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Thigh muscle specific strength and the risk of incident knee osteoarthritis: the influence of sex and greater body mass index

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Abstract

Objective—To determine whether lower thigh muscle specific strength increases risk of incident radiographic knee osteoarthritis (RKOA), and whether there exists a sex-specific relationship between thigh muscle specific strength and BMI.

Methods—161 Osteoarthritis Initiative participants (62% female) with incident RKOA (Kellgren-Lawrence grade 0/1 at baseline, developing an osteophyte and joint space narrowing grade ≥1 by year 4) were matched to 186 controls (58% female) without incident RKOA. Thigh muscle anatomical cross-sectional areas (ACSAs) were determined at baseline using axial MRI scans. Isometric extensor and flexor muscle strength were measured at baseline and specific strength (strength÷ACSA) calculated. Logistic regression assessed risk of incident RKOA associated with muscle specific strength (with and without adjustment for BMI).

Results—Lower knee extensor and flexor specific strength significantly increased the risk of incident RKOA in women (OR 1.47 [95%CI 1.10, 1.96] and 1.41 [1.06, 1.89], respectively) but not in men. The significant relationship in women was lost after adjustment for BMI. Lower specific strength was associated with higher BMI in women ($r=-0.29$, $p<0.001$), but not in men; whereas (absolute) strength was associated with BMI in men ($r=0.28$, $p=0.001$), but not in women.

Conclusion—Lower thigh muscle specific strength predicts incident RKOA in women, with this relationship being confounded by BMI. The sex-specific relationship between muscle specific strength and BMI provides a possible explanation why women with muscle strength deficits typically have a poorer prognosis than men with similar strength deficits.

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Potential conflict of interest: Wolfgang Wirth has a part time employment with Chondrometrics GmbH and is a co-owner of Chondrometrics GmbH, a company providing MRI analysis services to academic researchers and to industry. Torben Dannhauer has a part time employment with Chondrometrics GmbH. Felix Eckstein is CEO of Chondrometrics GmbH; he has provided consulting services to Merck Serono, Bioclinica/Synarc and Samumed, has prepared educational sessions for Medtronic, and has received research support from Pfizer, Eli Lilly, Merck Serono, Novartis, Stryker, Abbvie, Kolon, Synarc, Ampio, BICL and Orthotrophix. Adam Culvenor, Martina Sattler, Jingbo Niu and David Felson have no competing interests.

Keywords

muscle strength; osteoarthritis; incidence; risk factor; body mass index

Thigh muscle weakness is a common feature of individuals with radiographic knee osteoarthritis (RKOA). Reports on the relationship between thigh muscle strength and the development of RKOA have however, presented conflicting data (1). These inconsistent findings in relation to incident RKOA likely, in part, reflect an emphasis on gross measurements of muscle strength that do not consistently control for body weight (a potent incident RKOA risk factor) (2) or account for intrinsic muscle properties (e.g., muscle size, muscle coordination, and motor unit recruitment) (3).

Muscle specific strength, a measure of muscle quality (muscle strength per unit muscle area), is a potentially more physiologically relevant measure of strength that may more closely relate to RKOA outcomes (3). For example, individuals with established RKOA, who displayed no deficits in thigh muscle strength, had significantly poorer specific strength, regardless of pain status (3). In relation to incident RKOA, the influence of poor muscle specific strength on the risk of RKOA development is unclear but is clinically important, since muscle specific strength (i.e., muscle strength per unit and anatomical cross-sectional area [ACSA]) is a potential modifiable risk factor. Segal et al (4) observed that poor knee extensor specific strength did not predict incident RKOA over 30-months in the Multicenter Osteoarthritis (MOST) study. However, specific strength was calculated using entire thigh muscle mass obtained from dual energy X-ray absorptiometry (DXA) and not specifically the quadriceps ACSA that is responsible for providing knee extensor strength (4).

