Published in final edited form as:
Arthritis Care Res (Hoboken). 2010 October ; 62(10): 1433–1439. doi:10.1002/acr.20247.

Do worsening knee radiographs mean greater chance of severe functional limitation? The Multicenter Osteoarthritis Study

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Abstract

Objective—Development of functional limitation is thought to be unrelated to changes in severity of radiographic knee osteoarthritis (ROA). We evaluated the relation of change in ROA to the incidence of severe functional limitation.

Methods—Participants of the Multicenter Osteoarthritis (MOST) Study, a cohort study of persons with or at high risk of knee OA were evaluated at 0 and 30 months. Subjects were classified as having no, incident, stable, or worsening ROA. Incidence of severe functional limitation was defined as 1) WOMAC physical function scores (≥ 36/68) and 2) walking speed (≤ 1.0 m/s) at 30 months. The relation of change in ROA to the incidence of severe functional limitation was evaluated by calculating risk ratios adjusted for potential confounders.

Results—Of the 2110 subjects included (mean age 62, mean BMI 30 kg/m^2, female 60%), 53% had no, 6% incident, 14% stable, and 27% worsening ROA. Persons with incident ROA had 1.9 and 1.8 times the risk by WOMAC physical function and walking speed, respectively, to have incident severe functional limitation compared with those with no ROA over 30 months. Compared with those with stable ROA, persons with worsening ROA had 2.2 and 2.5 times the risk of incident severe functional limitation, respectively.

Conclusion—Changes in structural disease are associated with the development of severe functional limitations in persons with or even those at high risk of knee OA.

Introduction

Knee osteoarthritis (OA) is the most common type of arthritis and the leading cause of difficulty with physical functioning compared with any other chronic disease (1,2). While it is known that the presence and severity of knee OA is associated with functional limitation(3–6), the effect of worsening disease on functional limitation is not known. Worsening of disease, or OA progression, can occur at different rates. In particular, persons with fast progression may be at greater risk for functional limitation than those with slow progression, who have more opportunity to adapt to changes in physiology and increases in pain which may accompany worsening disease.

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Previous studies report little to no association between changes in knee joint structure and physical function among persons with knee OA. However, it is difficult to reconcile the notion that structural worsening of OA does not influence function. Yet in the largest study to date investigating changes in disease and functional limitation, Dieppe et al reported small or null associations between changes in knee radiographs and general physical functional in 500 persons with knee OA over three years(7). Similar findings have been reported in smaller studies as well(8,9). However, these studies used non-disease specific measures, self-report measures of function without performance-based measures, such as walking speed. Furthermore, continuous changes in disease may not result in proportional changes in function. A stronger disease-function association may exist when employing a clinically meaningful endpoint of severe functional limitation, such as selecting functional cut points consistent with persistent functional limitation or total joint replacement.

Thus, we examined whether persons with worsening structural disease were more likely to develop *severe* functional limitation compared with persons with stable or no disease. We employed an OA specific measure of function and used both self-report and performance measures to define clinically meaningful endpoints of *severe* functional limitation.

Patients and Methods

Study Sample

Participants were recruited as part of the Multicenter Osteoarthritis (MOST) study, a large multicenter prospective cohort study of 3026 community-dwelling persons who had or who were at high risk of developing symptomatic knee osteoarthritis (OA) at baseline. A more detailed description of recruitment and sampling for MOST has been published elsewhere(10). In brief, subjects aged 50 to 79 years were recruited from Birmingham, Alabama and Iowa City, Iowa. Participants were defined as being at risk of developing knee OA based on known risk factors, including older age, female gender, previous knee injury or operation, and high body weight. Baseline assessments took place between May 2003 and March 2005, and follow-up assessments 30 months later. The MOST study protocol was approved by the institutional review boards at the University of Iowa, University of California San Francisco, University of Alabama, and Boston University Medical Center.

We included subjects without end-stage structural disease or severe functional limitation at baseline based on study criteria below to examine the association of worsening disease with the incidence of severe functional limitation at 30 months. We anticipated that subjects undergoing a new knee or hip replacement would likely improve in function. Thus, we excluded those who underwent a new total knee or hip replacement after the baseline assessment.

