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IS PAIN IN ONE KNEE ASSOCIATED WITH ISOMETRIC MUSCLE STRENGTH IN THE CONTRALATERAL LIMB? - DATA FROM THE OSTEOARTHRITIS INITIATIVE (OAI)

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Abstract

Objective—Knee pain and muscle weakness confer risk for knee osteoarthritis incidence and progression. The purpose of this study was to determine whether unilateral knee pain influences contralateral thigh muscle strength.

Design—Of 4796 Osteoarthritis Initiative participants, 224 (mean±SD age 63.9±8.9 years) cases could be matched to a control. Cases were defined as having unilateral knee pain (numerical rating scale (NRS) 4/10; infrequent pain) and one pain-free knee (NRS 0–1; infrequent pain; WOMAC 1). Controls were defined as having bilaterally pain-free knees (NRS 0–1; infrequent pain; WOMAC 1). Maximal isometric muscle strength [N] was compared between limbs in participants with unilateral pain (cases), and between pain-free limbs of cases and controls.

Results—Knee extensor/flexor strength in pain-free limbs of cases was lower than in bilaterally pain-free controls (−5.5%/−8.4%; $p=0.043/p=0.022$). Within cases, maximum extensor/flexor strength was significantly lower in the painful than in the pain-free limb (−6.4%/4.1%; $p<0.0001/p=0.015$).

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Conflict of interest

The authors do not have any potential conflict of interest in the connection with the work submitted for publication.

Author's contribution

All authors have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Specific contributions are:

1. The conception and design of the study:
2. Acquisition of data:
3. Analysis and interpretation of data:
4. Drafting the article:
5. Revising the article critically for important intellectual content:
6. Final approval of the version submitted:
7. Statistical expertise:

Conclusions—These results suggest that strength in limbs without knee pain is associated with the pain status of the contralateral knee. The strength difference between unilateral pain-free cases and matched bilateral pain-free controls was similar to that between limbs in persons with unilateral knee pain. Lower strength due to contralateral knee pain might be centrally mediated.

Keywords

Central inhibition; Knee Osteoarthritis; Muscle strength; Pain

Introduction

Osteoarthritis (OA) is a major cause of knee pain,^{1,2} functional limitations and disability³ leading to substantial reductions in quality of life. Functional limitations and disability are associated with impairments in muscle strength.^{2–4} It has been suggested that this reduction in muscle strength with knee OA is due to disuse atrophy from avoidance of painful activities. However, several lines of evidence suggest arthrogenic muscle inhibition contributes to knee OA-related muscle weakness.⁵

A reduction in muscle strength may be mediated by altered afferent signals arising from painful joints, and these afferent signals appear to cause neural inhibition of the musculature surrounding the affected joint.^{6–8} There is also evidence that this process may influence muscle strength in the pain-free, contralateral limb.⁹ This may be explained by voluntary-activation deficits via inhibition from the central nervous system,^{10,11} a mechanism thought to balance the muscle activation level between limbs. However, the extent to which measurement of knee extensor/flexor strength in one limb depends on the pain status of the contralateral limb is currently unclear. This has implications for both rehabilitation interventions, which may require a bilateral approach to treatment of unilateral symptomatic knee OA, as well as the validity of research approaches that utilize the contralateral limb as a control for unilateral symptomatic knee OA.

Measurement of knee extension or flexion force/moments is an established means of quantifying muscle strength that is used diagnostically and for monitoring interventions aimed at improving strength. In contrast to other functional performance tests such as walking speed and chair-rise time that rely on contributions from both limbs, muscle strength testing can be applied to each limb separately, enabling investigation of whether unilateral knee pain influences muscle strength in both limbs.

The objective of this study, therefore, was to quantify the difference in maximum knee extensor and flexor muscle strength, comparing pain-free limbs of participants with unilateral knee pain with limbs of participants without knee pain, using a matched case-control design (primary aim). On an exploratory basis, we also studied differences of “time to produce 90% of maximum force” and “speed of force production.” *In order to assess the strength of evidence from the primary analysis*, analyses were repeated within a more strictly selected but smaller sample, in order to test the sensitivity of the results to the selection criteria. Participants were selected from a cohort of nearly 5000 participants in the Osteoarthritis Initiative (OAI), for whom isometric strength, pain, and other clinical data are available. To our knowledge, no study has previously investigated the impact of unilateral

pain on muscle strength in the non-osteoarthritic, asymptomatic knee in individuals with unilateral knee pain.

