Title

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Journal

Journal of Orthopaedic and Sports Physical Therapy, 51(6)

ISSN

0190-6011

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Publication Date

2021-06-01

DOI

10.2519/jospt.2021.9735

Peer reviewed

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Recent Injury, Severe Radiographic Change, and Lower Quadriceps Strength Increase Risk of Knee Pain Exacerbation During Walking: A Within-Person Knee-Matched Study

OBJECTIVE: To examine the associations of knee injury, radiographic osteoarthritis severity, and quadriceps strength with knee pain exacerbation during walking.

DESIGN: Within-person knee-matched case-control study.

METHODS: Participants from the Osteoarthritis Initiative who completed a 20-m walking test at the 24-month visit were included. Pain exacerbation was defined as an increase in pain intensity of 1 or more on a numeric rating scale (0 as no pain and 10 as the worst imaginable pain) while completing the 20-m walking test. We used conditional logistic regression to assess the relation of recent knee injury, Kellgren-Lawrence (KL) grade, and quadriceps strength to unilateral knee pain exacerbation during walking.

RESULTS: We included 277 people who experienced unilateral knee pain exacerbation during the walking test. Recent knee injury was associated with pain exacerbation during walking, with an odds ratio of 3.4 (95% confidence interval [CI]: 1.3, 9.2). Compared with knees with a KL grade of 0, the odds ratios of pain exacerbation during walking were 1.3 (95% CI: 0.7, 2.7), 3.3 (95% CI: 1.5, 7.1), and 8.1 (95% CI: 3.1, 21.1) for knees with KL grades of 2, 3, and 4, respectively. Painful knees with a deficit in quadriceps strength of greater than or equal to 4% had a 1.4-fold (95% CI: 1.0, 1.9) higher risk of pain exacerbation during walking than their pain-free counterparts.

CONCLUSION: Recent knee injury, more severe radiographic osteoarthritis, and lower quadriceps strength were associated with an increased risk of knee pain exacerbation during walking. *J Orthop Sports Phys Ther 2021;51(6):298-304. Epub 10 May 2021. doi:10.2519/jospt.2021.9735*

KEY WORDS: *disability, muscle strength, osteoarthritis, pain, risk factors*

Pain is the key reason why people with knee osteoarthritis (OA) seek medical care.[4,9] Pain exacerbation during walking is among the most commonly reported experiences by patients with knee OA[15] and a major barrier to promoting physical activity, which consequently contributes to physical disability.[10,25,30] However, despite its importance, few risk factors for exacerbated knee pain during walking have been identified, limiting the possibilities for developing a targeted prevention and treatment strategy. Interventions specific to common activity-related pain represent attractive potential therapeutic targets to decrease the burden of pain-related disability. However, deeper understanding of the risk associations of pain with individual activities is needed.

Pain is a subjective experience that varies between individuals. Many factors that differ from person to person, such as genetic predisposition to pain, coping strategies, and sociocultural environment, have not been collected or controlled for in most observational studies.[16] The results of previous studies may be susceptible to residual confounding.

Over the past decade, several studies have adopted a within-person knee-

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matched case-control study design to eliminate person-level time-invariant confounders and to improve the validity of study findings.[5,6,14,17,32] One study taking this approach found a strong association between Kellgren-Lawrence (KL) grade and the severity and consistency of prevalent frequent knee pain, which previously had not been reliably observed using conventional approaches.[17] Others also used this study design to assess the association of pain fluctuation over time with weather, buckling, knee injury, psychological factors, and magnetic resonance imaging–based structural lesions.[5,6,14,32]

Using a within-person knee-matched case-control study, we examined the relation of 3 knee-specific risk factors to pain exacerbation during walking. We assessed recent knee injury, KL grade, and maximum isometric quadriceps strength (hereafter referred to as quadriceps strength) for 2 reasons: (1) they are common risk factors correlated with knee pain that have not been studied for the association with knee pain exacerbation during walking, and (2) they have potential implications for clinical practice.

