

The biomechanical effects of focused muscle training on medial knee loads in OA of the knee: a pilot, proof of concept study

L.E. Thorp^{2,3}, M.A. Wimmer^{1,2}, K.C. Foucher¹, D.R. Sumner^{1,2}, N. Shakoor³, J.A. Block³

¹Department of Orthopaedic Surgery; ²Department of Anatomy & Cell Biology;

³Section of Rheumatology, Rush University Medical Center, Chicago (IL)

Abstract

Background: High dynamic loads of the medial knee are associated with tibiofemoral osteoarthritis (OA) severity and progression. The lower extremity acts as an integrated kinetic unit, thus treatments targeting adjacent segments may promote reductions in the loading of a symptomatic knee. This study examined the biomechanical effects of a lower extremity exercise regimen, emphasizing training of hip abductor musculature, on dynamic knee loads in individuals with knee OA. **Methods:** Six subjects with medial compartment knee OA participated in a proof of concept study of a four-week exercise program specifically targeting the hip abductor musculature in combination with traditional quadriceps and hamstring training. Assessments included gait analyses to measure the external knee adduction moment, a surrogate marker of medial knee joint loading as well as WOMAC questionnaires and strength evaluations. **Results:** All subjects demonstrated a decrease in their external knee adduction moment, with an average decrease of 9% ($p < 0.05$) following the exercise intervention. There was a 78% ($p < 0.05$) decrease in WOMAC knee pain scores. **Conclusions:** These results suggest that targeting hip, rather than only knee musculature, may represent an effective biomechanically-based treatment option for medial knee OA.

Keywords: Exercise, Knee, OA, Adduction Moment

Introduction

Osteoarthritis (OA) of the knee is a significant source of disability^{1,2} and impaired quality of life³⁻⁵. In contrast to the systemic inflammatory arthritides, which progress randomly in the lower extremities, OA progresses in a non-random manner that is directly related to asymmetric dynamic loading of the involved joints^{6,7}. High dynamic loads of the medial knee, as assessed by the external peak knee adduction moment, have been associated with tibiofemoral OA severity⁸⁻¹⁰, progres-

sion¹¹, and knee pain¹². The external knee adduction moment, a varus torque about the knee during gait, is widely used as a surrogate marker of loading of the medial knee compartment because it can be easily obtained non-invasively in the gait laboratory and has been widely validated^{13,14}.

Multiple variables can influence the external knee adduction moment, and hence dynamic loading of the medial knee. For example, varus alignment has been associated with high external knee adduction moments during gait in knee OA^{15,16}. Varus alignment results in an increased distance between the knee and the ground reaction force vector (Figure 1A). The knee, however, does not exist in mechanical isolation; instead, the entire lower extremity operates as an integrated mechanical unit, and alterations at any segment have consequences throughout the lower limb. Interventions at the foot, such as wedged orthotic inserts in shoes^{17,18}, or the toe-out angle during gait^{15,19} have been shown to affect the knee adduction moment; similarly, changes at the hip may be expected to influence the knee.

Exercise represents one of the mainstays of therapy for knee OA²⁰, and has been repeatedly demonstrated to yield significant pain palliation^{21,22}, yet historically these regimens have not exam-

This study was conducted with approval of the Institutional Review Board at Rush University Medical Center. The authors have no conflict of interest.

Corresponding author: Laura E. Thorp, MPT, Ph.D., Assistant Professor, Department of Anatomy and Cell Biology, Rush University Medical Center, 600 S. Paulina Street, Room 507 AAC Chicago, IL, USA
E-mail: Laura_Thorp@rush.edu