Methods

The Osteoarthritis Initiative

Data used in this study were obtained from the OAI database (February the 1st, 2013), which is available for public access at <http://www.oai.ucsf.edu/>.¹² We used data from the 2-year follow-up visit, because self-reported pain levels at baseline may be biased by the motivation of the subjects to participate in the study. The study rationale and general inclusion criteria for the OAI (e.g. age 45 to 79 years of age, presence of symptoms and/or knee radiographic OA, or risk factors for developing knee OA) have been published previously.¹² The study population (n=4,796) was recruited at the University of Maryland School of Medicine and Johns Hopkins University School of Medicine, the Ohio State University, the University of Pittsburgh, and the Memorial Hospital of Rhode Island. Informed consent was obtained from all participants and the study was approved by the local ethics committees.

Knee Radiographs

Semi-quantitative readings of the radiographic disease stage were performed centrally by readers from Boston University. For each knee, the Kellgren-Lawrence grade (KLG), osteophyte and joint space narrowing (JSN) scores were determined from the fixed-flexion radiographs obtained at 2-year follow up.^{12–14}

Knee Pain

Participants indicated frequency of knee pain and rated their average knee pain and pain during specific activities. Specifically, pain frequency over the past 12 months was defined as no pain (Sx0), infrequent pain (pain on less than most days of a month, Sx1) and frequent pain (pain on most days of a month in at least one of the past 12 months, Sx2). Participants also rated average knee pain for each knee covering the past seven days preceding the OAI appointment on a scale of 0 to 10 (numerical rating scale, NRS). Pain during five activities (walking, stairs, in bed, sit or lie down, standing) over the seven days preceding the OAI visit was also assessed for each knee using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale. Scores for the WOMAC pain subscale range from 0 to 20 with higher scores indicating greater pain. Both NRS and WOMAC knee pain were utilized to confirm pain free status contralateral to cases' symptomatic knees.

Isometric strength measurement

The maximum isometric strength of the quadriceps and of the hamstrings was measured using the “Good Strength Chair” (Metitur Oy Jyväskylä, Finland) at the baseline, 2-year, and 4-year follow-up (<https://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf>). Participants were seated upright with their legs hanging over the edge of the chair. The pelvis and thighs were stabilized using a seatbelt and two warm-up repetitions were performed at 50% effort. Measurements were performed by trained and certified research technicians who recorded the best of three maximal efforts. The maximal force [N] was

measured at 60° knee flexion, and participants were encouraged to push the leg forward against the pad (extension) and pull the leg back against the pad (flexion), respectively. In addition to the force measurements, a number of other electronically recorded variables from the same trial were also captured including the time to produce 90% of maximal force [s] and the speed of force production [N/s].

Measurement of physical activity

The physical activity level was determined using the validated Physical Activity Scale for the Elderly (PASE) questionnaire, which covers three domains of activity within the “past seven days” (<https://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf>): leisure activities, household activities and occupational activities”.¹⁵ The individual leisure activities consisted of sitting, walking, light sport/recreation, moderate sport/recreation, strenuous sport/recreation, and muscle strength/endurance training. The individual household activities consisted of light housework, heavy housework, home repairs, lawn work/yard care, outdoor gardening, and caring for another person. Each activity is scored for frequency and hours per day using a 4-point scale (0 = never; 1 = 1–2 days; 2 = 3–4 days; 3 = 5–7 days). The PASE score can range from 0 to >400.¹⁵

Participant selection

Of the 4796 OAI participants, 3078 had bilateral measurement of isometric muscle strength, full demographic information available at 2-year follow-up, and did not have end-stage radiographic knee OA (KLG4). Of these, 312 fulfilled the case definition of unilateral knee pain, while 1027 participants were bilaterally pain free and fulfilled the control definition.

Case definition

- a. one knee with a NRS pain intensity value of 0–1, either no pain ($S_x=0$) or infrequent pain ($S_x=1$) during the past 12 months, and a WOMAC score of 0–1, indicating no pain or mild pain during one of the five activities.
- b. the contralateral knee with a NRS pain intensity value ≥ 4 (i.e. greater than the patient acceptable symptom state) and either frequent pain ($S_x=2$) or infrequent pain ($S_x=1$) during the past 12 months

Control definition

Bilaterally pain-free knees, i.e. both knees had a NRS pain intensity value of 0–1, either no (or infrequent) pain during the past 12 months ($S_x=0-1$), and a WOMAC score of 0–1.

Of the 312 participants with unilateral knee pain, 224 could be matched to a control with the same sex and race (White/African American), and with similar age (± 5 years), body height (± 5 cm), BMI (± 3 kg/m²) and radiographic knee OA status (KLG 0/1 or 2/3).