METHODS

Study Sample

The Osteoarthritis Initiative (OAI) is a longitudinal cohort study of participants with or at high risk of knee OA, with all data publicly available (https://nda.nih.gov/oai). At baseline, the OAI cohort included 4796 participants, aged 45 to 79 years, who were recruited from 4 sites: Columbus, OH; Providence, RI; Baltimore, MD; and Pittsburgh, PA. Annual assessments included medical history, clinical examination, and radiography. We used the data collected at the 24-month visit by the OAI for the current analysis. Participants who had a total knee replacement before the 24-month visit were excluded. The Institutional Review Board at each of the sites approved the study, and informed consent was obtained from all participants.

Assessment of Knee Pain Before and During the Walking Test

In the physical performance test during the clinic visit, participants were asked to walk 20 m at their usual speed. Pain intensity was assessed for each knee at 2 time points, at the beginning and at the end of the walking test, using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (the worst imaginable pain). At the beginning of the walking test, participants were asked to rate their current knee pain at rest. At the end of the walking test, participants were asked to rate the maximum knee pain experienced during the walking test. Because the change in knee pain intensity was assessed over a short period, we defined knee pain exacerbation during walking as an increase of 1 point or more from the pain intensity at rest to the maximum pain experienced during the walking test. To assess the robustness of our definition, we performed a sensitivity analysis using an alternative definition of knee exacerbation, that is, an increase of 2 points or more from pain at rest to the maximum pain during the walking test, which is a threshold for a meaningful difference in pain for clinical trials.[21] To avoid ceiling effects, participants with a pain score of 10 in either knee at rest were excluded. Participants with either knee having a pain score of 9 or greater at rest were excluded for the sensitivity analysis.

Assessment of Knee Injury

A recent knee injury was defined as an injury that occurred within the last 12 months and was severe enough to limit the ability to walk for at least 2 days.

Assessment of Radiographic Knee OA Severity

Radiographic knee OA severity was assessed using KL grades for each knee.[13] Any disagreement as to whether the knee had radiographic OA at any time point was adjudicated by a panel of 3 experienced readers, including the 2 primary readers and 1 other.

Assessment of Quadriceps Strength

Quadriceps strength was measured using the Good Strength Chair (Metitur Oy; Jyväskylä, Finland) by trained and certified research technicians. Specifically, participants were seated upright, hanging their legs over the edge of the chair. The pelvis and thighs were stabilized using a seatbelt. After 2 warm-up repetitions performed at 50% effort, participants were encouraged to extend their knee against the pad to measure the maximal force (Newtons) at 60° of knee flexion. The best of 3 maximal efforts was recorded for each leg separately. Participants who had knee pain that prevented them from pushing as hard as they could during the quadriceps strength test were not eligible for the current analysis. We considered a difference in quadriceps strength between knees ([quadriceps strength of control knee – quadriceps strength of case knee]/quadriceps strength of case knee) of 4% or greater in a participant as a meaningful difference, which corresponds to the minimal clinically important difference in the Western Ontario and McMaster Universities Osteoarthritis Index function subscale.[22] We then classified each knee into 1 of 3 categories, based on the comparison of quadriceps strength in the case knee with that in the contralateral control knee: (1) its quadriceps strength was at least 4% lower than that of the contralateral knee, (2) its quadriceps strength was at least 4% higher than that of the contralateral knee, and (3) the absolute difference in quadriceps strength between knees was less than 4%.

Statistical Analysis

Matched Pair of Case-Control Knees The outcome of interest was knee pain exacerbation during the 20-m walking test. The selection criteria for eligible participants are depicted in **FIGURE 1**. Each matched pair within an eligible participant consisted of a case knee (pain exacerbation during walking) and a control knee (no pain exacerbation during walking). We fitted a conditional logistic regression

