to determine if the knee had unicompartmental osteoarthritis or osteoarthritis in multiple compartments. Two readers (JL and JD) reviewed MR images for the presence of a patellofemoral osteoarthritis, which required both a definite osteophyte and at least a partial cartilage thickness lesion [11]. The OAI MR protocol is publicly available on the OAI website [9].

Clinical Variables

Demographic, anthropometric, knee symptoms (WOMAC), knee range of motion, other health outcomes (i.e., Short Form-12 scores, 20-meter walk time, nonsteroidal anti-inflammatory drug use, and numeric rating of global arthritis impact) and knee ligamentous laxity were acquired based on standardized protocols [9]. Demographic, anthropometric, knee symptoms (WOMAC), and other health outcomes, were available at every annual visit. When WOMAC scores were missing we were conservative and assumed pain scores were unchanged from the last visit. Knee range of motion, based on the presence or absence of a flexion contracture (≥5 degrees)[12], was only assessed at baseline. At the 24- and 36-month visits, clinic staff assessed knees for varus-valgus laxity based on a varus and valgus stress test with the knee flexed 20 degrees. Baseline range of motion was used at every visit. Varus-valgus laxity from the most recent visit with data was used for the 48-month visit. If varus-valgus laxity was missing at the 36-month visit then the results from the 24-month visit were used. The protocol and data are publicly available (Files: enrollees (version 19), allclinical (version 0.2.2, 1.2.1, 3.2.1, 5.2.1, 6.2.1) [9].

Deployment of End-Stage Knee Osteoarthritis Algorithm within the OAI

To initially define esKOA based on clinical and radiographic criteria we started with appropriateness criteria developed in Spain in 1999 using a modified Delphi consensus procedure among a panel of nationally recognized specialists in orthopaedics and rehabilitation [8]. The criteria were later adapted for the Osteoarthritis Initiative, a large cohort study in the United States, to assess appropriateness of total knee replacement receipt in the United States [5]. The algorithm is particularly appealing because it accounts for clinical and radiographic criteria. To achieve our goal we reviewed the decision rules for surgical appropriateness and reclassified decision rules to define esKOA (Table 1).

The algorithm as operationalized by Riddle et al [5], classifies knees using decision rules that end in 16 nodes based on (1) knee pain and function (WOMAC pain and function in the

past 7 days), (2) radiographic severity (Kellgren-Lawrence [KL] grade), (3) number of compartments affected, (4) joint stability and range of motion (flexion contracture, collateral laxity), and (5) age (Table 1). Based on these 16 nodes, knees were initially characterized as "inappropriate", "inconclusive", or "appropriate" for total knee replacement. Since our focus was on esKOA we selected "appropriate" for total knee replacement as our starting point for definition for esKOA. Because we aimed to adapt the algorithm to define esKOA, instead of surgical appropriateness, we reached a consensus that esKOA could also be defined by any node that included at least moderate symptoms and KL = 4. Furthermore, age played a critical rule in classifying some nodes as not esKOA and therefore we reclassified those as esKOA (see Table 1). Additionally, we added information about mobility/stability to two nodes to properly classify knees as esKOA or not. These modifications ensured age was never a deciding factor for classifying someone as esKOA or not. The rest of the nodes originally classified as "inappropriate" and "inconclusive" were considered not esKOA. Table 1 presents how we reclassified the original nodes as esKOA or no esKOA.

The algorithm has been described in detail by the original authors who adapted the algorithm for the OAI [5]. Briefly, the original authors classified knee symptoms into four categories based on an aggregate score of WOMAC pain and function (aggregate score range=0 to 88): mild, moderate, severe, and intense symptoms, defined as aggregate WOMAC pain and function scores of ≤11, 12–22, 23–33, and > 33 respectively. Radiographic severity was based on KL grade and grouped as KL<3, KL=3, and KL=4. We defined the number of involved compartments as unicompartmental tibiofemoral osteoarthritis, bicompartmental osteoarthritis, or tricompartmental. Isolated patellofemoral osteoarthritis was not assessed due to the burden of reading the MR images. At baseline and the 12-month visit, knee range of motion and stability was categorized based solely on the presence or absence of a flexion contracture (≥5 degrees) because varus-valgus laxity was not collected until the 24-month visit. At the 24-, 36-, and 48-month visits, we classified knees into two groups: limited mobility-poor stability (severe varus-valgus laxity or presence of baseline flexion contracture) or normal mobility-stability (no-mild varus-valgus laxity and no baseline flexion contracture). To characterize people in each node we categorized age into three groups (<55 years, 55 to 65 years, >65 years); however, by reclassifying several nodes we ensured age was never a determinate of esKOA status (see Table 1). Missing data among variables used in the algorithm before imputation accounted for <11% of data at all knee-visits.