In a second step (sensitivity analysis), we used a stricter definition for pain-free knees in unilateral pain cases as follows:

- a. One knee with a NRS pain intensity value of 0, no pain ($S_x=0$) during the past 12 months, and a WOMAC score of 0

- b. A contralateral knee with an NRS pain intensity value ≥ 4 (i.e. greater than the patient acceptable symptoms state) and either frequent pain ($S_x=2$) or infrequent pain ($S_x=1$) during the past 12 months. Also, we used a stricter control definition, in which both knees had to have an NRS pain intensity value of 0, no pain ($S_x=0$) during the past 12 months, and a WOMAC score of 0.

A total of 76 participants fulfilling these stricter selection criteria could be matched to a case with the same sex and race (White/African American), and with similar age (± 5 years), body height (± 5 cm), BMI (± 3 kg/m²) and radiographic knee OA status (KLG 0/1 or 2/3).

An overview of the selection process is given in Figure 1.

Statistical analyses

Pain-free limbs of participants with unilateral knee pain (cases) were matched with the limb of bilaterally pain-free controls as previously described.¹⁶ In the first step, a matching algorithm was used to compute the difference for each matching criterion between all cases and controls. The differences were then normalized to a range of 0 to 1, to avoid weighting certain criteria over others. Next, the normalized differences were squared. In a second step, the sum of the squared differences was computed for the cases and controls and entered into a hash table, which provides a faster lookup for the matching process. At this stage, invalid matches were excluded (i.e. if the difference exceeded a threshold or fixed criteria such as same sex). In a third step, the optimal case-control match (i.e. minimal sum of squared differences) was determined from the hash table, selected as a matched pair, and then taken from the pool of cases and controls, to avoid matching one control to multiple cases. There were 88 case and control subjects who could not be matched for the primary analysis, because one or more of the predefined thresholds were exceeded (e.g. same sex or age ± 2 years).

Comparison of differences in the maximal isometric knee extension/flexion force between pain-free limbs of participants with unilateral pain (cases) and matched limbs of subjects who were bilaterally pain-free (controls) was the primary focus of the analysis. Differences in “time to 90% strength production [s]” and in “speed of force production [N/s]” were considered exploratory endpoints. *In order to assess the strength of evidence from the primary analysis*, analyses were repeated within a more strictly selected but smaller sample ($n=76$), in order to test the sensitivity of the results to the selection criteria.

Because demographic factors and radiographic OA status were controlled between cases and controls by matching, differences between matched cases and controls were assessed using paired t-tests. In the sensitivity analyses, these tests were repeated in the subpopulations with stricter criteria for unilateral pain status; this was done to explore the extent to which the primary results were sensitive to the selection process. The absolute differences were computed by using simple subtraction (value in painless knee of the cases minus that in the matched control knee). Percent differences were computed by relating the above difference to the value in the pain-free knee of cases. The level of significance was set at $p\text{-value} < 0.05$ and 95% confidence intervals (CIs) were computed for between-group differences. All

statistical tests were performed using Microsoft Office Excel 2010 (14.0.7128.5000 (32-Bit) Microsoft Inc. Redmond, WA, USA).

Results

Relevant demographic and clinical data are shown in Table 1. These did not differ significantly between cases and controls, as was expected due to the matched study design. Both groups included 129 women (95 men), who were White (203) or African-American (21). The PASE score tended to be lower in cases than controls, but the difference (−11.8) did not attain statistical significance (−8.0%; $p=0.124$).

Primary analytic focus (muscle strength)

The maximum extensor strength of pain-free knees in cases was 5.5% lower (−18.2N; 95% CI [−35.7N, −0.6N]; $p=0.043$) than in matched bilaterally pain-free controls. Similarly, the maximum flexor strength in the cases was 8.4% lower (−10.7N; [−19.9N, −1.6N]; $p=0.022$) than in the matched controls (Table 2, Figure 2). For comparison, a significant difference in extensor and flexor strength was observed between pain-free and painful knees in unilateral pain cases, with painful limbs exhibiting a 6.4% lower (19.8N; [11.2N,28.5N]; $p<0.0001$) extensor strength, and 4.1% lower (5.0N; [1.0N; 9.0N]; $p=0.015$) flexor strength (Table 3, Figure 2).

Secondary analytic focus (speed of force production)

There were no statistically significant differences in the “time to produce 90% of the maximum forces” or for the “speed of force production” for extension/flexion comparing cases with controls (Table 2).

