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Med Sci Sports Exerc. Author manuscript; available in PMC 2013 February 15.

Published in final edited form as:
Med Sci Sports Exerc. 2008 March ; 40(3): 422–427. doi:10.1249/MSS.0b013e31815ef285.

Mechanisms Undlerlying Quadriceps Weakness in Knee Osteoarthritis

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Abstract

Purpose—To identify determinants of quadriceps weakness among persons with end-stage knee osteoarthritis (OA).

Methods—One-hundred twenty-three individuals (mean age 64.9 ± 8.5 yr) with Kellgren/Lawrence grade IV knee OA participated. Quadriceps strength (MVIC) and volitional muscle activation (CAR) were measured using a burst superimposition test. Muscle composition (lean muscle cross-sectional area (LMCSA) and fat CSA (FCSA)) were quantified using magnetic resonance imaging. Specific strength (MVIC/LMCSA) was computed. Interlimb differences were analyzed using paired-sample *t*-tests. Regression analysis was applied to identify determinants of MVIC. An alpha level of 0.05 was adopted.

Results—The OA limb was significantly weaker, had lower CAR, and had smaller LMCSA than the contralateral limb. CAR explained 17% of the variance in the contralateral limb's MVIC compared with 40% in the OA limb. LMCSA explained 41% of the variance in the contralateral limb's MVIC compared with 27% in the OA limb.

Conclusion—Both reduced CAR and LMCSA contribute to muscle weakness in persons with knee OA. Similar to healthy elders, the best predictor of strength in the contralateral, nondiseased limb was largely determined by LMCSA, whereas CAR was found to be the primary determinant of strength in the OA limb. Deficits in CAR may undermine the effectiveness of volitional strengthening programs in targeting quadriceps weakness in the OA population.

Keywords

STRENGTH; ARTHRITIS; MUSCLE ACTIVATION; ATROPHY

Quadriceps weakness is a hallmark impairment of knee osteoarthritis (OA). Reduced quadriceps strength is one of the earliest clinical findings amon persons with knee OA emerging prior to patient-reported symptoms and observed disability and may play an integral role in disease development (31,32). Strength deficits in the OA population range

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Data were presented at The Association of Rheumatology Health Professionals Annual Scientific Meeting in San Antonio, TX, October 21, 2004.

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from 15 to 18% in persons prior to disease development (31,32), to 24% in persons with Kellgren/Lawrence (K/L) grade II OA (18), to as high as 38% in persons with K/L grade IV knee OA (27). Collectively, these data highlight the pervasiveness of quadriceps impairments in knee OA and suggest that quadriceps weakness may be an identifiable risk factor for the development of knee OA and/or indicative of disease progression.

Furthermore, quadriceps strength is an important determinant of functional performance (23,26). The presence of impairments in joint pain, instability, and stiffness as well as reduced physical activity and high incidences of functional disability are not surprising with the magnitude of strength deficits exhibited by individuals OA (23). Failing to address strength deficits may hold serious implications such as further joint deterioration and continued functional decline (24,29). Without appropriate intervention, the noted deficits associated with OA may persist following surgical intervention and limit functional recovery. To this end, a better understanding of the physiological basis of OA-related weakness is necessary to improve both early and preoperative management in persons with knee OA.

Age-related changes in muscle are characterized by decreased lean muscle mass, fiber size, and fiber number along with increased intramuscular fat and connective tissue contributing to reduced force-generating capacity in older adults (7,20). While lean muscle mass is directly related to muscle strength in persons without knee pathology (3,11–14,25,41), the rate of decline in muscle strength exceeds the rate of decline in lean muscle mass. Muscle strength in healthy adults decreases by approximately 1.5–2.5% per year, beginning around the fifth decade of life (10,16), whereas lean muscle mass only decreases at a rate of only 1% per year, beginning around the sixth decade (16,19,21), highlighting that muscle atrophy alone is not implicitly responsible for the magnitude of age-related strength declines.