Study Variables

Outcome—Our primary outcome was the incidence of severe functional limitation at 30 months. We defined severe functional limitation to represent substantial restrictions by employing cutoff scores associated with end stage disease or poor health outcome using both self-report and performance measures. For self-report, we classified severe functional limitation as a score greater than 36.1 on the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) physical function scale (0–68)(11), the mean score reported by persons awaiting total knee replacement(12). Since total knee replacement is typically performed in persons with a severe degree of pain and functional difficulty, this WOMAC score was applied to represent severe functional limitation. A score of 36 represents reporting at least moderate difficulty on all 17 items of the WOMAC, or extreme difficulty in 9 of the 17 items. For performance, we classified severe functional limitation as walking

speed less than 1.0 meter per second (m/s) during a 20-meter walk at a usual pace. Walking speed less than 1.0 m/s is a risk factor for poor health outcomes in older adults including persistent functional limitation, hospitalization, and death(13). WOMAC and walking speed have been shown to have high test-retest reliability in persons with knee OA(11,14), and older adults(15).

Exposure—All participants underwent bilateral weight-bearing posteroanterior (PA) and lateral fixed-flexion radiographic evaluations of the knee, as described elsewhere(10). Two experienced readers blinded to clinical data graded joint space narrowing (JSN) and osteophytes using the OARSI atlas(16) in both tibiofemoral (TF) and patellofemoral (PF) joints (both graded 0–3). The presence of JSN and osteophytes in the TF joint was also graded according to Kellgren and Lawrence (K/L) criteria (0–4). Any disagreements between readers were adjudicated by 3 readers to reach consensus. We defined ROA based on radiographic findings in either TF or PF joints. For the TF joint this was a KL grade ≥ 2, and for the PF joint an osteophyte score ≥ 2, or any joint space narrowing score ≥ 2 with any osteophyte, sclerosis, or cyst score of ≥ 1 on a lateral plain view film(17,18). The inter-rater reliability weighted kappa for the KL grade at baseline was 0.80.

Radiographic status was defined in four categories, no ROA, incident ROA, stable ROA, and worsening ROA. We defined ‘no ROA’ as persons who did not have ROA at baseline or at 30 months in either knee. We defined ‘incident ROA’ as persons who did not have ROA at baseline in at least one knee, and at 30 months met criteria for ROA in the previously non-diseased knee and had no ROA or no change in radiographic status in the other knee. We defined ‘stable ROA’ as persons who had ROA at baseline and had no change in JSN or K/L grades over 30 months in radiographic status in that knee and no ROA, no change in ROA, or an existing total knee replacement in the other knee. Lastly, we classified ‘worsening ROA’ as persons with ROA at baseline and increases in either K/L or JSN grades over 30 months in either knee. Persons were classified according to the ‘worse’ knee. For example, persons with no change in K/L or JSN grades in one knee but worse K/L or JSN grades in the other were classified as worsening ROA. Similarly, persons with no change in K/L or JSN grades in one knee and incident ROA in the other were classified as incident ROA.

Potential Confounders—The following baseline factors were considered as potential confounders based on existing literature linking them to function(10,19–23): age, sex, and race; Body Mass Index (BMI) computed from standardized weight and height assessments; depressive symptoms measured with the Center for Epidemiologic Studies Depression Scale (CES-D)(24); the presence of low back, hip, or foot pain recorded from self-report; and comorbidities estimated with a validated self-report measure, the modified Charlson comorbidity index(25). Since our interest was to examine the effect of change in ROA status on the incidence of severe functional limitation, we did not adjust for knee pain given its role as a likely intermediate.

Statistical Analysis

We first examined whether differences in physical function among the different radiographic status categories at baseline were clinically meaningful. Based on previous literature this was a difference greater than 6.2 out of 68 for WOMAC(26) and a difference greater than 0.10 meters per second for walking speed(27,28). To examine the relation of change in radiographic status to the incidence of severe functional limitation at 30 months, we used regression methods with a log-link function and robust standard errors to obtain risk ratios(29). All analyses were adjusted for age, sex (male/female), race (Caucasian, other), BMI, presence of depressive symptomatology (CES-D ≥16, yes/no)(24), low back, hip, or foot pain presence (yes/no), and comorbidities (none, ≥1). Age and BMI were entered as