Edited by: J. Rittweger
Accepted 24 March 2010

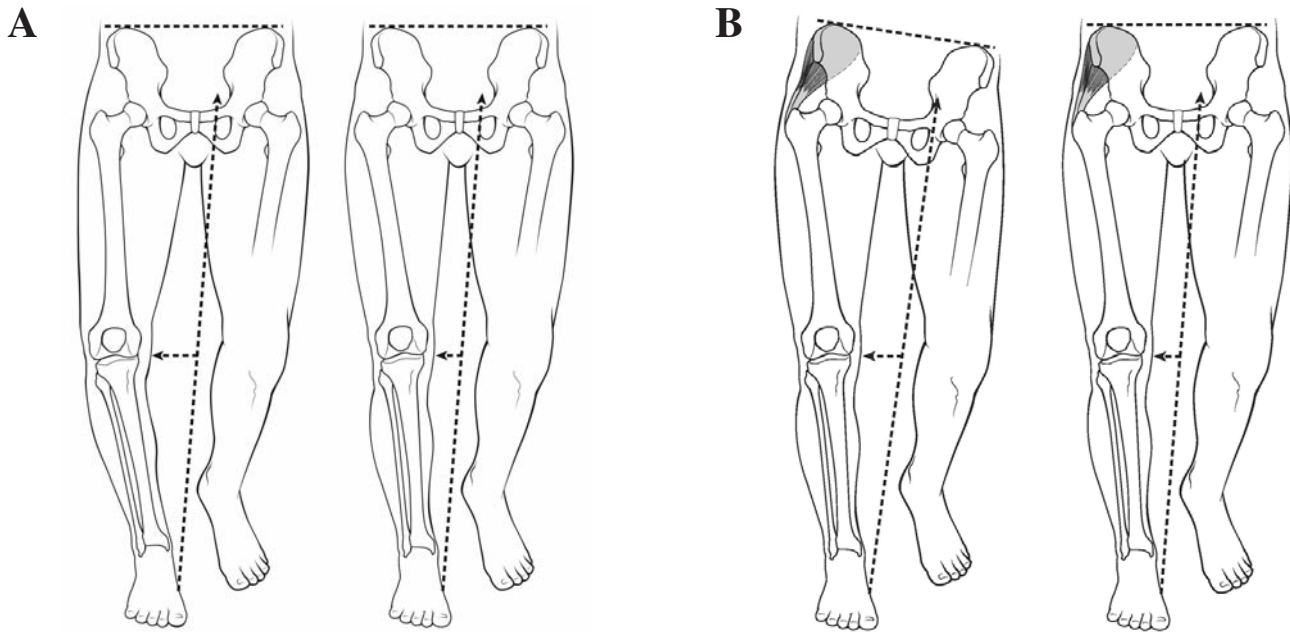


Figure 1. A. Limb alignment influences the external knee adduction moment. Note that the lever arm (horizontal dashed arrow) of the varus torque at the knee during unilateral stance in the knee with varus alignment (left) is longer than that of the knee with more neutral alignment (right), contributing to an elevated external adduction moment at the knee. The upwardly directed dashed arrow represents the ground reaction force. **B.** Pelvis posture influences the knee adduction moment. Note that the lever arm (horizontal dashed arrow) of the varus torque at the knee during unilateral stance with pelvis drop due to gluteus medius weakness (left) is longer than when the gluteus medius functions normally (right). This contributes to an elevated external adduction moment at the knee. The upwardly directed dashed arrow represents the ground reaction force.

ined what effect exercise might have on the aberrant biomechanical loading at the knee which characterizes knee osteoarthritis. Conventionally, exercise regimens for knee OA have focused on strengthening the quadriceps and hamstrings because these muscles function to stabilize the knee joints^{23,24}. However, this strategy alone may not be ideal to favorably alter the biomechanical milieu of the knee joints. The quadriceps and hamstrings, acting primarily in the sagittal plane, likely have little effect in the frontal plane, which would be necessary to counteract the varus torque and shift the load from the medial to the lateral compartment. Two studies have observed that conventional exercise regimens, with a focus on knee musculature, do not result in decreases in the external knee adduction moment during walking^{25,26}.

It has been observed that individuals with hip OA have both decreased strength and decreased evidence of contractile components in the hip abductor musculature of their affected versus unaffected limb²⁷. Decreased activity of hip abductor musculature during gait has also been suggested in individuals with knee OA and activity of the hip abductors may play a role in disease progression²⁸. In healthy adults, hip abductor strength has been shown to explain some variance in the external hip adduction moment with higher strength resulting in lower external hip adduction moments during gait²⁹. The external hip adduction moment has been reported to be reduced in knee OA^{8,30}, which initially might appear counterintuitive given the reports of deficient hip muscle strength in these patients. However, a larger than normal lateral trunk lean

over the affected side during gait has been observed in patients with medial knee osteoarthritis and has been suggested as a mechanism by which individuals with knee OA reduce their external hip adduction moments^{30,31}. The tendency of individuals with knee OA to exhibit this type of compensatory gait pattern may be in part the result of hip abductor weakness. If uncompensated, biomechanically deficient function of the hip abductor muscles affects the posture of the lower extremity by causing the contralateral pelvis to drop in the frontal plane during the stance phase of gait, increasing the magnitude of frontal plane external joint moments^{31,32}, such as the external knee adduction moment, by moving the ground reaction force medially, and thus increasing the varus torque lever arm (Figure 1B).

We hypothesized that muscle training focused on the hip abductors in addition to quadriceps and hamstring training would beneficially affect the dynamic loading of the knees during gait in knee OA, as reflected by a reduction in external knee adduction moment, an established risk factor for progression of knee OA, and our primary study outcome. Here, we report the results of a “proof of concept” pilot study employing an exercise regimen which expanded on the existing “standard of care” for knee OA exercise interventions. In addition to traditional quadriceps and hamstring training, which have been shown to palliate pain but do not affect the external knee adduction moment during gait, we specifically targeted the hip abductor musculature in order to reduce dynamic loading of the medial knee.