Sensitivity analyses (muscle strength)

Relevant demographic and clinical data are shown in Table 4. Both groups included 41 women (35 men), who were White (71) or African-American (5). The PASE score tended to be lower in cases than controls, but the difference (−17.1) again did not attain statistical significance (−11.7%; $p=0.355$). Sensitivity analyses produced similar results, though the magnitude of differences was slightly greater. Specifically, the maximum extensor strength of pain-free knees in cases was 6.2% lower (−21.1N; 95% CI [−49.5N,7.4N]; $p=0.151$) than in matched bilaterally pain-free controls. The maximum flexor strength for the pain-free knees in the cases was 9.3% lower (−12.3N; [−27.6N,3.0N]; $p=0.119$) than in the matched controls (Table 5). Within cases, a significant difference in extensor and flexor strength was observed between pain-free and painful knees of the more strictly selected cases, with painful knees exhibiting a 11.9% lower extensor strength (36.1N; [22.6N,49.5N]; $p<0.0001$), and 8.2% lower flexor strength (10.1N; [2.1N;18.0N]; $p=0.008$; Table 6).

For secondary analyses, again there were no statistically significant differences in the “time to produce 90% of the maximum forces” or for the “speed of force production” for extension/flexion comparing more strictly selected cases with controls (Table 5).

In contrast to the finding within the case population, no significant differences were noted for extensor/flexor strength of bilaterally pain-free controls, neither in the larger group of 224 OAI participants nor in the sensitivity analyses with 76 more strictly selected bilaterally pain-free participants (Table 7).

Discussion

The objective of this study was to advance knowledge of the relationship between knee pain and knee function, as measured through muscle strength. Specifically, this study investigated whether muscle strength differed between limbs of participants with unilateral knee pain compared to limbs of matched bilaterally pain-free controls. The results of this study showed significantly lower isometric extensor and flexor strength in the pain-free limbs of cases with unilateral pain, when compared with bilaterally pain-free controls. For control purposes, we also observed significantly lower strength in the painful limb than in the pain-free limb of the cases with unilateral knee pain, while no significant differences were detected between the two pain-free knees of the controls. To minimize sources of bias in this study, case and control subjects were matched for a number of anthropometric and demographic parameters (leg dominance, age, sex, height, BMI, race, and radiographic OA stage), which otherwise may have confounded associations between thigh muscle strength measurements and pain. Since no significant differences for anthropometric or demographic data were observed within the study samples, the matching appears to have been successful. To our knowledge, this is the first study to observe differences that could potentially reflect an impact of central inhibition on thigh muscle strength in the asymptomatic limb in people with limbs discordant for knee pain.

Differences in muscle strength may be caused by differences in age, sex, height, BMI, physical activity or presence of OA. To minimize the potential impact of these above-mentioned factors, a very intensive matching was performed. It has to be stated that minimal differences regarding anthropometric factors, physical activity or radiographic state cannot totally be sourced out through the matching. It is also noteworthy that although participants were intensively matched, differences in muscle morphology cannot be excluded. In the sensitivity analyses, height in controls tended to be higher than in cases, and mass tended to be greater. However, the matching procedure was successful and a residual mean difference of <1cm in body height and <1kg in body mass between cases and controls should not confound the analysis. Unfortunately we could not present data on muscular strength per unit of muscle cross sectional area. The availability of muscle cross sectional areas would enable identification of whether the reduction in strength is accompanied by a similar reduction in cross sectional areas, or if it represents a reduction in specific strength (loss of strength without loss of muscle bulk). This limitation could be addressed in follow-up studies. The reduction of muscle strength as presented in this work is statistically significant. The extent to which a reduction in muscle strength of 5–10% is clinically relevant is unclear, but has been found to be clinically meaningful in younger adults.

Reduced quadriceps strength is one of the earliest clinical findings among persons with knee pain and may play an important role in the development of OA.¹⁷ The quadriceps muscle essentially stabilizes the knee joint and absorbs mechanical shocks during physical activity

and body movement.¹⁸ Quadriceps weakness is thought to be an essential factor for knee pain, disability, and progression of joint damage.¹⁹ Whereas muscle weakness is consistently found in patients with knee OA, greater muscle strength is associated with a reduced risk for OA development and progression.¹⁷ Given the lack of treatment for established knee OA, the prevention of progression is highly important for patients, to avoid or delay pain, functional limitations and eventually joint replacement surgery. Current treatment guidelines therefore recommend people with or at risk for OA to strengthen the quadriceps muscles.^{5,20} However, it is not clear whether such recommendations may have a symptom-modifying effect,^{18,21} nor how treatments should be modified to address strength deficits when one limb is more affected than the other.