Neuromuscular changes (e.g., reduced voluntary muscle activation and decreased contractile rate) help to explain the age-related discrepancy between the rates of strength decline and changes in muscle size (36,38). Unlike the relationship between strength and lean muscle mass, a linear model underestimates the presence of activation deficits (35). Use of a curvilinear model to estimate voluntary muscle activation demonstrates that muscle activation in healthy older adults (mean = 0.868 ± 0.018) is 11% lower than young adults (mean = 0.978 ± 0.005), helping to explain the discrepancy of strength loss with aging (38).

Chronic disease such as OA seems to accelerate age-related changes in muscle properties (13,15,26). Muscle activation impairments are magnified in persons with knee OA ranging from 8 to 25% in populations of varying disease severity (4,13,18,37). Lower-extremity lean muscle mass is also smaller in persons with OA; however, the magnitude of this impairment and its role in explaining OA-related weakness is unclear (8,32,39). Gur and Cakin (8) found a moderate relationship between quadriceps cross-sectional area (CSA) and isokinetic strength in persons with bilateral K/L grade II–MI knee OA changes. This relationship between strength and CSA may be skewed because the computed topography measurements did not account for intramuscular fat. Furthermore, the study participants had bilateral involvement, so the degree of muscle atrophy could not be quantified without a control limb; comparison of the CSA values of Gur et al. with previously reported values in healthy persons suggests that muscle atrophy may not present in persons with OA (39), contradicting reports of decreased muscle mass in OA (32). Without data highlighting the degree of OA-related changes in muscle properties, the relative contributions of muscle atrophy and reduced voluntary muscle activation to explain quadriceps weakness in knee OA remain unknown.

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A better understanding of the mechanistic properties of quadriceps weakness in knee OA and the potential interactions between muscle atrophy, activation impairment, and strength will aid the development of appropriate and effective treatment interventions for persons with OA. The purpose of the current study was twofold: to quantify impairments in muscle composition and muscle activation in persons with K/L grade IV knee OA, and to determine the contributions of these impairments to explain quadriceps strength deficits. We hypothesized that compared with the contralateral, nondiseased limb, the OA limb would exhibit greater quadriceps weakness, greater muscle atrophy, and larger deficits in muscle activation. Secondly, we hypothesized that muscle activation deficits would have a larger impact on muscle strength in the OA limb than would lean muscle CSA.

MATERIALS AND METHODS

One-hundred twenty-three individuals (56 males and 67 females, mean age 64.9 ± 8.5 yr, mean height 1.70 ± 0.1 m, mean weight 91.00 ± 16.35 kg, and mean body mass index (BMI) 31.36 ± 4.76) with physician-diagnosed end-stage, primary, unilateral knee OA and candidates for total knee arthroplasty participated in this study. All participants met the criteria for the presence of symptomatic knee OA defined by the American College of Rheumatology's criteria (1) and had K/L grade IV osteoarthritic changes in one or more compartments of the knee. Individuals were excluded from the study if they had uncontrolled hypertension, diabetes mellitus, active neoplasms in the lower extremities, planned staged TKA, or neurological disorders. Subjects were also excluded from study participation if they had a cardiac pacemaker, heart valve or stint, brain clips, carotid clips, neurostimulator wires or electrodes, insulin pump, metal implants, or prostheses, because of the inherent risks associated with magnetic resonance imaging (MRI). Contralateral knee OA and/or pain was measured by an 11-point verbal analog scale (0 = no knee pain; 10 = worst knee pain imaginable). Patients were excluded if self-reported contralateral knee pain was greater than 4/10. This study was approved by the human subjects review board at the University of Delaware, and all participants provided written informed consent prior to participation.