Method

Subjects. With the approval of the Rush University Institutional Review Board, subjects were recruited from the practices of the Section of Rheumatology and by local advertising and provided informed consent prior to participation. Subjects were included if they met all inclusion criteria and had none of the exclusions. Inclusion criteria consisted of provision of informed consent; symptomatic OA of the knee, as defined by the American College of Rheumatology's *Clinical Criteria for Classification and Reporting of OA of the knee*³³; radiographic OA of the more painful knee (index knee) of grade 2 or 3 based on the Kellgren and Lawrence scale³⁴ as modified by Felson, et al.³⁵, with evidence of radiographic involvement of the contralateral knee of grade 1, 2, or 3; ambulatory knee pain, defined as at least 30 mm (of a 100 mm visual analog scale) of knee pain while walking on a level surface, corresponding to question #1 of the Western Ontario and MacMaster Universities OA Index (WOMAC)³⁶; predominantly medial compartment involvement³⁷. Exclusion criteria included: subjects currently involved in regular physical therapy for knee OA; clinically evident OA involving any lower extremity joint other than the knees; inability to ambulate unassisted or flexion contracture in either knee $>15^\circ$; valgus deformity $>3^\circ$, or varus $>12^\circ$ in either knee, defined by the full limb radiographic knee alignment angle^{38,39}; substantial obesity, defined as a body mass index (BMI) >35 kg/m²; presence of any inflammatory arthropathy; any prior arthroplasty in any lower extremity joint, or anticipation of surgery in the next 12 months; arthroscopy of either knee in the previous 6 months; intra-articular hyaluronans in the previous 6 months or glucocorticoids in the previous 3 months in either knee.

Clinical Protocol. This was a "proof of concept" pilot trial of a novel lower extremity training regimen, which was designed to reflect the current "standard of care" for knee OA exercise regimens by including training of quadriceps and hamstring musculature; however, in addition to the knee musculature, the regimen was specifically and primarily designed for hip abductor musculature training. Eligible subjects were scheduled for a baseline visit, during which evaluations of clinical status, including physical examination, comprehensive medication history, WOMAC, and site-directed WOMAC pain surveys for the lower extremity joints were completed. In addition, gait evaluations and quantitative strength testing were performed. After the initial visit, each subject was scheduled for a 4 week course of individualized training with a licensed physical therapist. All clinical and laboratory evaluations were repeated after the training period.

Gait testing protocol. A standard gait analysis protocol was employed⁴⁰. All tests were conducted by the same, trained individual. Briefly, four optoelectronic cameras (Qualysis – Gotenburg, Sweden) tracked the motion of six passive retroreflective markers, placed at the iliac crest, greater trochanter, lateral knee joint line, lateral malleolus, lateral aspect of calcaneus, and the head of the fifth metatarsal. The three-dimensional locations of each joint center were calculated based on the measured marker

trajectories and anthropometric measurements. A hidden multi-component force plate (Bertec – Columbus, Ohio, USA) recorded ground reaction force data. Sagittal plane kinematics were calculated from the marker positions. Inverse dynamics were used to calculate three-dimensional external moments (CFTC – Chicago, Illinois). Each segment, e.g. thigh or shank, is modeled as a slender rod with the assumption that no rotation occurs about its long axis. The three-dimensional locations of each joint center are known throughout gait, based on the measured marker trajectories and anthropometric measurements. Therefore by assuming no axial rotation and knowing the three dimensional location of the joint center, the three-dimensional moments can be determined even though only two markers were placed on each segment. At each visit, seven trials were collected – three trials at a self-selected "normal speed", and two each at self-selected "fast" and "slow" speeds, and external moments normalized to percent body weight multiplied by height (%BW*Ht) were calculated⁴¹. To minimize the effects of gait speed on the external moments, pre and post intervention trials were speed-matched for each subject.

Evaluation of Muscle Strength. Isometric and isokinetic strength of both hips and knees were assessed using a Biodex™ (Shirley, NY) isokinetic dynamometer and peak torques (T_{max}) were divided by subjects' weights for between-subjects comparisons. Hip strength assessments were performed with subjects standing and knee strength measurements were performed while sitting. The axis of rotation of the dynamometer was aligned with the axis of rotation of the joint being tested. For the hip, the force transducer pad was strapped to the lower thigh and the hip was in neutral starting position (0° of flexion in the standing position). For the knee, the force transducer was attached at the lower leg across the tibia and the knee was in neutral starting position (90° in the sitting position). Each joint underwent isometric followed by isokinetic testing. Range of motion at the hip was set at 0° to 40° in both planes (extension-flexion and adduction-abduction) and at the knee between 90° and 180° of flexion-extension at the knee. For isometric muscle strength assessment, hip flexion, extension, abduction and adduction were evaluated and knee extension and flexion were assessed. Subjects were instructed to push their leg against pad of the force transducer, in respective directions depending on the muscle group being tested. The measurements were repeated five times with 10-second rest intervals in between. Isokinetic muscle strength was evaluated for hip flexion-extension, hip abduction-adduction and knee flexion-extension at an angular velocity of 60° /second. Each set consisted of five concentric contractions followed by five eccentric contractions. A rest period of 2 minutes was provided between the sets.