continuous variables. Analyses were conducted for incidence of severe functional limitation measured by self-report (WOMAC) and performance (walking speed). Persons meeting criteria for severe functional limitation at baseline were excluded from these incidence analyses. To determine whether persons with worsening structural disease were more likely to develop severe functional limitation, we conducted two separate analyses. In the first, we examined the association of incident ROA with severe functional limitation incidence over 30 months among those with no ROA at baseline. In the second, we evaluated the relation of worsening of ROA to severe functional limitation incidence among those with ROA at baseline. We also compared the incidence of severe functional limitation among persons with stable ROA with those with no ROA. Lastly, we examined the relation of change in radiographic status with change in WOMAC physical function and walking speed as a continuous outcome. We found change scores to be approximately normally distributed (Kolmogorov-Smirnov test not statistically significant), hence we applied t-tests and multiple linear regression adjusting for the aforementioned potential confounders.

Results

Of the 3026 MOST subjects at baseline, 461 had end-stage ROA at baseline. At 30 months, 74 had a new total joint replacement, 249 had incomplete data and 32 were lost to follow up. Of the 2210 remaining subjects, the mean age was 62 years, mean BMI was 30 kg/m^2, and 106 and 354 had severe functional limitation at baseline measured by self-report and performance, respectively. The majority of subjects were female (60%), Caucasian (85%), reported pain elsewhere besides the knee (76%), and did not have any comorbidities (64%). (Table 1) There were 1173 (53%) subjects with no ROA, 127 (6%) with incident ROA, 310 (14%) with stable ROA (*i.e*., *no change in disease*), and 600 (27%) with worsening of existing ROA over the course of observation period.

In our first set of analyses, we examined the group of participants who had no ROA at baseline. Among persons who continued to have no ROA at follow-up, 2% (19/1137) and 5% (51/1069) had developed severe functional limitation by self-report and performance, respectively, while persons who developed incident ROA, 4% (5/119) and 11% (12/105) had new severe functional limitation, respectively. There were no clinically meaningful differences in function at baseline. Persons with incident ROA were 1.9 and 1.8 times more likely to have incident severe functional limitation by self-report and performance, respectively, compared with those with no ROA [adjusted risk ratio (adj RR) 1.9 (95% CI 0.8–4.8) for self report and adj RR 1.8 (95% CI 1.0–3.3) for performance]. (Table 2)

In our second set of analyses, we examined the group of participants who had existing ROA at baseline. Among those with stable ROA at follow-up, 3% (8/287) and 5% (13/262) had new severe functional limitation by self-report and performance, respectively, and for persons with worsening ROA, 6% (33/544) and 13% (62/498) had developed severe functional limitation, respectively. There were no clinically meaningful differences in function at baseline. Those with worsening ROA had 2.2 and 2.3 times greater risk of severe functional limitation by self-report and performance, respectively, than those with stable ROA [RR 2.2 (95% CI 1.1–4.7) for self report and adj RR 2.3 (95% CI 1.3–4.1) for performance]. (Table 3)

There was no statistically significant difference in risk of severe functional limitation among persons with stable ROA compared with those with no ROA as measured by self-report or performance [adj RR 1.4 (95% CI 0.6–3.0), 0.7 (95% CI 0.4–1.3), respectively].

Greater decline occurred on average for both self-report and performance outcomes measured continuously for persons with incident ROA compared with those with no ROA,

and for persons with worsening ROA compared with those with stable ROA. However, these differences did not meet statistical significance (data not shown).

Discussion

We found that persons who developed or had worsening of ROA over 30 months were more likely to develop severe limitations in function compared with those without existing disease and those with stable disease, respectively. These findings suggest that it is not just the presence, but rather the change (i.e., development or worsening) in structural disease at the knee that is important for the incidence of severe functional limitation in persons with knee OA. Specifically, we found that both persons with worsening of existing disease and those who developed radiographic disease had about a two fold risk of developing severe functional limitation as compared with their counterparts. In contrast, we found that persons with stable disease had a similar risk of severe functional limitation incidence as those with no disease. Hence, it is not the mere presence of structural disease at the knee that is important for the development of severe functional limitation, but rather the worsening of structural disease in both persons with or without radiographic disease at baseline.