Total Knee Replacements

We accounted for any confirmed total knee replacement within the first 48 months of the OAI. If a participant reported a total knee replacement then the coordinating center confirmed the reported total knee replacement from medical records and/or post-operative x-rays (Files: outcomes 99 (version 4)). No other surgeries were considered (e.g., unicompartmental procedures, osteotomies).

Statistical Analyses

We identified two groups of individuals: 1) Never esKOA: neither knee met the criteria for esKOA at any visits and 2) Incident esKOA: neither knee met the criteria for esKOA at

baseline but at follow-up ≥1 knee met the esKOA criteria. We calculated baseline and longitudinal descriptive statistics of individuals that never had esKOA or had incident esKOA. Longitudinal change was calculated based on value from the last available visit minus baseline values. We conducted independent samples t-tests and chi-square tests to determine differences between groups. To account for multiple comparisons, we used a Bonferroni-adjusted criteria to determine statistical significance ($p \leq 0.05$ divided by 9 comparisons, $p \leq 0.0056$).

To evaluate if incident esKOA (outcome) was associated with osteoarthritis risk factors, we conducted unadjusted logistic regression analyses and then adjusted logistic regression analyses that included variables that were statistically significantly associated with esKOA in unadjusted analyses. Prior to conducting the primary analyses, we confirmed that each risk factor had a linear relationship with the log odds for esKOA. We ensured there were no concerns regarding colinearity within the adjusted model. Regression diagnostics, including the deviance residuals and dfBETA were conducted. For all analyses individuals that never had esKOA was the reference group. All analyses were conducted in SAS 9.4 (Cary, NC, USA).

RESULTS

The eligible cohort consisted of 3,916 participants and had a mean age of 61 (SD=9) years, mean body mass index of 28.4 (4.7) kg/m^2, and 59% were female. Within this group of participants 9.7% developed incident esKOA over a 48-month observation period. Only 82 (2.1%) of participants received a total knee replacement within the same period. Tables 2 and 3 present descriptive characteristics of individuals who developed esKOA compared with those who did not. Those with incident esKOA had poorer health outcomes at baseline and greater declines in health outcomes, with the exception of SF-12 mental health score. Five out of 9 person-level osteoarthritis risk factors were associated with incident esKOA: age > 65 years, race other than white/Caucasian, greater maximum adult body weight, greater body mass index, and weaker average knee extension strength (normalized to body weight, Table 4). Being female, engaging in at least one frequent knee bending activity, having Heberden's nodes, or having a blood relative that had knee replacement surgery were not statistically associated with incident esKOA. After adjusting for other risk factors age ≥ 65 years (odds ratio=1.44, 95% confidence interval=1.19 to 1.83) and weaker average knee extension strength (odds ratio=0.78, 95% confidence interval=0.71 to 0.86) were still statistically significantly associated with esKOA.

DISCUSSION

We have shown that the esKOA algorithm, developed in consensus from a previously validated appropriateness of arthroplasty algorithm, identifies individuals with characteristics typical of severe knee osteoarthritis – evidence of its content and construct validity. Also importantly, the rate of participants who developed esKOA in the cohort is 4.6 times greater than the number that received a total knee replacement, which suggests that smaller sample sizes may be necessary in future studies than would be needed to detect effects on other outcomes such as arthroplasty [7]. This study gives an indication of the

characteristics of individuals who develop esKOA based on a definition that considers structural damage, pain and functional limitations, and/or other clinical complications (e.g., joint laxity, flexion contractures). Individuals with incident esKOA had poorer health-related outcomes and greater declines in those outcomes over time. Furthermore, many established osteoarthritis risk factors are associated with incident esKOA. Therefore, use of esKOA as an outcome offers a more reasonable prospect for testing disease-modifying interventions for knee osteoarthritis and could be a new clinically relevant outcome measure for osteoarthritis research.