Increased age has been purported to explain risk for pain, progression of OA and reduced muscle strength. Independent of OA, approximately 45% of the older adults in the U.S. are affected by a loss of skeletal muscle mass with age.²² This loss might be one of the reasons for an increased incidence and progression of OA in older adults, but in our study, cases were matched to controls with a maximum difference of age of ± 5 years, and therefore age would be unlikely to account for differences in strength. To prevent advanced muscle loss and weakness in an aging muscle, strengthening exercises are recommended to increase muscle mass, physical function, and quality of life.^{23,24} These recommendations are based on evidence that physically active subjects have greater muscle strength than less active ones. Therefore, a less active life style seems to have a potential role for severity and progression of OA. Consequently, differences in strength between both groups may also be caused by a less active lifestyle but should be detectable using the questionnaire for physical activity, the PASE-score.¹⁵ Within this study, the PASE-score was quite similar in cases and controls within the overall sample as well as in the stricter sample. Therefore, less physical activity did not account for impairments in muscle strength in the pain-free limbs of cases with unilateral knee pain versus matched bilaterally pain-free controls. These findings may indicate a potential role of central inhibition accounting for the impaired muscle strength in the pain-free limbs of older adults with unilateral knee pain, in comparison with matched participants without knee pain.²⁵

Radiographic severity is another factor that has been proposed to account for pain and loss of muscle strength. Within our study, the pain-free limb of cases was matched to the control limb by KLG grade as well, allowing us to eliminate disease severity as a potential contributor to differences in strength. Although participants were matched for KLG ([0–1]; [2–3]) very small differences in KLG were observed (pain-free limb of cases with unilateral knee pain: KLG 0: 100, KLG 1: 55, KLG 2: 49, and KLG 3: 20 vs. the bilateral pain-free matched control limb: KLG 0: 107, KLG 1: 48, KLG 2: 46, and KLG 3: 23). Several studies investigated the relationship between muscle strength and pathological changes, such as radiographic stage, cartilage loss, knee pain and physical function in subjects with and without radiographic OA.^{26,27} A new strategy for understanding the relationship of radiographic OA, muscle strength, knee function and pain was reported by Sattler et al.²⁷ Within the same radiographic severity, frequently painful knees were found to have lower quadriceps muscle cross-sectional areas and strength than contralateral pain-free knees, whereas Ruhdorfer et al.²⁸ reported that once knees have reached frequent pain status, the longitudinal decline in quadriceps properties and physical function were not associated with

radiographic severity of OA. Due to matching on this factor, the reduction in muscle strength within the non-affected limb could not be explained by the radiographic stage. Therefore, our data suggest that, in participants with unilateral pain, pain accounts for lower measurements of muscle strength not only on the symptomatic side, but also in the contralateral pain-free limb.

The systematic review of Hart et al.⁵ reported bilateral quadriceps weakness or activation failure to be observed after unilateral injury, which provides corroborative evidence of bilateral quadriceps central activation failure. Additionally, the meta-analysis of Pietrosimone et al.¹⁰ reported that previous studies that investigated a central inhibitory effect may have been limited in that they did not strictly exclude participants with possible cartilage degeneration in the contralateral control knee. If central inhibition were to account for these findings, this effect could influence measurements of strength and should be considered in conducting strength measurements in subjects with knee pain. Ruhdorfer's study²⁸ was conducted to address this limitation in knee classification and our current study classified pain-free knees of cases (those contralateral to the painful knee in subjects with unilateral pain) and control knees entirely on pain scales and matched knees within no radiographic OA (KLG 0/1) and definite radiographic OA (KLG 2/3). Participants with late stage radiographic OA were excluded. Additionally, in a recent study by Ruhdorfer et al.²⁹, pain was found to have a much stronger influence on strength than radiographic status.

Pietrosimone et al.¹⁰ suggested that reflexive or cortical central nervous system modulations may influence quadriceps volitional activation deficits.^{6,7,30} A typical consequence of joint injury is the arthrogenic muscle inhibition, a reflexive down-regulation of a joint's surrounding musculature to initially protect the joint from further damage,^{5,9,30} which also prevents full muscle activation that may contribute to pathological overloading of a joint with OA. In our study, we found that this reflexive down-regulation also appears to occur, to an extent, in the pain-free limb. This could potentially indicate a mechanism intended to protect the pain-free knee from damage and to balance the strength bilaterally for control of movement.