Exercise Program. During the four week period, each subject underwent a total of eight training sessions in a 1:1 setting with a physical therapist: 3 sessions per week for the first two weeks followed by 1 session per week for the next two weeks. In each session, the therapist ensured efficient and proper performance of the muscle stretching and strengthening regimen. In addition, subjects performed an independent home exercise

program on days when they did not have a session with the therapist (i.e. four times per week for the first two weeks and six times per week over the next two weeks), thus resulting in daily exercises, either supervised or independent. The home regimens were designed to take approximately 15 minutes each day, and it was emphasized to subjects that adherence was critical to successful completion of the protocol. The isometric exercises were intended simply to teach subjects awareness of the sensation of muscular contraction in the muscles to be trained. Repetitions of all exercises were progressed to a maximum of 30 (3 sets, 10 repetitions each) as tolerated by the subject. Weights or elastic resistance were added when subjects could complete 30 repetitions with ease and independent maintenance of proper alignment. Subjects received regular telephone reminders by the study coordinator, and completed weekly diaries.

Subjects performed traditional exercises for strengthening of the hamstrings and quadriceps. Hamstrings: (1) **Isometric**: With subjects positioned supine or long sitting with the knee slightly flexed, they gently pressed the heel into the treatment table (2) **Strengthening**: This was performed in both standing and prone positions; each knee was sequentially flexed to 90° and then slowly lowered. Quadriceps: **Strengthening**: (a) Subjects sat with legs over the edge of the table, allowing the knees to flex to 90°, and slowly extended the knee to full extension and then returned to the flexed position. (b) Subjects stood with their backs flat against a wall and slowly flexed the knees and hips, lowering the body along the wall and then raising up again. As strength increased, knee flexion could be gradually increased to a maximum of 60°.

Subjects also completed focused hip muscle training targeting the gluteus medius and tensor fascia latae. The focused hip muscle training protocol was as follows: (1) **Isometric**: With the subject in the lateral decubitus position and the limb in slight extension, the therapist provided downward resistance to the subject's shank below the knee and asked the subject to attempt to raise the limb against resistance; no movement was allowed. This was performed only during sessions with the therapist. (2) **Strengthening**: (a) With subjects in the lateral decubitus position, the hip was actively abducted while assuring that it remained in slight extension and that no rotation occurred. (b) Subjects performed standing hip abduction exercises with the hip in slight extension. (c) Subjects stood with one leg on a 2-4 inch step positioned close to a wall to aid in balance, and alternately lowered and raised the pelvis on the unsupported side, eliciting contraction of the abductor musculature of the stance leg. **Stretching**: (3 repetitions, 15 seconds hold each repetition) (a) The subject stood with the limb to be stretched crossed behind the other limb. While maintaining both feet flat on the ground, the subject leaned the trunk away from the target limb while allowing the pelvis to move horizontally in the direction of the target limb. The knee of the other limb was allowed to bend. An additional stretch of the limb could be obtained if it was positioned with the hip in external rotation. (b) The subject lay on the side with the limb to be stretched on top and the bottom limb flexed for support.

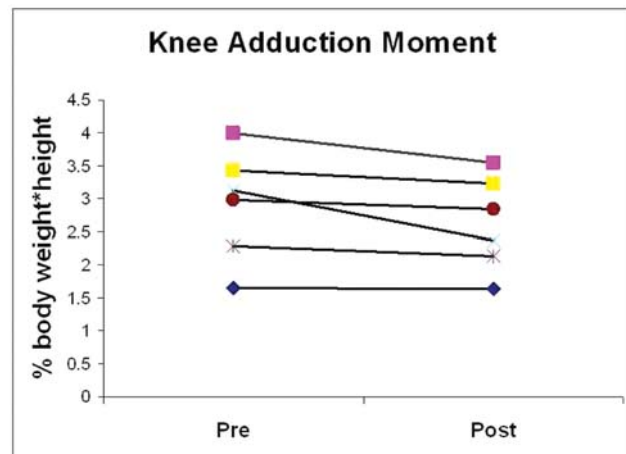


Figure 2. The knee adduction moment before and after participation in the exercise regimen taken from speed matched gait trials with speed differences smaller than 1%. Each symbol type reflects the peak knee adduction moment of a patient before and after exercise. Lines indicate the slope of change in the adduction moment.

The therapist assisted in positioning the target limb into hip abduction and slight extension. The limb was then externally rotated and adducted until a stretch was felt.

Statistical Analyses. All outcome parameters were compared prior to and after completion of the exercise intervention, and differences were assessed using paired t-tests for all data analyses with the exception of the WOMAC (pain) data which was assessed with non-parametric Wilcoxon signed rank tests due to the non-normal distribution of this specific data. Differences in gait parameters were investigated using speed matched walking trials; $p < 0.05$ was considered significant for all variables. All data are expressed as mean \pm standard deviation (SD) with the exception of the WOMAC data which is expressed as median and range values due to its non-normal distribution.

Results

Subjects. Five women and one man met study criteria for this pilot study and completed the exercise protocol. Ages ranged from 31 to 84 years with a mean (\pm S.D.) of 59.7 ± 17.2 years. Body mass index (BMI) ranged from 26 to 35 kg/m² with a mean (\pm S.D.) of 30 ± 4.1 kg/m².