Quadriceps strength and volitional muscle activation

Quadriceps strength and volitional muscle activation were measured using a burst superimposition technique (17). The burst superimposition technique is a validated quadriceps strength assessment widely used in a variety of populations with and without knee pathologies (18,22,33,36,37). Subjects were positioned in an isokinetic dynamometer (KinCom, Chattanooga Corporation, Chattanooga, TN) with the hip flexed to approximately 80° and the knee flexed and stabilized at 75°. A force transducer was positioned approximately 2 cm above the lateral malleolus. Inelastic Velcro straps were placed around the patient's chest and waist for stabilization. Prior to electrode placement, the skin was cleansed with rubbing alcohol. Two 3-inch by 5-inch electrodes (ConMed Corp, Utica, NY) were placed over the motor points of the rectus femoris muscle belly proximally and the vastus medialis muscle belly distally.

Prior to the test administration, participants practiced generating a maximal volitional isometric contraction (MVIC) of their quadriceps by performing isometric knee extension at 50, 75, and 100% of their maximal effort. Following set-up and familiarization, an electrical stimulation unit (Grass 8800, Grass Instruments, Warwick, RI) administered a burst of electrical impulses (100 ms, 100-pps stimulation train at 135 V) approximately 4 s into an MVIC. A noted increase in force when the electrical impulses were administered signified insufficient muscle recruitment. The testing procedure was repeated up to a maximum of three times. The trial with the largest MVIC production was used for data analysis. Pain during the MVIC production (pain MVIC) was recorded.

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Data were collected and analyzed using custom-written software (LabView, National Instruments Corporation, Austin, TX). Muscle activation was calculated using a modification to the central activation ratio (CAR) method that accounts for the tendency of the CAR to overestimate activation (17,35). MVIC was defined as the patient's force output just prior to the superimposed electrical burst. The electrically augmented force was defined as force output during the administered burst of electrical stimulation. CAR was derived by dividing the MVIC by the electrically augmented force:

$$\mathrm{CAR}=F_{\mathrm{volitional}}/F_{\mathrm{electrical}} \quad [1]$$

The corrected CAR was calculated using an equation that modeled the curvilinear relationship between CAR and %MVIC force:

$$y=-0.000097x^2+0.019036x \quad [2]$$

y in equation 2 (35) is equivalent to the CAR value from equation 1 and x represents the %MVIC force that the subject produced or the corrected CAR value. The CAR obtained from equation 1 was substituted for y into equation 2, and x was solved for using the quadratic formula and then divided by 100 to obtain the corrected CAR value. Activation of less than 1.0 represents incomplete muscle activation, whereas activation of 1.0 represents complete muscle activation.

Quadriceps cross-sectional area

MRI was used to assess quadriceps femoris CSA. A 1.5-T magnet (Signa, General Electric, Waukesha, WI) scanned the length of the thigh from the greater trochanter to the tibial plateau at 7-mm interslice intervals. The MRI scans were T1-weighted images in the axial plane acquired using a body coil with the patient positioned in supine. The imaging protocol was a standard GE SPGR sequence (2D spoiled gradient echo, a pulse-repetition time (TR) of 500 ms, an echo time (TE) of 8 ms, a 256 × 256 encoding matrix, and a 480 × 480-mm field of view).

Each 7-mm slice was processed using a digitizing pen/tablet (Intuos 2 tablets, Wacom Corporation, Vancouver, WA) and IMOD software package (The Boulder Laboratory for 3D Electron Microscopy of Cells at the University of Colorado, Boulder, CO) to outline the four quadriceps muscles, the vastus lateralis, vastus medialis, vastus intermedius, and rectus femoris. Custom-developed software was used to scale each outline and calculate the enclosed CSA (intraclass correlation coefficient$_{\mathrm{intrarater}}$ = 0.99; intraclass correlation coefficient$_{\mathrm{interrater}}$ = 0.98) (Fig. 1). Investigators analyzing the MRI scans were blinded to limb.

A thresholding operation discriminated intramuscular fat and connective tissue from contractile tissue based on grayscale value (intraclass correlation coefficient = 0.99). A value was chosen individually for each scan, which eliminated the greatest number of fat pixels without removing lean muscle tissue based on visual interpretation. Image pixels representing intramuscular fat and connective tissue (FCSA) were subtracted from the total CSA to obtain lean muscle CSA (LMCSA). The slice with the largest LMCSA was used for data analysis.