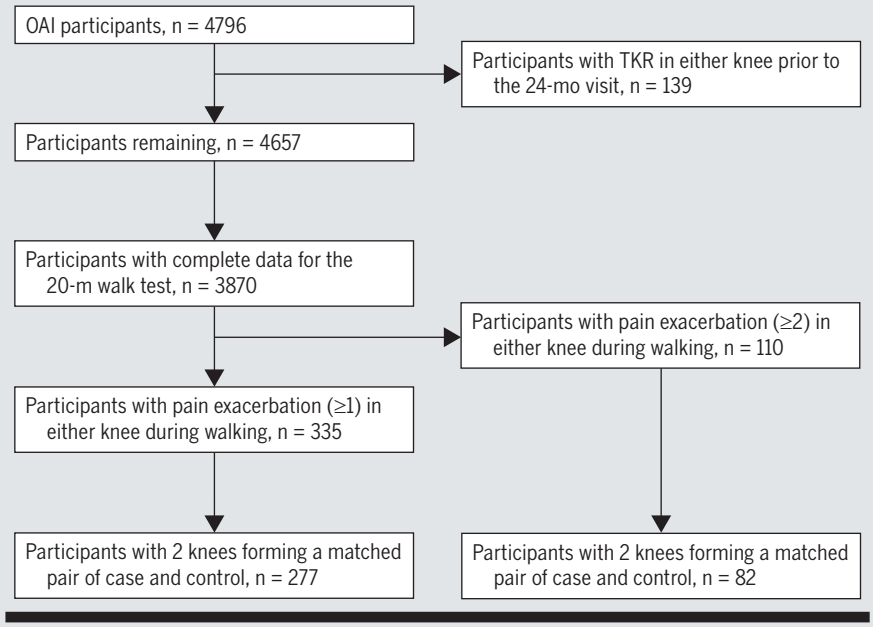

FIGURE 1. Participants in the OAI included in final analyses. Abbreviations: OAI, Osteoarthritis Initiative; TKR, total knee replacement.

TABLE 1 Frequency of Recent Knee Injury Within Pairs of Knees With Unilateral Pain Exacerbation During Walking[a]

	Recent Injury to Case Knee	
Recent Injury to Control Knee	**No**	**Yes**
No	245	17[b]
Yes	5[c]	5

[a]*Values are n.*
[b]*Frequency of case knees with a recent injury and control knees without a recent injury.*
[c]*Frequency of control knees with a recent injury and case knees without a recent injury.*

model to examine the association between each risk factor and risk of pain exacerbation during walking.

Models for Knee Injury and KL Grade We hypothesized that weak quadriceps strength could be a consequence of injury and KL grade (**APPENDIX**)[19,22]; thus, we adjusted for a recent knee injury for the association between KL grade and knee pain exacerbation during walking. When we examined the association between KL grade and knee pain, we did not adjust for quadriceps strength, because it may be an intermediate variable between KL grade and pain, and adjusting for quadriceps strength may introduce selection bias.[26] We performed sensitivity analyses, mutually adjusting for 3 risk factors (**APPENDIX**).

Model for Quadriceps Strength In the analysis of the relation of quadriceps strength to knee pain exacerbation during walking, we adjusted for a recent knee injury and KL grade.[28] We did not adjust for person-level confounders, because both knees within the same person share the same values of person-level confounders (eg, age, sex, and body mass index). We compared the difference in quadriceps strength between the case knee and control knee using a paired *t* test and depicted the dose-response relationship between quadriceps strength and the risk of knee pain exacerbation during walking using a restricted cubic spline curve. We also performed sensitivity analyses among corresponding eligible participants, identified according to the alternative definition of knee pain exacerbation during walking (**FIGURE 1**). All statistical analyses were performed using Stata/SE 14.0 (StataCorp LLC, College Station, TX).

RESULTS

Three hundred thirty-five (8.7%) of 3870 participants who completed the 20-m walking test experienced pain exacerbation during walking in either knee at the 24-month visit conducted by the OAI (**FIGURE 1**). We identified 277 matched pairs of case and control knees. Approximately two thirds (64%) of participants were women, the mean ± SD age was 63.6 ± 9.2 years (range, 47-81 years), and the mean ± SD body mass index was 29.2 ± 4.9 kg/m^2 (range, 18.5-48.8 kg/m^2). When we used an increase of 2 or more points to define knee pain exacerbation during the walking test, 110 (2.8%) of 3870 participants experienced pain exacerbation in either knee, among whom 82 matched pairs of case and control knees were identified.