Interestingly, a 19.8N difference was observed in isometric knee extensor strength, comparing the painful and the pain-free limbs of cases with unilateral pain. This finding implies that exercise may be indicated bilaterally for patients with unilateral knee pain, as the painless limb appears to have reduced strength as well. The observed difference of the unilateral pain-free limb within cases compared to the matched pain-free controls was 18.2N in the full cohort and 21.1N in the stricter sample. These findings are remarkable due to the fact that the painful limb was defined by an NRS 4, a non-acceptable symptom stage for knee pain. Again, age, sex or other anthropometric data could not influence these findings due to the matching process.

A potential limitation of this study is that a substantial number of participants had to be excluded because of the strict selection criteria. Further, during the matching process, a large number of eligible cases (n=88, 28%) could not be matched with the pool of eligible controls (n=803, 78%) due to the a priori decision to match on multiple factors simultaneously. Consequently, the sample size, while adequate for the primary analyses,

may have been insufficient to confirm additional significant effects on other muscle strength parameters (the “time to produce 90% of the maximum forces” and the “speed of force production” for extension/flexion) or in the sensitivity analysis cohort (strict sample: n=76). Nonetheless, the highest absolute difference is seen within the strict sample (6.2%), although not reaching significance in contrast to 5.5% in the full cohort.

Conclusions

The results suggest that strength measurements in pain-free limbs depend on pain status of the contralateral knee. The magnitude of this difference in strength is similar to that between painful and pain-free limbs of cases with unilateral knee pain. Effects from the contralateral painful knee on strength measurements might be mediated by central nervous system inhibition.

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Abbreviations

BMI	Body Mass Index
EMF	extension maximum force [N]
ESFP	extension speed of force production [N/s]
ETFP	extension time to produce 90% of max force [s]
FMF	flexion maximum force [N]
FSFP	flexion speed of force production [N/s]
FTFP	flexion time to produce 90% of max force [s]
JSN	Joint space narrowing
KLG	Kellgren-Lawrence Grade
NRS	Numerical Rating Scale
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
PASE	Physical Activity Scale for the Elderly

WOMAC the Western Ontario and McMaster Universities Arthritis Index

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Figure 1. Selection process of “cases” with unilateral pain, and bilaterally pain-free controls
 Abbreviations: KLG - Kellgren-Lawrence grade; Sx – variable for knee pain frequency;
 NRS – numerical rating scale; WOMAC - the Western Ontario and McMaster Universities
 Arthritis Index

Figure 2. Thigh muscle strength differences between cases (unilateral pain-free) and controls (bilaterally pain-free)

Legend: Cases: pain-free limbs of participants with unilateral knee pain (n=224)

Controls: pain-free limbs of participants with bilateral pain-free knees (n=224)

* statistically significant [95% confidence interval]

Table 1

Characteristics of Cases Compared with Controls

	Case (mean±SD)	Control (mean±SD)	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-TEST
Age [years]	63.9±8.9	63.8± 8.8	0.1	[-0.1,0.3]	0.2	p=0.298
Height [cm]	167.9±10.7	168.7± 9.3	-8.3	[-18.5,1.9]	-0.5	p=0.113
Weight [kg]	79.4±16.2	80.1±14.3	-0.6	[-1.6,0.4]	-0.8	p=0.231
BMI [kg/m²]	28.1±4.2	28.1± 4.2	0.0	[0.0,0.1]	0.0	p=0.766
PASE score	147.7±69.2	157.8±83.0	-11.8	[-24.6,1.0]	-8.0	p=0.124

Legend: Values are the mean±SD,

* is considered statistically significant; p-values for comparison of absolute differences.

Cases; pain-free limbs of participants with unilateral knee pain; Controls; pain-free limbs of participants with bilateral pain-free knees; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference for each matched pair and the average percent difference among matched pairs; Abbreviations: BMI, body mass index; PASE, physical activity scale for the elderly;

Table 2

Parameters for Muscle Strength of Cases Compared with Controls

	Case (mean±SD)	Control (mean±SD)	Absolute Difference	Confidence Interval[CI]	Percent Difference (%)	Paired T-TEST
EMF [N]	332.5±108.0	350.6±145.5	-18.2	[-35.7,-0.6]	-5.5	p=0.043*
FME [N]	128.0±52.4	138.8±74.1	-10.7	[-19.9,-1.6]	-8.4	p=0.022*
ETFP [s]	1.6±0.7	1.6±0.7	0.0	[-0.1,0.2]	0.4	p=0.581
FTFP [s]	1.5±0.6	1.5±0.6	0.0	[-0.1,0.2]	2.7	p=0.525
ESFP [N/s]	462.1±344.6	546.9±611.1	-80.0	[-165.8,5.8]	-17.3	p=0.119
FSFP [N/s]	173.3±148.5	189.0±160.6	-17.7	[-45.2,9.8]	-10.2	p=0.125

Legend: Values are the mean ± SD.