Pain. The median WOMAC pain subscale scores (maximum=500 mm) in the index knees at baseline and after completion of the four week exercise protocol were 211 mm and 24 mm respectively ($p=0.028$). The range of pain subscale scores at baseline was 83mm-348 mm and after the exercise the range in pain subscale scores was 3mm-109mm. The median of the total WOMAC scores (max=2400 mm) before and after completion were 879 mm and 205 mm respectively ($p=0.046$). The range of total WOMAC scores at baseline was 425 mm-1369 mm and after the exercise regimen this range was 55mm-483 mm.

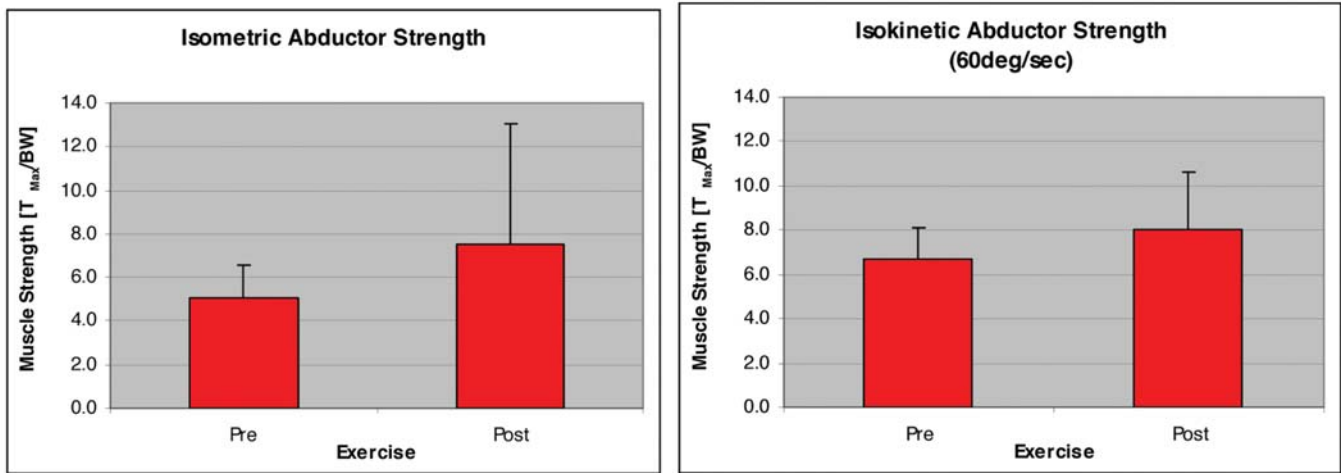


Figure 3. Isometric and isokinetic hip abductor strength before and after participation in the exercise regimen. On average both isokinetic and isometric strength of the patients increased, though this was not statistically significant. Error bars indicate standard deviations.

	Isometric (T_{max}/BW)		Isokinetic (T_{max}/BW)	
	Hamstrings	Quadriceps	Hamstrings	Quadriceps
Pre Training	14.0±4.0	21.6±6.5	11.5±6.3	12.7±9.5
Post Training	12.8±3.6	18.3±4.7	15.3±6.4	13.2±4.8
<i>p-value</i>	0.442	0.142	0.116	0.855

Table 1. Isometric and isokinetic strength of knee musculature before and after participation in the exercise regimen. Data are expressed as mean±standard deviations.

Gait. At completion of the four week exercise program, the self-selected “normal” walking speeds of the subjects did not significantly differ from their pre-treatment baselines, 1.18±0.12 m/s vs. 1.21±0.20 m/s (mean±SD) ($p=0.924$). An overall 9% reduction in the peak external knee adduction moments at the index knees (2.9±0.8 vs. 2.6±0.7 %BW*Ht; $p<0.05$) was observed when speed matched trials were compared (Figure 2). The change in hip external adduction moment was not statistically significant (3.4±1.2 vs. 3.1±0.8 %BW*Ht; $p=0.2$). Interestingly, the hip range of motion of flexion-extension excursion during stance phase increased in five out of six patients an overall mean of 3 degrees (27.6°±5.2° and 30.5°±6.0°, respectively; $p<0.05$).

Strength. The strength measurements were more variable than the moment measurements, and no significant strength alterations for hip abductor musculature were observed (Figure 3). The mean isometric hip abductor strength at baseline and after completion of the exercise regimen was 5.0±1.5 T_{max}/BW and 7.5±5.5 T_{max}/BW , respectively ($p=0.246$). The mean isokinetic hip abductor strength was 6.7±1.4 T_{max}/BW and 8.0±2.4 T_{max}/BW , respectively ($p=0.286$). No significant changes in strength of knee musculature were observed after completion of the intervention (See Table 1).