Recent knee injury was associated with 3.4-fold higher odds (95% confidence interval [CI]: 1.3, 9.2) of pain exacerbation during walking (**TABLE 1**). When the analysis was restricted to knee pain exacerbation defined by at least a 2-point increase in pain from pain at rest to that during the walking test, the association was stronger (odds ratio [OR] = 9.0; 95% CI: 1.1, 71.0). The results after mutually adjusting for 3 risk factors are shown in the **APPENDIX**.

A higher KL grade was associated with increased risk of knee pain exacerbation during walking (**TABLE 2, FIGURE 2**). Compared with knees with a KL grade of 0, knees with KL grades of 1, 2, 3, and 4 had 1.0 (95% CI: 0.5, 2.0), 1.3 (95% CI: 0.7, 2.7), 3.3 (95% CI: 1.5, 7.1), and 8.1

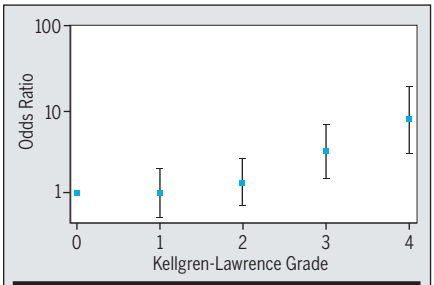

FIGURE 2. Association between Kellgren-Lawrence grade and knee pain exacerbation during walking (adjusting for recent knee injury). Bars and whiskers represent 95% confidence intervals.

(95% CI: 3.1, 21.1) times higher odds of pain exacerbation during walking, respectively (P<.001 for trend) (**FIGURE 2**). A similar association was observed (P = .013 for trend) when pain exacerbation was defined as at least a 2-point increase in pain from pain at rest to that during the walking test.

Knees with pain exacerbation during walking had lower quadriceps strength than the contralateral knees without pain exacerbation, with a mean difference in quadriceps strength of −20.5 N (95% CI: −28.9, −12.2 N). The OR for pain exacerbation for knees whose quadriceps strength was at least 4% lower than the contralateral knee was 1.4 (95% CI: 1.0, 1.9) (**TABLE 3**). As depicted in **FIGURE 3**, lower quadriceps strength was associated with a higher risk of knee pain exacerbation during walking. In the sensitivity analyses where pain exacerbation was defined as at least a 2-point increase from pain at rest to that during the walking test, lower quadriceps strength was associated with 2-fold higher odds of pain exacerbation (95% CI: 1.1, 3.7), and a similar dose-response relationship was also observed.

TABLE 2 Frequency of KL Grades Within Pairs of Knees With Unilateral Pain Exacerbation During Walking[a]

	KL Grade in Case Knee				
KL Grade in Control Knee	**0**	**1**	**2**	**3**	**4**
0	37	10	7	8	7
1	11	12	10	9	4
2	6	8	30	23	10
3	2	2	10	27	16
4	0	2	1	7	3

Abbreviation: KL, Kellgren-Lawrence.
[a]*Values are n.*

TABLE 3 Difference in Quadriceps Muscle Strength Within Pairs of Knees With Unilateral Pain Exacerbation During Walking

Strength Difference Between Matched Knees	Matched Sets, n	Odds Ratio[a]	*P* Value
Strength lower by ≥4% in control knee	73	1.0 (reference)	
Strength lower by ≥4% in case knee	117	1.4 (1.0, 1.9)	.045
Absolute difference <4%	24	...	

[a]*Values in parentheses are 95% confidence interval. Adjusted for recent knee injury and Kellgren-Lawrence grade.*