* is considered statistically significant; p-values for comparison of absolute differences.

Cases: pain-free limbs of participants with unilateral knee pain; Controls: pain-free limbs of participants with bilateral pain-free knees; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference for each matched pair and the average percent difference among matched pairs;

Abbreviations: EMF, extension maximum force [N]; FME, flexion maximum force [N]; ETEP, extension time to produce 90% of max force [s]; FTEP, flexion time to produce 90% of max force [s]; ESFP, extension speed of force production [N/s]; FSFP, flexion speed of force production [N/s];

Table 3
Lower Limb Muscle Measurements in the Pain Free Compared with the Painful Limb in Cases

	Pain-Free Limbs of Cases(n=224)	Painful Limbs of Cases (n=224)	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-TEST
EMF [N]	332.5±108.0	312.6±112.8	19.8	[11.2,28.5]	6.4	p<0.0001*
FMF [N]	128.0±52.4	123.0±52.8	5.0	[1.0,9.0]	4.1	p=0.015*
ETFP [s]	1.6±0.7	1.5±0.7	0.0	[-0.1,0.1]	0.3	p=0.782
FTFP [s]	1.5±0.6	1.5±0.6	0.0	[-0.1,0.1]	-0.1	p=0.957
ESFP [N/s]	462.1±344.6	454.2±340.5	4.7	[-39.1,48.6]	1.0	p=0.801
FSFP [N/s]	173.3±148.5	157.3±136.0	13.7	[-2.9,30.3]	8.7	p=0.154

Legend: Values are the mean ± SD.

* is considered statistically significant; p-values for comparison of absolute differences.

Cases: pain-free limbs of participants with unilateral knee pain; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference between the painful and the pain-free limb of cases and their average percent difference;

Abbreviations: EMF, extension maximum force [N]; FMF, flexion maximum force [N]; ETFP, extension time to produce 90% of max force [s]; FTFP, flexion time to produce 90% of max force [s]; ESFP, extension speed of force production [N/s]; FSFP, flexion speed of force production [N/s];

Table 4

Characteristics within the Sensitivity Analyses of Cases Compared with Controls

	Case	Control	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-TEST
Sex (male/female)	35/41	35/41	-	-	-	-
Race (White/African American)	71/5	71/5	-	-	-	-
Age [years]	64.9±8.9	64.8±8.8	0.1	[-0.2/0.5]	0.2	p=0.390
Height [cm]	167.1±9.5	168.8±9.2	-17.2	[-34.8/0.3]	-1.0	p=0.058
Weight [kg]	78.6±13.1	80.3±13.2	-1.7	[-3.4/0.0]	-2.2	p=0.050
BMI [kg/m²]	28.1±3.4	28.1±3.4	-0.0	[-0.1/0.1]	-0.1	p=0.756
PASE-score	145.7±79.3	157.6±79.2	-17.1	[-42.4/8.2]	-11.7	p=0.355

Legend: Values are the mean±SD; p-values for comparison of absolute differences.

Abbreviations: BMI, body mass index; PASE, physical activity scale for the elderly;

Cases: pain-free limbs of participants with unilateral knee pain; Controls: pain-free limbs of participants with bilateral pain-free knees; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference for each matched pair and the average percent difference among matched pairs;

Table 5
Parameters for Muscle Strength in the Sensitivity Analyses of Cases Compared with Controls

	Pain-Free Limbs of Cases	Matched Pain-Free Control	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-Test
EMF [N]	338.7±121.3	359.8±115.5	-21.1	[-49.5/7.4]	-6.2	p=0.151
FMF [N]	132.8±62.5	145.1±55.6	-12.3	[-27.6/3.0]	-9.3	p=0.119
ETFP [s]	1.5±0.5	1.5±0.6	0.0	[-0.2/0.2]	1.0	p=0.634
FTFP [s]	1.5±0.6	1.4±0.6	0.1	[-0.1/0.3]	7.9	p=0.277
ESFP [N/s]	420.1±299.7	539.6±418.2	-118.0	[-242.4/6.4]	-28.1	p=0.115
FSFP [N/s]	151.5±119.0	192.8±146.9	-38.9	[-81.9/4.1]	-25.7	p=0.144

Legend: Values are the mean±SD; p-values for comparison of absolute differences.