Data management and analysis

All data were processed using a statistical software package (SPSS v. 13.0, SPSS Inc., Chicago, IL). Values were expressed as means ± standard deviation (Table 1). Paired-samples t-tests were used to analyze interlimb differences in quadriceps strength, voluntary muscle activation, muscle composition, and specific force, strength relative to LMCSA

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(MVIC/LMCSA). The relationships between CAR and MVIC and LMCSA and MVIC were plotted, and a regression analysis was performed to calculate the coefficient of determination (R^2). The relationship between CAR and MVIC is curvilinear (34); therefore, an exponential regression was applied. Linear regression was used to test the relationship between LMCSA and MVIC. A linear regression was also applied to determine whether pain MVIC influenced quadriceps MVIC, because pain can influence force-generating ability (2). An alpha level of $P < 0.0125$ (Bonferroni correction) was used to determine significance for the paired *t*-tests and $P < 0.05$ for the regression analyses.

RESULTS

Quadriceps MVIC (mean ± standard deviation) of the OA limb (575 ± 219 N) was 20% lower than MVIC of the contralateral limb (714 ± 242 N) ($P < 0.001$). Quadriceps CAR of the OA limb (0.76 ± 0.21) was 8% lower than that of the contralateral limb (0.83 ± 0.16) ($P < 0.001$). Quadriceps LMCSA in the OA limb (35.47 ± 12.90 cm^2) was 12% smaller compared with the contralateral limb (40.28 ± 13.64 cm^2) ($P < 0.001$) (Table 1). Quadriceps FCSA was similar between the OA limb (12.50 ± 5.90 cm^2) and the contralateral limb (12.60 ± 6.19 cm^2) ($P = 0.803$). There was no difference in pain MVIC reported during the strength and activation testing between the OA limb (1.38 ± 2.55) and the contralateral limb (0.11 ± 0.72). Specific strength in the OA limb (18.02 ± 10.27 $N \cdot cm^{-2}$) was 7% smaller compared with the contralateral limb (19.40 ± 10.00 $Nlcm^2$) ($P = 0.008$). Pain MVIC did not significantly influence quadriceps strength (OA limb: R^2. = 0.01, $P = 0.279$; contralateral limb: $R^2 = 0.001$, $P = 0.718$).

R^2 for the relationship between CAR and MVIC in the OA limb was 0.40 ($P < 0.001$), and R^2 for the contralateral limb was 0.17 ($P < 0.001$) (Fig. 2). R^2 for the relationship between LMCSA and MVIC OA limb was 0.27 ($P < 0.001$), and the R^2 value for the contralateral limb was 0.41 ($P < 0.001$) (Fig. 3).

DISCUSSION

The present investigation assessed the influence of muscle cross-sectional area and voluntary muscle activation on quadriceps strength in persons with end-stage knee OA prior to total knee replacement. The OA limb exhibited significantly weaker quadriceps strength, larger voluntary activation deficits, smaller LMCSA, and decreased specific strength compared with the contralateral, nondiseased limb. Muscle activation explained the majority of the variance in the quadriceps strength of the OA limb. LMCSA explained the majority of the variance in the quadriceps strength of the contralateral, nondiseased limb. The relative contribution of volitional activation and LMCSA deficits to quadriceps weakness in the knee OA was, therefore, opposite that of the contralateral knee.

Several studies have demonstrated decreased lower-extremity lean muscle mass in persons with knee OA (32,40). However, few studies have investigated quadriceps-specific muscle atrophy in persons with late stage knee OA. Ikeda et al. (15) compared females in their 60s with and without knee K/L grade II knee OA. Despite having no history, signs, or symptoms of knee OA, women with early degenerative changes in the knee joint had a 12% reduction in quadriceps CSA compared with age-matched women without degenerative x-ray changes (15). Muscle strength was not assessed in these women; therefore, it is difficult to know the impact of the evidenced muscle atrophy on force-generating ability. Interestingly, the current study produced similar results in a larger population with more advanced disease; quadriceps LMCSA was 12% smaller in the OA limb compared with the contralateral limb in persons with K/L grade IV knee OA, which had a moderate effect on maximal quadriceps

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strength. While it is apparent that LMCSA is an important determinant of muscle strength, it is clearly not the sole factor involved.