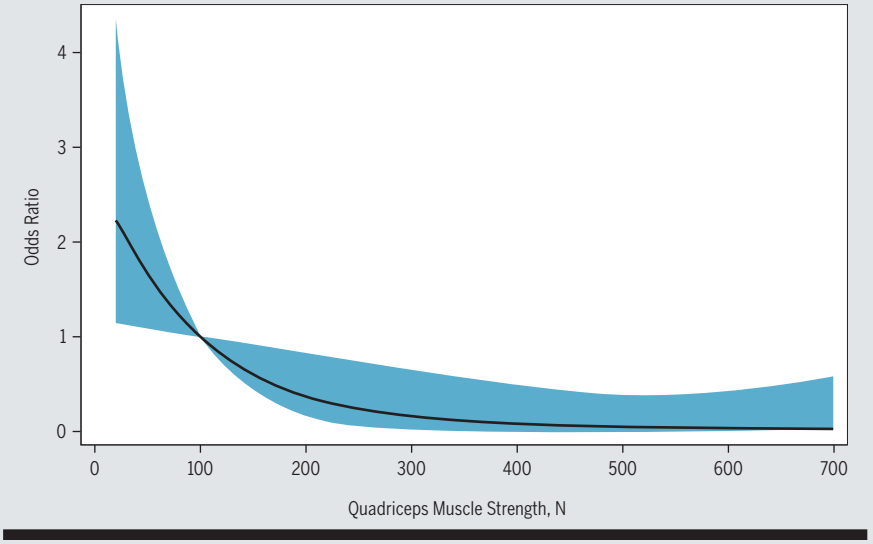

FIGURE 3. Dose-response relation of quadriceps strength to the risk of knee pain exacerbation during walking (adjusting for Kellgren-Lawrence grade and recent knee injury). The gray shaded areas represent 95% confidence intervals.

DISCUSSION

Using a within-person knee-matched case-control study design, we found that knee injury, more severe radiographic change, and weak quadriceps strength increased the risk of knee pain exacerbation during walking among people with or at high risk of knee OA. Sensitivity analyses using a more stringent definition of pain exacerbation showed similar results. The prevalence of knee pain exacerbation during walking varies dramatically with the cutoffs used. In addition, the prevalence of knee pain exacerbation during walking was much lower than that during the repeated sit-to-

stand test (31.8%),[24] suggesting that the type and intensity of physical activity may affect change in knee pain.[20]

Walking is one of the most common types of physical activity and is promoted to maintain function.[1,29] Knee pain exacerbation during walking, a daily activity, is a common experience and often results in activity avoidance[10,15] or alteration of gait mechanics[3] among patients with knee OA. Prior work has identified likely pain feedback loops between pain and psychological state, with pain causing changes in mental health and mental health state being associated with a subsequent increase in pain.[31] There may also be other feedback loops acting in symptomatic knee OA related to the interaction of centralized pain with peripheral pain.[18] We postulate that the association between quadriceps strength and knee pain exacerbation during walking may represent another OA-related pain feedback loop. Knee pain exacerbation during walking could engender and reinforce a cycle of activity avoidance and disuse of the quadriceps over time, contributing to higher susceptibility to knee pain during walking. Pain during walking is associated with fear of movement, which contributes to the vicious cycle.[7,8,12,30] Interventions may be warranted to break the self-perpetuating cycle of knee pain exacerbation during walking and related activity avoidance.

We found 2 modifiable risk factors for knee pain exacerbation during walking: knee injury and quadriceps strength. Exercise (eg, structured strength training) is beneficial for preventing knee injury and strengthening the quadriceps.[11,27] Exercise may reduce pain and disability among patients with knee OA through its effect on quadriceps strength.[23] An increase of 30% to 40% in quadriceps strength has beneficial effects on pain and disability in people with knee OA.[2]

Previous studies have found a structure-symptom discordance in knee OA, where only a weak association was observed between radiographic OA grade and severity of pain. However, such a weak association may be susceptible to bias from either potential confounders or pain measurement errors.[16] We eliminated person-level confounders, because the case knee and control knee share the same person-level confounders in a within-person knee-matched study design. Furthermore, assessment of pain intensity for each knee within the same person is less susceptible to measurement error compared with that for knees of different individuals. Our findings of a strong association between radiographic OA severity (ie, KL grade) and knee pain exacerbation during walking provide additional evidence that structural lesions are important risk factors for the occurrence of knee pain in OA.[17,32]

Strengths and Limitations

We assessed knee pain exacerbation while participants were walking at a usual gait speed, representing a common pain experience of patients with knee OA in daily life.[15] Thus, our results apply to the real-life setting. The measurement of pain exacerbation in our study is less susceptible to recall bias because the pain assessment was completed shortly after the walking test, making it possible to detect a meaningful difference of 1 point on a numeric rating scale of 0 to 10 between the case and control knees within the same person.