By design no one had esKOA at baseline but we found that individuals who developed incident esKOA over a 48-month observation period had greater disease severity at baseline based on greater self-reported knee pain, functional limitations, lower physical health, and greater global impact of arthritis, as well as walking slower, and consuming more nonsteroidal anti-inflammatories. These findings complement prior studies that demonstrated that individuals often have greater knee symptoms prior to osteoarthritis progression [13–15]. Many individuals with incident esKOA experienced a clinically meaningful change in pain. The development of esKOA corresponded to an average increase in WOMAC pain of 2.9 (out of 20), which is considered clinically meaningful and meant many participants were no longer in an acceptable state of knee pain [16,17]. Individuals who developed esKOA also reported an increase in global arthritis impact, which would translate to many of these participants reaching an unacceptable symptom state (3.2 on a 10-point scale) [18]. Finally, individuals who developed esKOA also slowed on average more than one second during a 20-meter walk, which is unusual since gait speed is typically stable or slowly declines in adults – as evidenced by the small changes among those who never had esKOA. Hence, individuals with esKOA have greater disease severity at baseline and worsen over time.

Several osteoarthritis risk factors were associated with incident esKOA. For example, we found that older age and baseline quadriceps weakness, established risk factors for osteoarthritis [19–21], are associated with incident esKOA. We found that individuals who were not white/Caucasian were more likely to have incident esKOA but the finding was no longer statistically significant after adjusting for other risk factors. In comparison, findings from the Johnston County Osteoarthritis Project demonstrate that African Americans have a slightly higher incidence rate of knee symptoms and knee osteoarthritis [22], radiographic progression [23], but not cumulative incidence for radiographic knee osteoarthritis [23]. Our findings may be attributable to over adjusting the model or a limited sample size of African Americans in the Osteoarthritis Initiative, which caused us to be underpowered. Finally, we found that maximum adult body weight and current body mass index were associated with incident esKOA but the findings were no longer statistically significant after adjusting for other risk factors. Body weight has consistently been reported a risk factor for osteoarthritis [24,21]; however, some data indicate that body weight is a stronger risk factor among knees with neutral or valgus alignment and not a risk factor among individuals with varus alignment [25]. Hence, our analyses may have demonstrated borderline significance because we included people regardless of knee alignment or because the model was over adjusted.

Our study helped characterize individuals who develop esKOA but there are some important limitations. For example, the OAI was not originally designed for these analyses and data were not collected at every visit for range of motion and laxity. Furthermore, we were unable to consider knees with isolated patellofemoral osteoarthritis. This may have led us to underestimate the number of knees that changed status of esKOA, possibly attenuating the strengths of the observed associations. Despite these limitations, we believe these findings demonstrate the utility of this definition of esKOA.

In conclusion, this algorithm for esKOA has good content and construct validity and can be deployed in osteoarthritis research. The incidence rate of esKOA was 4.6 times greater than the incidence of total knee arthroplasty and individuals with incident esKOA had poorer health-related outcomes and greater declines in those outcomes over time. Individuals over 65 years of age or experiencing quadriceps weakness are more likely to develop esKOA. This definition of esKOA, which accounts for structural severity and clinical severity, has the potential to be a powerful new clinically relevant outcome measure for osteoarthritis research.

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Table 1

Definitions and Prevalence of the 16 nodes for all knee-visits

Definitions of the 16 Nodes that Define End-stage Knee Osteoarthritis Status[a]					
Symptoms	**KL Grade**	**Compartments Involved**	**Age**	**Stability/Mobility**	**Original Status**
End-stage Knee Osteoarthritis					
Intense/Severe[b]	4	n/a	≥ 55	n/a	Appropriate (1)
Intense/Severe[b]	4	2 or 3	< 55	n/a	Appropriate (2)
Intense/Severe[b]	4	1	< 55	n/a	Inconclusive (3)
Moderate[c]	4	1	≥ 55	n/a	Inappropriate (15)
Moderate[c]	4	2 or 3	≥ 55	n/a	Inconclusive (16)
Moderate[c]	4	n/a	< 55	n/a	Inappropriate (14)
Severe[d]	< 3	n/a	> 65	Limited	Appropriate (6)
Intense[d]	< 3	n/a	> 65	Limited	Inconclusive (5)
Intense/Severe[d]	3	n/a	≥ 55	Limited	Appropriate (4)
Intense/Severe[d]	< 3	n/a	55–65	Limited	Inconclusive (11)
Intense/Severe[d]	≤ 3	1 or 2	< 55	Limited	Inappropriate (10b)
Intense/Severe[d]	≤ 3	3	< 55	Limited	Inconclusive (9b)
Not End-stage Knee Osteoarthritis					
Slight/Moderate	≤ 3	n/a	n/a	n/a	Inappropriate (12)
Slight	4	n/a	n/a	n/a	Inappropriate (13)
Intense/Severe[e]	< 3	n/a	≥ 55	Normal	Inappropriate (8)
Intense/Severe[e]	3	n/a	≥ 55	Normal	Inconclusive (7)
Intense/Severe[e]	≤ 3	1 or 2	< 55	Normal	Inappropriate (10a)
Intense/Severe[e]	≤ 3	3	< 55	Normal	Inconclusive (9a)

Notes. n/a, not applicable to that node.