Further, the relationship between thigh muscle weakness and RKOA onset and progression has typically been observed in women only, but not in men (5, 6), which may relate to a sex-specific muscle response to obesity (7). However, whether the relationship between thigh muscle (specific) strength characteristics and body mass index (BMI) differs between men and women, and drives poorer clinical outcomes and greater likelihood of incident RKOA in women with muscle strength deficits is not known. Therefore, the aims of this study were to determine: i) whether lower thigh muscle specific strength (using ACSAs from MRI) increases the risk of incident RKOA in men and women (and whether this relationship is confounded by BMI); and ii) whether the relationship between muscle specific strength (and ACSAs and strength) and BMI differ between men and women. This investigation may identify possible mechanisms driving commonly observed sex differences in the risk of poor RKOA prognosis in the presence of thigh muscle weakness. We hypothesized that thigh muscle specific strength would predict the risk of incident RKOA in women, but not in men, and that this difference may, at least in part, be explained by a sex-specific response of thigh muscle ACSAs and specific strength to variability in BMI.

METHODS

Participants

Participants were selected from the Osteoarthritis Initiative (OAI), an ongoing multicenter longitudinal study of 4,796 subjects aged 45–79 years, designed to identify risk factors for RKOA incidence and progression (http://oai.epi-ucsf.org/). The OAI was approved by each of the study site's institutional review board, and all participants gave informed consent.

The current ancillary study focusses on evaluating RKOA incidence; therefore, we selected all knees from participants who demonstrated incident RKOA over 48-month follow-up from the central readings of fixed-flexion anteroposterior radiographs (i.e., cases). Incident RKOA was defined as knees with Kellgren-Lawrence grade (KLG) 0/1 at baseline that developed both an osteophyte and joint space narrowing (JSN) (OARSI atlas JSN grade ≥1) by 48-month follow-up, as defined previously (8). If both knees of one participant met inclusion criteria, only the right knee was included. Participants needed to have both baseline T1-weighted axial-spin-echo MRI acquisitions of the thigh (imaging dataset 0.E.1) and baseline isometric maximal strength measures of the knee extensors and flexors available. Participants with incident RKOA were frequency matched by baseline KLG 0/1 (approximately 30%/70%, respectively) to control participants also with baseline thigh MRI and thigh strength measures, but without incident RKOA at 48-month follow-up.

Muscle ACSA and strength evaluation

Using custom software developed at our institution (9), ACSAs of the knee extensors (quadriceps) and flexors (hamstrings) were manually segmented by a trained observer (MS) from a single axial baseline MRI slice at anatomically consistent locations (33% femoral length; distal-proximal), with good test-retest precision and sensitivity to pain (10). A 'convex hull' algorithm from Open CV (http://opencv.org/) was used to delineate a 'sling' enclosing the manually segmented muscle tissue as tightly as possible, to separate intermuscular tissue (within the sling) and subcutaneous tissue (between the sling and outer thigh circumference) (9). The knee extensor and flexor ACSAs thus excluded intermuscular fat, vessels and fibrous tissue. Intramuscular adipose tissue could not be assessed by MRI and was therefore included in the ACSA measurements. Nevertheless, non-contractile intramuscular tissue should result in a lower specific strength value and thus be indirectly reflected by the target variable used in the current analysis. Maximal isometric knee extensor and flexor strength (best of three trials) was assessed at the baseline visit using the 'Good Strength Chair' (Metitur Oy, Jyvaskyla, Finland) at 60° flexion (10). Specific strength was calculated as strength per unit ACSA (N/cm^2).

Statistical analysis

Differences in demographic and thigh muscle parameter data between cases with incident RKOA and controls were evaluated using chi-square tests for binary data and independent samples *t*-tests for continuous data, independently for men and women. Sex-specific logistic regression analyses were used to assess whether low specific strength increased the risk of incident RKOA, with and without adjusting for baseline BMI and age (primary analysis). An odds ratio >1 represents greater odds of incident RKOA in the presence of low specific strength. To provide insights into the potential sex-specific mechanisms driving incident RKOA, the relationships between muscle ACSA, strength, and specific strength with BMI were evaluated using Pearson correlation coefficients (secondary analysis). Correlation coefficients were considered weak (<0.40), moderate (0.40–0.59), strong (0.60–0.79), or very strong (>0.80). All analyses were performed with SPSS V.20.0. *P*-values <0.05 were considered significant.