Our findings of reduced quadriceps muscle activation are not novel; deficits in quadriceps muscle activation have been well documented among persons with knee OA (13,18,37). However, we were able to clarify differences between age- and disease-related changes in muscle properties and their influence on force-generating ability by assessing both morphological and neural properties. While both LMCSA and voluntary muscle activation influence quadriceps strength, the degree to which each factor influenced force output varied between the diseased and contralateral, nondiseased limbs. Muscle activation explained a larger proportion of the variance in quadriceps strength than did LMCSA in the OA limb, whereas, LMCSA explained the majority of the variance in quadriceps strength in the contralateral limb. Our data highlight that small impairments in activation deficits have a profound impact on quadriceps strength in OA limbs, suggesting that muscle activation may be the primary underlying mechanism of OA-related muscle weakness. The argument that voluntary muscle activation is the primary determinant of OA-related weakness is further strengthened by our data, which suggests that specific strength is also lower in the OA limb.

These results provoke interesting questions regarding the mechanism of quadriceps strength changes in persons with OA. Both muscle atrophy and activation deficits have been reported to occur early in the disease process (14,15,32,40,43); however, to date, no longitudinal studies have been published to show the time course of the emerging activation deficits or to show which impairment emerges first, those in LMCSA or those in activation deficits. Determining the timing and relative effects of atrophy and activation failure can shed insight into the mechanisms of OA progression. If muscle activation deficits emerge first, failure to activate a muscle's full potential may be related to decreased activity and also may contribute to maladaptive changes in LMCSA.

Several implications can be discussed concerning the physical therapy management of patients with knee OA in relation to these findings. Traditional strengthening programs advocate for resistance training at 60–80% of an individual's one-repetition maximum to elicit muscle strengthening (28). Research has demonstrated that while activation deficits do not prevent muscle strengthening, the complete reversal of muscle weakness does not seem to be possible when activation deficits are present (13). If individuals can not achieve high levels of muscle activation, training doses may fall below the threshold to see large changes in muscle strength. In light of these results, treatment modalities such as neuromuscular electrical stimulation may be a useful strengthening tool in the OA population because it targets the larger type II muscle fibers by recruiting muscle fibers in a more random order than what occurs with volitional contraction (5,6,9,30,42).

There are several limitations to the present study. First, while all individuals were physician diagnosed with unilateral knee OA, x-ray data were not available to confirm the presence or absence of knee OA in the contralateral limb. Regardless, there were still significant impairments in the OA limb compared with the contralateral limb. This suggests that if in fact the contralateral limb were to exhibit osteoarthritic changes on x-ray, the limb undergoing TKA was in fact more impaired. Second, this study only assesses individuals at one time interval. Longitudinal studies should assess the change in impairments over time in order to better understand the emergence and progression of said impairments and their correlation with degenerative x-ray changes.

In summary, persons with K/L grade IV knee OA changes have impairments in quadriceps strength, LMCSA, and muscle activation. Small changes in volitional muscle activation largely seem to contribute more than atrophy to the quadriceps weakness seen in the limbs

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affected by OA. Failing to address and reverse these impairments may predispose individuals to a more difficult recovery following total knee arthroplasty.

Acknowledgments

Funding was provided by the National Institutes of Health (RO1HD041055 and T32HD07490). We would like to thank First State Orthopaedics, specifically Drs. Axe, Bodenstab, Newcomb, and Raisis, for patient referral.