Thus, our results support the notion that worsening disease is an important and relevant risk factor for severe functional limitation in persons with knee OA. We also recently demonstrated that a strong association between structure and symptoms does exist when confounding is adequately addressed(30). However, this is in contrast to the existing literature, which highlights a discordance between structural disease with patients symptoms, such as pain and function(31,32). A recent systematic review concluded that radiographic knee OA is an imprecise guide to the future presence or absence of pain or functional limitation(33). While this may be true when examining the relation of worsening of structural disease to smaller incremental changes in function, our findings suggest an association exists between worsening disease and clinically meaningful endpoints of function. For instance, we did not find significant differences between persons with incident or worsening disease compared with those with no ROA or stable disease when function was measured continuously. However when characterizing functional loss as substantial, a relationship emerges between worsening of structural disease and severe functional limitation. This may point to the ‘noise’ or sensitivity to change associated with such functional measures, limiting the ability to precisely measure small changes, particularly when there can be substantial between-person variability. Furthermore, it is questionable if such small changes, if detected, are clinically relevant or meaningful to the patient or provider. Thus, employing a strategy to highlight persons who decline below a clinically meaningful endpoint may be more fruitful in understanding the influence changes in structural disease may have on poor functional outcomes.

We selected definitions of *severe* limitations in function from values consistent with persons awaiting total knee replacement and who were at risk of poor health outcomes. In addition, we performed sensitivity analyses using cutoffs for severe functional limitation ranging from 35 to 37/68 for WOMAC physical function and 0.95 to 1.05 m/s for walking speed, and found similar results. It is noteworthy that differences in WOMAC physical function and walking speed at baseline among radiographic status categories were not clinically meaningful and far from thresholds values for *severe* limitations in function. This indicates that persons with worsening disease were not closer to threshold values of severe functional limitation at baseline compared with those with stable or no disease.

We found worsening of structural disease of the knee to be a risk factor for the development of severe functional3 limitation regardless of whether it is measured by self-report (WOMAC physical function) or performance (walking speed during a 20 meter walk).

These outcomes examine different aspects of physical function; walking speed focuses on one specific functional task, while WOMAC assesses a much broader spectrum of 17 daily activities ranging from sitting to going shopping. Despite this difference, we found persons with incident or worsening disease to have an increased risk of severe functional limitation regardless of whether measured by self-report or performance, compared with those with no or stable disease, respectively. This is consistent with previous literature, where at least a moderate correlation ($r > 0.3$) between self-report and performance based measures of physical function has been reported in persons with hip osteoarthritis(34), and older adults(35–37).

Why are persons with worsening structural disease more likely to have severe functional limitation compared with those with stable or no disease? Worsening disease is likely associated with knee pain and muscular weakness(30,38,39). Other consequences include decreased proprioception and instability or buckling(40–44). All of these impairments could result in the development of functional limitation. One possible reason why those with worsening structural disease are more prone to severe functional limitation is that they have less time to adapt to the development of these underlying impairments due to progressive disease, versus those with stable or slowly progressive disease.

There are some limitations to our study. First, we had a limited number of persons who had an onset of severe functional limitation in this sample, which limits our ability to precisely estimate the effect of change in ROA status with severe functional limitation. This may be due in part to inadequate sample size and/or insufficient follow-up time for such changes to occur. Second, given that our study examined changes in disease with changes in function, we cannot infer causality or directionality directly from our data. While it is plausible that limited function may cause worsening of disease, this seems unlikely, particularly for those who developed incident knee ROA. Third, we did not specifically examine persons whose knee radiographs worsened from KL grade 0 to 1 as this group was too small to precisely estimate effects, and instead included them within the no ROA group. However, when we examined this group separately, we found no substantial differences for risk of severe functional limitation compared with persons with no ROA at baseline and 30 months, albeit without adequate precision due to the small numbers. Fourth, given the complex nature of the effects of function from total joint replacement, persons with existing or new total joint replacement may have had different functional outcomes compared with those without replacements. To address this issue we separately analyzed our data first excluding those with existing joint replacements at baseline and second including persons with new joint replacements. We used observed outcomes and also assigned persons with new joint replacement as having developed severe functional limitation, a reasonable assumption given that persons awaiting total joint arthroplasty are likely do so in part due to functional decline. We found similar effect estimates across all of these analyses, although the effect estimates were highest when incident severe limitation in function was assumed for persons with new joint replacement. Fifth, we were unable to examine the association of change in OA status taking into account unilateral versus bilateral ROA changes given the complexity of the numerous possible combinations that can occur in two knees within a person. Lastly, we did not specifically examine the role of impairments due to disease, such as knee pain or muscular weakness, proprioception, and knee instability, on the development of severe functional limitation because these are likely intermediates on the causal pathway. That is, the effects of structural disease on function is a reflection of the varying contributions of these associated impairments that can influence function. Investigation of the mechanisms by which structural disease can lead to functional decline is of interest for future studies.