RESULTS

Participants

Of the 5,028 OAI participant knees without RKOA at baseline (i.e. KLG 0/1), 496 case and control knees were identified. Of those, 372 had baseline thigh MRIs and strength assessment. Of the 372 participant knees (186 case knees and 186 control knees), 25 participants had bilateral incident RKOA; in these only the right knee was analyzed (i.e., 25 left knees excluded), resulting in a total of 161 incident case knees (161 participants) and 186 frequency-matched control knees (186 participants) included in analyses. One-hundred (62%) and 108 (58%) case and control knees were female, respectively. Baseline age (61±9 years and 60±9 years) and frequency of KLG 1 (115 (71%) and 134 (72%)) did not differ between cases and controls, respectively (p>0.05). Whereas a higher BMI existed in knees with incident RKOA, in both men (cases 29.4±3.9; controls 27.8±3.7, p=0.015) and women (cases 28.9±4.4; controls 27.0±4.2, p=0.001).

Thigh muscle specific strength and risk of incident RKOA

In women with incident RKOA, the 5% greater knee extensor ACSA and 7% lower knee extensor strength compared to control knees resulted in knee extensor specific strength significantly increasing incident RKOA risk in non-adjusted analyses (Table 1). In men, in contrast, knee extensor ACSAs and strength (and hence specific strength) were similar between case and control knees (Table 2). In adjusted analyses (covariates: BMI, age), low knee extensor specific strength trended towards remaining statistically significant in women (p=0.060) and remained not significantly associated with incident RKOA in men (p=0.446). A similar pattern of results were observed in knee flexor ACSAs, strength and specific strength in men and women (Table 1, Table 2).

Relationship between thigh muscle characteristics and BMI

The relationship between thigh muscle characteristics and BMI did not differ between case and control knees (p>0.159), therefore case and control knees were combined for this part of the analysis. A moderate positive association was observed between knee extensor ACSA vs. BMI in both men (r=0.44, p<0.001) and women (r=0.46, p<0.001). Correlation graphs are presented in Supplementary File. There also was a weak (but statistically significant) association of knee extensor strength vs. BMI in men (r=0.28, p=0.001), but not in women (r=0.02, p=0.805). In women, a greater BMI was weakly (but significantly) associated with lower muscle specific strength (r=−0.29, p>0.001), while knee extensor specific strength in men was not significantly associated with BMI (r=0.01, p=0.962). A similar pattern of results were observed in the relationship between knee flexor characteristics and BMI (Supplementary File).

DISCUSSION

In this first evaluation of thigh muscle specific strength using ACSA from MRI as a predictor of incident RKOA, results show that deficits in knee extensor and flexor specific strength increase the risk of RKOA development in women only, and not in men. These findings in women were not significant in adjusted analyses, as the relationship between lower specific strength and incident RKOA risk was confounded by BMI (and age). The sex-specific response of thigh muscle characteristics to variations in BMI reveals a possible explanation for the divergent risk of incident RKOA in men and women with muscle deficits.

Until now, the relationship between thigh muscle weakness and incident RKOA has been mostly based on measures of muscle torque, with inconsistent conclusions in both men and women (1). By obtaining thigh muscle ACSA measures alongside thigh muscle strength, we were able to identify measures of specific strength that significantly increased the risk of incident RKOA (whereas typical muscle ACSA and strength per unit parameters did not) (Table 1). Our results extend previous cross-sectional data showing that muscle specific strength is more closely related to RKOA presence than muscle strength (3), possibly due to adipose deposition, muscle specific strength accentuating voluntary activation deficits, mitochondrial dysfunction or muscle fiber disorientation.