1 Definitions of each node were defined by Riddle et al [5] who based their Escobar et al. [8].

b–e represent nodes that were originally influenced by age when identifying surgical appropriateness but we grouped together to eliminate age as a deciding factor for esKOA.

Table 2

Baseline Characteristics Among Individuals With or without End-stage Knee Osteoarthritis

Variable	Never end-stage knee osteoarthritis (n = 3,537) Mean (SD) or n (%)	Incident end-stage knee osteoarthritis (n = 379) Mean (SD) or n (%)
SF-12 – Physical (range: 0 to 100)	50.3 (8.3)	**45.8 (8.9)** *
SF-12 – Mental (range: 0 to 100)	53.6 (7.8)	53.9 (8.6)
Global Arthritis Impact (range: 0 to 10)	1.4 (1.9)	**2.5 (1.9)** *
20-Meter Walk Time (s)	15.0 (2.6)	**15.8 (2.7)** *
NSAID Use	800 (23%)	**123 (32%)** #

*Statistically different than knees that never had end-stage knee osteoarthritis (t-test $p < 0.0056$).

#Statistically different than individuals who never had end-stage knee osteoarthritis (Chi-Square test, $p < 0.0035$).

Table 3

Longitudinal Characteristics Among Individuals With or without End-stage Knee Osteoarthritis

Variable	Never end-stage knee osteoarthritis (n = 3,537) Mean (SD) or n (%)	Incident end-stage knee osteoarthritis (n = 379) Mean (SD) or n (%)
Change in SF-12 – Physical	−1.7 (8.2)	**−3.5 (8.7)** *
Change in SF-12 – Mental	0.1 (8.2)	−0.4 (8.5)
Change in Global Arthritis Impact	−0.1 (1.9)	**0.6 (2.6)** *
Change in 20-Meter Walk Time (s)	0.3 (2.1)	**1.1 (3.6)** *

*Statistically different than knees that never had end-stage knee osteoarthritis (t-test $p < 0.0056$).

#Statistically different than individuals who never had end-stage knee osteoarthritis (Chi-Square test, $p < 0.0056$).

Table 4

Risk Factors for End-stage Knee Osteoarthritis (esKOA)

Variable	Never esKOA (n = 3,537) Mean (SD) or n (%)	Incident esKOA (n = 379) Mean (SD) or n (%)	Unadjusted	Adjusted
Age ≥ 65 years *	1300 (37%)	175 (46%)	**1.48 (1.19, 1.83)**	**1.44 (1.14, 1.82)**
Female	2070 (59%)	228 (60%)	1.07 (0.86, 1.33)	n/a
Race – white/Caucasian	2871 (81%)	291 (77%)	**0.77 (0.60, 0.99)**	0.90 (0.67, 1.21)
Maximum adult weight (kg)	84.1 (16.9)	88.4 (17.7)	**1.02 (1.01, 1.02)**	1.01 (1.00, 1.02)
Body mass index (kg/m^2)	28.3 (4.7)	30.0 (4.8)	**1.08 (1.05, 1.10)**	1.03 (1.00, 1.07)
Engage in at least one frequent knee bending activity	2576 (73%)	268 (71%)	0.92 (0.72, 1.16)	n/a
Heberden's Nodes: Hard bumps on fingers	1103 (31%)	134 (36%)	1.21 (0.97, 1.51)	n/a
Blood relative had knee replacement surgery	547 (16%)	63 (17%)	1.08 (0.81, 1.44)	n/a
Average isometric strength: knee extension, MAX force normalized for body weight (N/kg)	4.4 (1.4)	3.8 (1.3)	**0.73 (0.67, 0.79)**	**0.78 (0.71, 0.86)**

* Age was dichotomized because it did not have a linear relationship with the probability of incident esKOA.

n/a = not included in the model because of no significant univariate associations.

Adjusted estimates include every other variable in the model