Discussion

In this study, we demonstrate that knee joint loading, a known mechanical risk factor for OA progression, can be favorably altered, i.e. decreased, when focused hip muscle exercises, targeting the hip abductor muscles, are added to a conventional knee OA exercise regimen. It has recently been reported that neither quadriceps strength nor the interaction between quadriceps strength and alignment explain variance in the peak knee adduction moment in individuals with symptomatic medial knee osteoarthritis⁴². In addition, while quadriceps training has been shown to reduce pain in individuals with knee OA, strengthening the quadriceps did not result in reductions of the knee adduction moment²⁶. In contrast, we speculate it is the *hip* musculature which controls medial-lateral balancing at the knee both directly, through the ilio-tibial tract shifting the compressive joint force at the knee laterally, and indirectly, through pelvis stabilization. At completion of the exercise intervention, the peak knee adduction moment was reduced in every subject, with an overall 9% mean reduction. We hypothesize that this decrease in the external knee adduction moment was due to training of the hip abductor musculature in the prescribed exercise regimen.

No significant increases in hip abductor, hamstring or quadriceps strength were seen, although on average there was an increase. This may have been due to insufficient power, as this was a small pilot study; to ensure 80% power to detect a 30% difference between pre and post-intervention strength values, approximately 16 subjects would have been required. However, the absence of a significant change in muscle strength despite the observed decrease in the knee adduction moment may also have been due to the nature of the strength testing. Muscle strength is defined as “the greatest measurable force that can be exerted by a muscle or muscle group to overcome resistance during a single maximal effort”⁴³. During gait, muscles do not contract to their maximal potential⁴⁴, hence joint moments may not be reflective of the absolute strength of a muscle.

While not formally assessed in the present work, we speculate one potential mechanism for the decreased knee adduction moments seen after completion of the exercise regimen, is increased activity of the hip abductor musculature during gait. While no direct cause and effect relationship can be drawn here, we speculate that increased hip abductor muscle activity following the intervention would allow better control of frontal plane ground reaction forces, and is a plausible explanation for the decreased external knee adduction moment. Although not significant, it is interesting to note that on average the subjects of this study showed an increase in abductor strength and lowered the hip adduction moment during gait. In healthy adults, hip abductor strength has been shown to explain variance in the external hip adduction moment²⁹. The observation of improved hip range of motion during gait following the intervention, with sagittal plane excursion trending towards normal values⁴⁵, provides some support to our hypothesis that postural changes are occurring at the hip, despite the absence of direct measures of lateral trunk leaning in these subjects. Alternatively, the beneficial effects of a hip exercise program on knee loading may be related to improved endurance of muscles or improvements in timing of muscular contraction during gait. Although the contribution of these potential mechanisms is important, an analysis of their contributions would require a larger study and was beyond the scope of the present work.

Recently it has been suggested that a generalized program of lower extremity strengthening and proprioceptive/balance training can reduce the knee adduction moment during a one-leg rise, but no significant changes during level walking were observed²⁵. Muscle weakness may be one of the earliest features of OA; it has been reported in asymptomatic subjects with only radiographic evidence of OA, and it may predict the development of both radiographic and symptomatic OA⁴⁶. Thus, muscle weakness itself appears to be pathophysiologically related to OA and not simply a consequence of advanced OA-induced pain and disuse. This is substantiated by animal models⁴⁷⁻⁴⁹, where muscle dysfunction has been associated with OA pathophysiology⁵⁰. In these models, OA developed solely due to muscle weakness, without trauma or joint instability^{47,48,51}. Thus, training the appropriate muscles may well influence disease progression⁵².

In addition to the reduced dynamic loading at the knee, each subject experienced a dramatic decrease in knee pain during the study. Because this pilot study was neither blinded nor placebo-controlled, it is not possible to assess the overall significance of this pain palliation. In general, there are high placebo responses in studies of pain, and interventions involving active exercise are also likely to result in perceived pain relief independent of any biomechanical benefit. Nonetheless, the dramatic reductions in the WOMAC pain subscale and in the total WOMAC scores observed here suggest that this exercise regimen may be at least comparable in its palliative effect on pain to more traditional programs of quadriceps and hamstring strengthening alone^{21,22}. While the lack of a control group limits the conclusions which can be drawn regarding pain data, the biomechanical endpoints are non-subjective and known to be stable over time in untreated individuals⁵³; hence, the objective loading reductions at the knee experienced by every subject are likely ascribable to the biomechanical intervention rather than to a placebo effect. In addition, the magnitude of the external knee adduction moments for the subjects in the present work following the intervention are approaching the normal values for healthy age-matched asymptomatic individuals without radiographic evidence of knee OA¹⁰.

Conclusion

In conclusion, in this proof of concept pilot study, a training regimen emphasizing hip abductor musculature in addition to traditional quadriceps and hamstring training reduced the dynamic loading of the medial knee in symptomatic patients with knee OA. The present work highlights the need for further research on this topic, specifically larger randomized controlled trials. Such future work is necessary to corroborate these findings in a larger cohort as well as to elucidate the potential mechanisms causing these reductions in the external knee adduction moment, determine the ideal exercise prescription including ideal frequency, intensity, and duration of exercise, and to examine whether the effects of the exercise are sustained over a longer period.