Our study has some important clinical implications. First, changes in structural disease are relevant for the development of severe functional limitations in persons with or even those at

high risk of knee OA. Though previous literature found structural disease to not be important for functional limitation, our results suggest otherwise when using meaningful clinical endpoints to define function. Persons who have worsening or new structural disease over 30 months are at a 1.8 to 2.5 fold higher risk of developing substantial limitations in daily functional activities, such as walking, climbing stairs, and getting up from a chair compared with those without disease or stable disease. Second, not only should clinicians be aware of the presence of structural disease, but also be aware of the speed of change in disease in persons with or at high risk of knee OA. While no current intervention is known to halt the progression of OA, rehabilitation such as strengthening exercises and self management approaches have been shown to minimize functional limitations in persons with knee OA(45–47). Thus, persons at risk for developing incident or worsening disease may be the most appropriate candidates for early referral to rehabilitation.

Acknowledgments

Supported by NIH U01 AG18820, U01 AG 18832, U01 AG 18947, U01 AG 19069, AR007598, AR 47785, ARHP New Investigator Award, NIH AR47885, NIAMS K23AR055127, Arthritis Foundation New Investigator Award, ACR/REF Junior Career Development Award in Geriatrics (T Franklin Williams Scholar Award)

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Table 1

Subject characteristics

	All subjects n=2110
Age in years [Mean (sd)]	61.9 (7.9)
Female [n (%)]	1315 (60)
Caucasian [n (%)]	1885 (85)
BMI* [kg/m] [Mean (sd)]	30.2 (5.6)
CES-D† ≥16 [n (%)]	270 (12)
Low back, hip, or foot pain [n (%)]	1670 (76)
No Comorbidity [n (%)]	1500 (68)

*BMI = Body Mass Index

†CES-D= Center for Epidemiologic Studies Depression Scale

Table 2

Risk of severe functional limitation as measured by WOMAC physical function and walking speed during a 20m walk among persons without ROA at baseline.

		Baseline Scores [Mean (sd)]	Incident severe functional limitation*/Total	%	Adj RR† [95% CI]
WOMAC Physical Function (0–68)	No ROA	8.5 (9.2)	19/1137	2	1.0 Ref
	Incident ROA	12.1 (10.1)	5/119	4	1.9 [0.8–4.8]
Walking speed (m/s)	No ROA	1.30 (0.17)	51/1069	5	1.0 Ref
	Incident ROA	1.26 (0.16)	12/105	11	1.8 [1.0–3.3]

*Severe functional limitation defined as WOMAC physical function scores ≥ 36.1

†Adjusted for age, sex, BMI, race, depressive symptoms, number of comorbities, and pain at lower extremity sites other than the knee

Table 3

Risk of severe functional limitation as measured by WOMAC physical function and walking speed during a 20m walk among persons without ROA at baseline.

		Baseline Scores [Mean (sd)]	Incident severe functional limitation*/Total	%	Adj RR† [95% CI]
WOMAC Physical Function (0–68)	Stable ROA	14.4 (10.0)	8/287	3	1.0 Ref
	Worsening ROA	14.8 (10.6)	33/544	6	2.2 [1.1–4.7]
Walking speed (m/s)	Stable ROA	1.25 (0.15)	13/262	5	1.0 Ref
	Worsening ROA	1.25 (0.16)	62/498	13	2.3 [1.3–4.1]

*Severe functional limitation defined as WOMAC physical function scores ≥ 36.1

†Adjusted for age, sex, BMI, race, depressive symptoms, number of comorbities, and pain at lower extremity sites other than the knee