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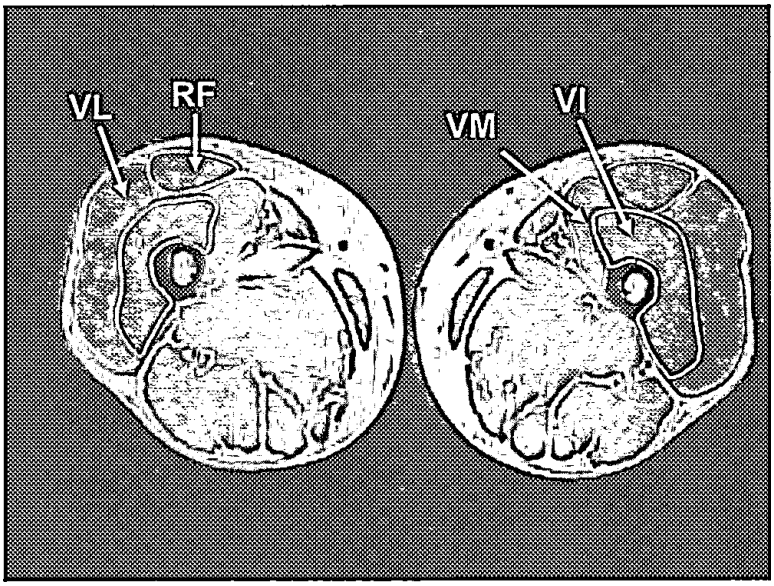

FIGURE 1.
Muscle identification of the quadriceps femoris muscle group on magnetic resonance image. The OA limb is on the left, and the contralateral, nondiseased limb is on the right. RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; VI, vastus intermedius.

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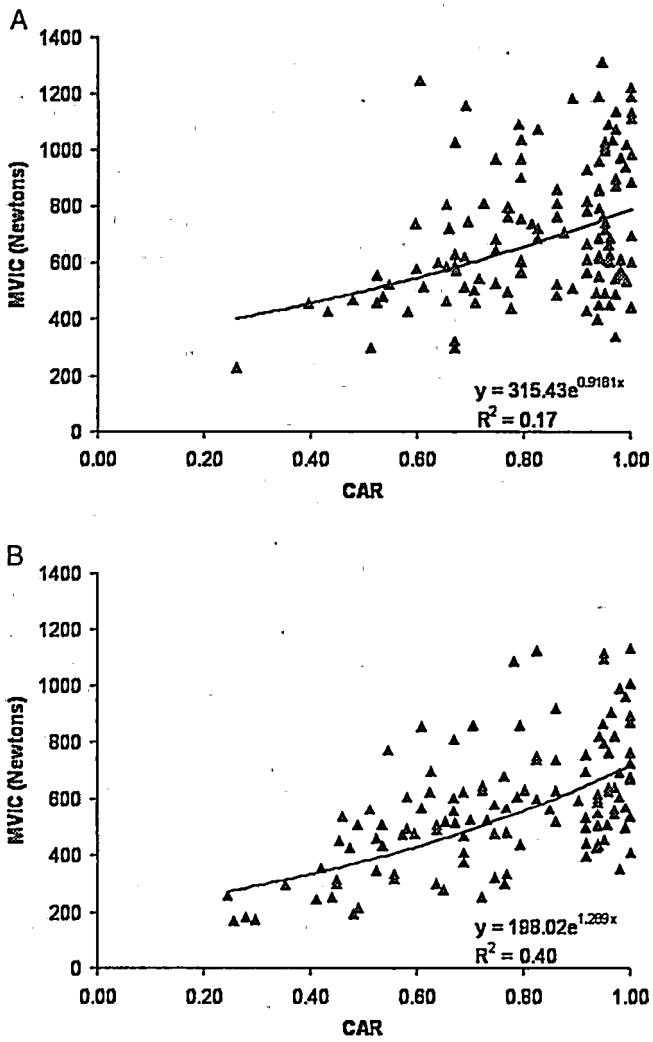

FIGURE 2.

The influence of central activation ratio (CAR) on quadriceps femoris muscle strength (MVIC). The equation shows the relationship between CAR and MVIC, and the line represents the line of best fit from the results of the exponential regression analysis. The *y*-axis is presented in Newtons. *A*, Contribution of CAR to the contralateral, nondiseased limb's quadriceps stirength. *B*, Contribution of CAR to the OA limb's quadriceps strength.