References

1. Ettinger WH, Davis MA, Neuhaus JM, Mallon KP. Long-term physical functioning in persons with knee osteoarthritis from NHANES. I: Effects of comorbid medical conditions. *J Clin Epidemiol* 1994;47(7):809-15.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994;84(3):351-8.
3. Creamer P, Lethbridge-Cejku M, Hochberg MC. Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology (Oxford)* 2000;39(5):490-6.
4. Hopman-Rock M, Kraaijmaat FW, Bijlsma JW. Quality of life in elderly subjects with pain in the hip or knee. *Qual*

- Life Res 1997;6(1):67-76.
5. Jordan J, Luta G, Renner J, Dragomir A, Hochberg M, Fryer J. Knee pain and knee osteoarthritis severity in self-reported task specific disability: the Johnston County Osteoarthritis Project. *J Rheumatol* 1997;24(7):1344-9.
 6. Shakoor N, Block JA, Shott S, Case JP. Nonrandom evolution of end-stage osteoarthritis of the lower limbs. *Arthritis Rheum* 2002;46(12):3185-9.
 7. Shakoor N, Hurwitz DE, Block JA, Shott S, Case JP. Asymmetric knee loading in advanced unilateral hip osteoarthritis. *Arthritis Rheum* 2003;48(6):1556-61.
 8. Mundermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: Increased load at the ankle, knee, and hip during walking. *Arthritis Rheum* 2005;52(9):2835-44.
 9. Sharma L, Hurwitz DE, Thonar EJMA, Sum J.A., Lenz ME, Dunlop DD et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. *Arthritis Rheum* 1998;41(7):1233-40.
 10. Thorp LE, Sumner DR, Block JA, Moision KC, Shott S, Wimmer MA. Knee joint loading differs in individuals with mild compared with moderate medial knee osteoarthritis. *Arthritis and Rheumatism* 2006;54(12):3842-9.
 11. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis* 2002;61(7):617-22.
 12. Thorp LE, Sumner DR, Wimmer MA, Block JA. Relationship between pain and medial knee joint loading in mild radiographic knee osteoarthritis. *Arthritis & Rheumatism (Arthritis Care & Research)* 2007;57(7):1254-60.
 13. Schipplein OD, Andriacchi TP. Interaction between active and passive knee stabilizers during level walking. *J Orthop Res* 1991;9:113-9.
 14. Foroughi N, Smith R, Vanwanseele B. The association of external knee adduction moment with biomechanical variables in osteoarthritis: a systematic review. *Knee* 2009;16(5):303-9.
 15. Hurwitz DE, Ryals AB, Case JP, Block JA, Andriacchi TP. The knee adduction moment during gait in subjects with knee osteoarthritis is more closely correlated with static alignment than radiographic disease severity, toe out angle and pain. *J Orthop Res* 2002;20(1):101-7.
 16. Wada M, Maezawa Y, Baba H, Shimada S, Sasaki S, Nose Y. Relationships among bone mineral densities, static alignment and dynamic load in patients with medial compartment knee osteoarthritis. *Rheumatology (Oxford)* 2001;40(5):499-505.
 17. Kerrigan DC, Lelas JL, Goggins J, Merriman GJ, Kaplan RJ, Felson DT. Effectiveness of a lateral-wedge insole on knee varus torque in patients with knee osteoarthritis. *Arch Phys Med Rehabil* 2002;83(7):889-93.
 18. Hinman RS, Bowles KA, Payne C, Bennell KL. Effect of length on laterally-wedged insoles in knee osteoarthritis. *Arthritis Rheum* 2008;59(1):144-7.
 19. Chang A, Hurwitz D, Dunlop D, Song J, Cahue S, Hayes K et al. The relationship between toe-out angle during gait and progression of medial tibiofemoral osteoarthritis. *Ann Rheum Dis* 2007;66(10):1271-5.
 20. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N et al. OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence. *Osteoarthritis Cartilage* 2007;15(9):981-1000.
 21. Fisher NM, Gresham GE, Abrams M, Hicks J, Horrigan D, Pendergast DR. Quantitative effects of physical therapy on muscular and functional performance in subjects with osteoarthritis of the knees. *Arch Phys Med Rehabil* 1993;74(8):840-7.
 22. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. *Ann Rheum Dis* 2005;64(4):544-8.
 23. Roddy E, Zhang W, Doherty M, Arden NK, Barlow J, Birrell F et al. Evidence-based recommendations for the role of exercise in the management of osteoarthritis of the hip or knee—the MOVE consensus. *Rheumatology* 2005;44(1):67-73.
 24. Lewek MD, Rudolph KS, Snyder-Mackler L. Quadriceps femoris muscle weakness and activation failure in patients with symptomatic knee osteoarthritis. *J Orthop Res* 2004;22(1):110-5.
 25. Thorstensson CA, Henriksson M, von Porat A, Sjødahl C, Roos EM. The effect of eight weeks of exercise on knee adduction moment in early knee osteoarthritis - a pilot study. *Osteoarthritis Cartilage* 2007.
 26. Lim BW, Hinman RS, Wrigley TV, Sharma L, Bennell KL. Does knee malalignment mediate the effects of quadriceps strengthening on knee adduction moment, pain, and function in medial knee osteoarthritis? A randomized controlled trial. *Arthritis Rheum* 2008;59(7):943-51.
 27. Rasch A, Bystrom AH, Dalen N, Berg HE. Reduced muscle radiological density, cross-sectional area, and strength of major hip and knee muscles in 22 patients with hip osteoarthritis. *Acta Orthop* 2007;78(4):505-10.
 28. Chang A, Hayes K, Dunlop D, Song J, Hurwitz D, Cahue S et al. Hip abduction moment and protection against medial tibiofemoral osteoarthritis progression. *Arthritis Rheum* 2005;52(11):3515-9.
 29. Rutherford DJ, Hubley-Kozey C. Explaining the hip adduction moment variability during gait: Implications for hip abductor strengthening. *Clin Biomech (Bristol, Avon)* 2009; 24(3):267-273.
 30. Briem K, Snyder-Mackler L. Proximal gait adaptations in medial knee OA. *J Orthop Res* 2009;27(1):78-83.
 31. Hunt MA, Birmingham TB, Bryant D, Jones I, Giffin JR, Jenkyn TR et al. Lateral trunk lean explains variation in dynamic knee joint load in patients with medial compartment knee osteoarthritis. *Osteoarthritis Cartilage* 2008;16(5):591-9.
 32. Mundermann L, Corazza S, Mundermann A, Lin T, Chaud-