Our study has several limitations. First, this was a cross-sectional study, thus we were unable to definitively clarify the directionality of the exposures and outcome; that is, there is a possibility of reverse causation. Second, although every effort was made to identify and confirm reports of recent knee injury, some misclassification bias may remain. Nevertheless, such bias, if occurring, would bias our results toward the null. Third, because this is a within-person knee-matched case-control study, the concordant pair (ie, 2 knees that have the same exposure level) will not contribute to the estimation of the relation of a risk factor to pain exacerbation. Therefore, our findings cannot be generalized to people with 2 knees that are concordant in exposures of interest (eg, those who are bilaterally weak in quadriceps strength). Finally, other knee-specific risk factors, such as peripheral sensitization and knee joint instability, were not evaluated in our study, thus residual confounding from other knee-specific risk factors could not be ruled out.

CONCLUSION

Knee injury, KL grade, and quadriceps strength were associated with knee pain exacerbation during walking. ◉

KEY POINTS

FINDINGS: Recent knee injury and quadriceps strength are modifiable risk factors for knee pain exacerbation during walking.

IMPLICATIONS: Our results may help clinicians develop a targeted strategy for promoting physical activity among people with or at high risk of knee osteoarthritis.

CAUTION: There is a possibility of reverse causation, and residual confounding from other knee-specific risk factors could not be ruled out. The generalizability of our findings is limited due to study design.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: Drs Liu, Lin, and Zhang and Zhikun Li contributed to study conception and design and the analysis and interpretation of data. Drs Liu, Tao, and Lin and Zhikun Li contributed to the acquisition of data. All authors drafted the article or revised it critically for important intellectual content, gave final approval of the article, and take responsibility for the integrity of the data and the accuracy of the data analysis.

DATA SHARING: The data sets generated and/or analyzed during the current study are available in the Osteoarthritis Initiative repository (https://nda.nih.gov/oai).

PATIENT AND PUBLIC INVOLVEMENT: Patients were not involved in the design, conduct, or interpretation of the current research.

ACKNOWLEDGMENTS: *We would like to thank the Osteoarthritis Initiative participants, investigators, and clinical center staff for generating this publicly available data set.*

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APPENDIX

SUPPLEMENTARY FIGURE AND TABLE

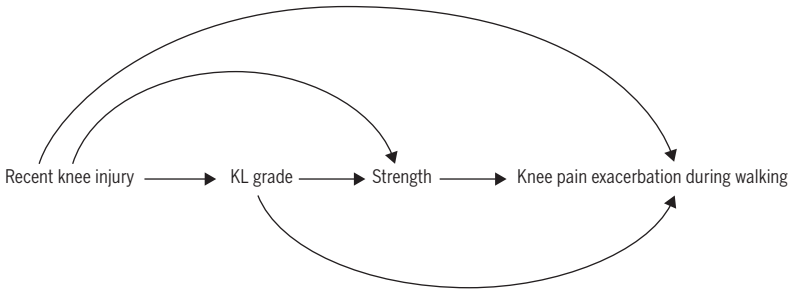

FIGURE. A directed acyclic graph to guide the selection of potential confounders when assessing a specific risk factor in relation to knee pain exacerbation. Abbreviation: KL, Kellgren-Lawrence.

Results After Mutually Adjusting for 3 Risk Factors

Risk Factor	Odds Ratio[a]	*P* Value
Recent knee injury		
No	1.0 (reference)	
Yes	2.6 (0.8, 8.3)	.12
Kellgren-Lawrence grade		
0	1.0 (reference)	
1	0.9 (0.4, 1.9)	.77
2	1.0 (0.5, 2.2)	.91
3	2.6 (1.1, 6.0)	.03
4	5.5 (2.0, 15.2)	<.001
Quadriceps strength difference between matched knees		
Strength lower by ≥4% in control knee	1.0 (reference)	
Strength lower by ≥4% in case knee	1.4 (1.0, 1.9)	.045
Absolute difference <4%	...	

[a]*Values in parentheses are 95% confidence interval.*