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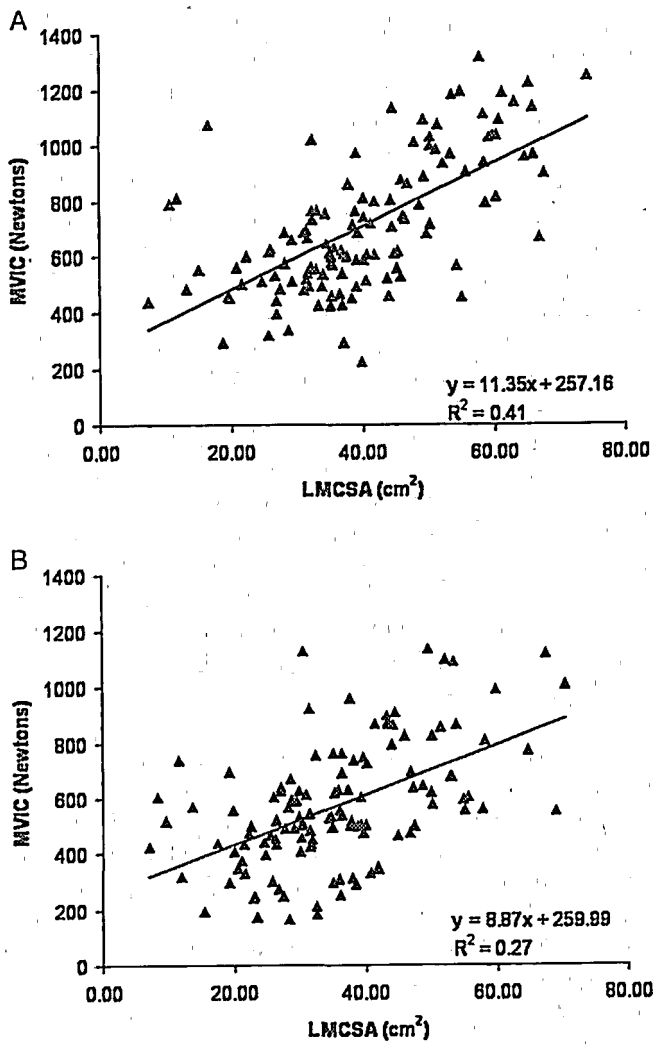

FIGURE 3.

The influence of lean muscle cross-sectional area (LMCSA) on Quadriceps femoris muscle strength (MVIC). The equation shows the relationship between LMCSA and MVIC, and the fine represents the line of best fit from the results of the linear regression analysis. The *y*-axis is presented in Newtons, and the *x*-axis is presented in centimeters squared. *A*, Contribution of LMCSA to the contralateril, nondiseased limb's quadriceps strength. *B*, Contribution of LMCSA to the OA limb's quadriceps strength.

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TABLE 1

Range, mean, standard deviation, and interlimb differences of quadriceps femoris muscle characteristics.

	Contralateral, Nondiseased Limb				OA Limb				
	Min	**Max**	**Mean**	**SD**	**Min**	**Max**	**Mean**	**SD**	***P* Value**
MVIC (N)	227	1317	714	242	167	1135	575	219	< 0.001
CAR	0.26	1.00	0.83	0.16	0.25	1.00	0.76	0.20	< 0.001
LMCSA (cm^2)	7.50	74.14	40.28	13.64	7.02	70.41	35.47	12.90	< 0.001
FMCSA (cm^2)	1.94	36.66	12.60	6.19	2.32	31.20	12.50	5.90	0.803
Specific force (MVIC/LMCSA) ($Nlcm^2$)	5.70	73.58	19.40	10.00	5.59	72.96	18.02	10.27	0.008

OA, osteoarthritis; MVIC, maximal volitional isometric contraction; CAR, central activation ratio; LMCSA, lean muscle cross-sectional area; FMCSA, fat-mass cross-sectional area; min, minimum; max, maximum; SD, standard deviation.