Our results contrast other muscle specific strength data from 1,303 participants in the MOST cohort, in which no statistically significant relationship was observed between knee extensor specific strength and incident RKOA (4). However, in this previous study whole thigh muscle mass measured by DXA was used rather than quadriceps ACSA, suggesting that specific strength determined by MRI may be more sensitive in detecting the relationship with incident RKOA. It is also possible that the inclusion of intramuscular adiposity in the MRI measurement of specific strength in the current study (which was corrected for in the previous DXA measurement) (4) explains the different results. Nevertheless, our findings of the relationship between thigh muscle specific strength and incident RKOA in women suggests that targeting specific impairments in muscle activation to increase strength per ACSA may be important in women at risk of RKOA. The ability of muscle activation interventions, such as muscle biofeedback and neuromuscular electrical stimulation, which attempt to optimize muscle specific strength and in turn reduce the risk of RKOA development, should be a focus of future research.

Low muscle specific strength increased the risk of incident RKOA in unadjusted analysis (and trended towards statistical significance in adjusted analyses) in women only. These data add to the growing body of evidence that women, but not men, with thigh muscle weakness are at an increased risk of RKOA, including joint space narrowing (11), worsening knee pain (12), and knee replacement (6).

A high BMI is a well-established risk factor for incident RKOA in both men and women. In our study, a higher BMI was associated with greater thigh muscle ACSA, which, due to a lack of association between BMI and muscle strength, likely reflects addition of non-contractile tissue (i.e., intramuscular adiposity) in women. In men, while a higher BMI was also associated with greater thigh muscle ACSA, a corresponding increase in thigh muscle strength occurred, likely reflecting addition of contractile tissue (i.e., muscle). This resulted in a lower muscle specific strength in women with a higher BMI, with this specific strength deficit trending towards being an independent risk factor for incident RKOA. In men, in contrast, not only ACSAs, but also strength was associated with a higher BMI, so that no relationship between muscle specific strength and BMI was observed. Similar sex-specific findings between knee extensor specific strength and BMI strata (from obese to moderately-severely obese) in those with and without RKOA support these findings (7). Despite muscle specific strength (i.e., quality) being independent of BMI in men, it was not sufficient to protect men with a higher BMI from an elevated risk of incident RKOA; the risk of incident RKOA with an elevated BMI may thus not depend on muscle specific strength in men. In women, the increased risk of incident RKOA with elevated BMI may, however, be somewhat influenced by a reduction in muscle specific strength, whereas in men, the relationship between BMI and incident RKOA may be driven by other mechanisms, such as altered biomechanics (13) or frontal plane knee alignment (14). The divergent response of muscle to a high BMI in men and women may provide an explanation why women with thigh muscle deficits are at a greater risk of incident RKOA and generally poorer prognosis than men with similar muscle deficits.

Although we included a comprehensive assessment of thigh muscles (size, strength, quality), a limitation of the current study is the lack of an exact voluntary muscle activation measure (i.e., electromyography), which was not available in the OAI. Similarly, assessment of intramuscular fat may have provided additional insights into the sex-specific response of thigh muscle to different levels of BMI; however, the thigh muscle MRI sequences acquired in the OAI are not suited for determining intramuscular fat ACSA. Intramuscular fat was therefore included in the ACSA muscle measurements in the current study. While we were able to include ≥100 incident RKOA female cases and controls, the trend for significant differences in muscle specific strength when adjusted for BMI suggests that this analysis may have been underpowered. With greater participant numbers, the association between specific strength and incident RKOA may be greater. Although we studied fewer men, the mean differences in muscle parameters were much less, and men who developed RKOA were actually on average slightly stronger (approximately 2–5%), which was also observed recently in the progression of previously existing RKOA (15).