- hari AM, Andriacchi TP. Gait Retraining to Reduce Medial Compartment Load at the Knee Assessed using Markerless Motion Capture. Transactions of the 52nd Annual Meeting of the Orthopedic Research Society, 2006; 0170.
33. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29(8):1039-49.
 34. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis* 1957;16:494-502.
 35. Felson DT, Zhang Y, Hannan MT, Naimark A, Weissman BN, Alibadi P. The incidence and natural history of knee osteoarthritis in the elderly: the Framingham osteoarthritis study. *Arthritis Rheum* 1995;38(10):1500-5.
 36. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988; 15(12):1833-40.
 37. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995; 3 Suppl A:3-70.
 38. Goker B, Block JA. Improved precision in quantifying knee alignment angle. *Clin Orthop Relat Res* 2007; 458:145-9.
 39. Cooke D, Scudamore A, Li J, Wyss U, Bryant T, Costigan P. Axial lower-limb alignment: comparison of knee geometry in normal volunteers and osteoarthritis patients. *Osteoarthritis Cartilage* 1997;5(1):39-47.
 40. Andriacchi TP, Johnson TS, Hurwitz DE, Natarajan RN. Musculoskeletal Dynamics, Locomotion, and Clinical Applications. In: Mow VC, Huiskes R, editors. *Basic Orthopaedic Biomechanics and Mechano-Biology*. Philadelphia: Lippincott, Williams, and Wilkins, 2005: 91-121.
 41. Moisio KC, Sumner DR, Shott S, Hurwitz DE. Normalization of joint moments: a comparison of two techniques. *J Biomech* 2003;36:599-603.
 42. Lim BW, Kemp G, Metcalf B, Wrigley TV, Bennell KL, Crossley KM et al. The association of quadriceps strength with the knee adduction moment in medial knee osteoarthritis. *Arthritis Rheum* 2009;61(4):451-8.
 43. Kisner C, Colby LA. Resistance Exercise. *Therapeutic Exercise Foundations and Techniques*. F.A. Davis Company, 2002: 58-148.
 44. Fosang A, Baker R. A method for comparing manual muscle strength measurements with joint moments during walking. *Gait Posture* 2006; 24(4):406-411.
 45. Norkin CC, Levangie PK. *Gait Analysis. Joint Structure and Function*. Philadelphia: F.A. Davis Company, 2005: 517-568.
 46. Slemenda C, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP et al. Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med* 1997; 127(2):97-104.
 47. Longino D, Frank C, Leonard TR, Vaz MA, Herzog W. Proposed model of botulinum toxin-induced muscle weakness in the rabbit. *J Orthop Res* 2005;23(6):1411-8.
 48. Herzog W, Longino D, Clark A. The role of muscles in joint adaptation and degeneration. *Langenbecks Arch Surg* 2003;388(5):305-15.
 49. Arsever CL, Bole GG. Experimental osteoarthritis induced by selective myectomy and tendotomy. *Arthritis Rheum* 1986;29(2):251-61.
 50. Suter E, Herzog W. Does muscle inhibition after knee injury increase the risk of osteoarthritis? *Exerc Sport Sci Rev* 2000;28(1):15-8.
 51. Youssef A, Seerattan R, Leonard T, Herzog W. Muscle Weakness Causes Joint Degeneration in Rabbits. Transactions of 54th Annual Meeting of the Orthopedic Research Society, 2008; 0054.
 52. Bennell K, Hinman R. Exercise as a treatment for osteoarthritis. *Curr Opin Rheumatol* 2005;17(5):634-40.
 53. Birmingham TB, Hunt MA, Jones IC, Jenkyn TR, Giffin JR. Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. *Arthritis Rheum* 2007;57(6):1012-7.