Cases: pain-free limbs of participants with unilateral knee pain; Controls: pain-free limbs of participants with bilateral pain-free knees; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference for each matched pair and the average percent difference among matched pairs;

Abbreviations: EMF, extension maximum force [N]; FMF, flexion maximum force [N]; ETFP, extension time to produce 90% of max force [s]; FTFP, flexion time to produce 90% of max force [s]; ESFP, extension speed of force production [N/s]; FSFP, flexion speed of force production [N/s];

Table 6

Sensitivity analysis comparing the painful and pain-free limb of the 76 OAI participants with discordant knee pain status (cases)

	Pain-Free Limbs of Cases (n=76)	Painful Limbs of Cases (n=76)	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-TEST
EMF [N]	338.7±121.3	302.7±113.8	36.1	[22.6,49.5]	11.9	p<0.0001*
FMF [N]	132.8±62.5	122.7±60.5	10.1	[2.1,18.0]	8.2	p=0.008*
ETFP [s]	1.5±0.5	1.5±0.6	-0.1	[-0.2,0.1]	-3.4	p=0.836
FTFP [s]	1.5±0.6	1.6±0.7	-0.1	[-0.2,0.1]	-3.4	p=0.434
ESFP [N/s]	420.1±299.7	384.3±271.0	26.0	[-37.8,89.8]	6.8	p=0.041*
FSFP [N/s]	151.5±119.0	139.1±140.6	10.9	[-19.0,40.9]	7.9	p=0.020*

Legend: Values are the mean ± SD,

* is considered statistically significant; p-values for comparison of absolute differences.

Cases: pain-free limbs of participants with unilateral knee pain; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference between the painful and the pain-free limb of cases and their average percent difference;

Abbreviations: EMF, extension maximum force [N]; FMF, flexion maximum force [N]; ETFP, extension time to produce 90% of max force [s]; FTFP, flexion time to produce 90% of max force [s]; ESFP, extension speed of force production [N/s]; FSFP, flexion speed of force production [N/s];

Table 7

Comparison between both pain-free limbs of the 224 and the 76 (sensitivity analyses) OAI participants with bilaterally pain-free limbs (control)

	Control (n=224) (matched knee)	Control (n=224) (non-matched knee)	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-TEST
EMF [N]	350.6±145.4	353.2±141.8	-2.5	[-11.0,6.0]	-0.7	p=0.562
FMF [N]	138.8±74.1	136.5±75.5	2.3	[-1.5,6.0]	1.6	p=0.235
ETFP [s]	1.6±0.7	1.6±0.7	0.0	[-0.1,0.1]	-0.9	p=0.895
FTFP [s]	1.5±0.6	1.5±0.7	0.0	[-0.1,0.1]	-2.2	p=0.540
ESFP [N/s]	546.9±611.1	523.5±549.7	20.4	[-32.2,72.9]	3.7	p=0.620
FSFP [N/s]	189.0±160.6	194.8±154.5	-5.1	[-28.4,18.3]	-2.7	p=0.672
	Control (n=76) (matched knee)	Control (n=76) (non-matched knee)	Absolute Difference	Confidence Interval [CI]	Percent Difference (%)	Paired T-TEST
EMF [N]	359.8±115.5	365.7±118.9	-18.9	[-49.4,11.5]	-5.2	p=0.332
FMF [N]	145.1±55.6	143.4±58.2	-4.1	[-19.3,11.2]	-2.8	p=0.614
ETFP [s]	1.5±0.6	1.6±0.6	0.0	[-0.2,0.2]	0.8	p=0.603
FTFP [s]	1.4±0.6	1.5±0.8	0.0	[-0.3,0.2]	-2.6	p=0.869
ESFP [N/s]	539.6±418.2	527.7±400.6	9.0	[-117.8,135.8]	1.7	p=0.841
FSFP [N/s]	192.8±146.9	228.6±254.5	-2.9	[-52.4,46.5]	-1.3	p=0.232

Legend: Values are the mean±SD,

* is considered statistically significant; p-values for comparison of absolute differences.

Controls: pain-free limbs of participants with bilateral pain-free knees; The absolute differences, the percent differences (%) and 95% confidence intervals [CI] were calculated using the percent difference for each matched pair and the average percent difference among matched pairs;

Abbreviations: EMF, extension maximum force [N]; FMF, flexion maximum force [N]; E/TFP, extension time to produce 90% of max force [s]; F/TFP, flexion time to produce 90% of max force [s]; ESFP, extension speed of force production [N/s]; FSFP, flexion speed of force production [N/s];