In conclusion, poor knee extensor and flexor muscle specific strength increased the risk of incident RKOA in women, but not in men, over a 48-month observational period. This relationship was confounded by BMI, which itself is known as a risk factor for incident RKOA, although currently not entirely clear by which mechanism. The response of thigh muscle to variations in BMI differed between men and women, with apparently more contractile tissue (and strength) being present in men with greater BMI, and apparently more non-contractile (adipose) tissue in women with greater BMI. The lower muscle specific strength in the presence of higher BMI in women (possibly driven by greater intramuscular adiposity), but not in men, may provide a possible explanation for the divergent risk of incident RKOA and other RKOA outcomes in men and women with muscle strength deficits, and in the mechanism by which BMI increases the risk of incident RKOA in men and women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE AND INNOVATIONS

1. Lower knee extensor and flexor muscle specific strength increases the risk of incident radiographic knee osteoarthritis in women, but not in men, with this relationship being confounded by body mass index.
2. Targeting specific impairments in muscle activation to increase strength per anatomical cross-sectional area may be important in women at risk of knee osteoarthritis.
3. The different response of muscle to a high body mass index in men vs women may provide an explanation why women with thigh muscle deficits have a generally poorer prognosis than men with similar muscle deficits.

Table 1

Women: Mean and standard deviation for knee extensor and flexor strength in incident vs non-incident radiographic knee osteoarthritis

	Incident Mean±SD	Non-incident Mean±SD	Difference %	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted P-value	Adjusted* P-value
Knee extensor cross sectional area, cm^2	42.8±9.0	40.7±7.8	5.2	0.77 (0.58, 1.02)	0.87 (0.60, 1.27)	0.066	0.464
Knee extensor strength, N	279.4±76.9	299.1±87.5	−7.1	1.28 (0.96, 1.69)	1.30 (0.97, 1.75)	0.088	0.076
Knee extensor specific strength, N/cm^2	6.7±2.0	7.5±2.3	−11.9	1.47 (1.10, 1.96)	1.33 (0.99, 1.82)	0.009	0.060
Knee flexor cross sectional area, cm^2	27.5±4.9	26.7±5.0	3.0	0.85 (0.64, 1.11)	1.03 (0.73, 1.44)	0.236	0.864
Knee flexor strength, N	109.1±41.4	120.8±44.1	−10.7	1.32 (1.00, 1.75)	1.30 (0.97, 1.75)	0.052	0.078
Knee flexor specific strength, N/cm^2	4.0±1.5	4.6±1.7	−13.0	1.41 (1.06, 1.89)	1.28 (0.94, 1.72)	0.017	0.113

*Adjusted for age and BMI. ORs are based on standardized measures (per SD of respective muscle parameter).

N, Newtons; SD, standard deviation; OR, odds ratio; CI, confidence interval.

Table 2

Men: Mean and standard deviation for knee extensor and flexor strength in incident vs non-incident radiographic knee osteoarthritis

	Incident Mean±SD	Non-incident Mean±SD	Difference %	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)	Unadjusted P-value	Adjusted* P-value
Knee extensor cross sectional area, cm^2	63.9±12.6	62.2±9.2	2.7	0.85 (0.61, 1.19)	0.93 (0.61, 1.41)	0.354	0.733
Knee extensor strength, N	470.5±136.3	447.8±122.4	5.1	0.83 (0.60, 1.17)	0.88 (0.61, 1.28)	0.303	0.517
Knee extensor specific strength, N/cm^2	7.4±1.8	7.2±1.7	2.8	0.88 (0.63, 1.23)	0.87 (0.62, 1.23)	0.460	0.446
Knee flexor cross sectional area, cm^2	39.3±8.2	39.3±6.4	0	1.00 (0.71, 1.39)	1.33 (0.85, 2.08)	0.961	0.210
Knee flexor strength, N	183.9±72.6	184.9±70.7	−0.5	1.01 (0.72, 1.41)	1.04 (0.73, 1.49)	0.938	0.817
Knee flexor specific strength, N/cm^2	4.8±2.0	4.8±1.9	0	1.00 (0.71, 1.39)	0.93 (0.66, 1.32)	0.985	0.692

*Adjusted for age and BMI. ORs are based on standardized measures (per SD of respective muscle parameter).

N, Newtons; SD, standard deviation; OR, odds ratio; CI, confidence interval.