Journal of Biomechanics 47 (2014) 1409–1415

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

Selective lateral muscle activation in moderate medial knee osteoarthritis subjects does not unload medial knee condyle

Scott C.E. Brandon [a,*], Ross H. Miller [a], Darryl G. Thelen [b], Kevin J. Deluzio [a]

[a] Department of Mechanical and Materials Engineering, Queen's University, McLaughlin Hall, Kingston, Ontario, Canada K7L 3N6
[b] Department of Mechanical Engineering, University of Wisconsin-Madison, WI 53706, USA

ARTICLE INFO

Article history:
Accepted 20 January 2014

Keywords:
Osteoarthritis
Gait
Computer Model
Knee Contact

ABSTRACT

There is some debate in the literature regarding the role of quadriceps-hamstrings co-contraction in the onset and progression of knee osteoarthritis. Does co-contraction during walking increase knee contact loads, thereby causing knee osteoarthritis, or might it be a compensatory mechanism to unload the medial tibial condyle? We used a detailed musculoskeletal model of the lower limb to test the hypothesis that selective activation of lateral hamstrings and quadriceps, in conjunction with inhibited medial gastrocnemius, can actually reduce the joint contact force on the medial compartment of the knee, independent of changes in kinematics or external forces. "Baseline" joint loads were computed for eight subjects with moderate medial knee osteoarthritis (OA) during level walking, using static optimization to resolve the system of muscle forces for each subject's scaled model. Holding all external loads and kinematics constant, each subject's model was then perturbed to represent non-optimal "OA-type" activation based on mean differences detected between electromyograms (EMG) of control and osteoarthritis subjects. Knee joint contact forces were greater for the "OA-type" than the "Baseline" distribution of muscle forces, particularly during early stance. The early-stance increase in medial contact load due to the "OA-type" perturbation could implicate this selective activation strategy as a cause of knee osteoarthritis. However, the largest increase in the contact load was found at the lateral condyle, and the "OA-type" lateral activation strategy did not increase the overall (greater of the first or second) medial peak contact load. While "OA-type" selective activation of lateral muscles does not appear to reduce the medial knee contact load, it could allow subjects to increase knee joint stiffness without any further increase to the peak medial contact load.

1. Introduction

It is theoretically possible to perform two gait cycles with identical kinematics and ground reaction forces but using very different muscle activation patterns. While there is evidence that humans normally adopt an optimal muscle activation strategy to minimize metabolic cost (Anderson and Pandy, 2001; Holt et al., 1991; Umberger and Martin, 2007), it has also been found that subjects with knee osteoarthritis walk with abnormal patterns of muscle activation despite exhibiting similar kinematics (Heiden et al., 2009; Hubley-Kozey et al., 2006; Zeni et al., 2010).

Why do subjects with osteoarthritis deviate from "optimal" muscle activation patterns? Given that the presence, severity, and risk of progression of knee osteoarthritis are strongly linked with excessive joint loading (Baliunas et al., 2002; Bennell et al., 2011; Miyazaki et al., 2002; Mundermann et al., 2005), and that muscle forces contribute greatly to knee contact forces (Shelburne et al., 2006), some researchers have speculated that abnormal muscle forces could be a primary cause of knee osteoarthritis (Bennell et al., 2008; Felson, 2009). Indeed, one of the hallmarks of knee osteoarthritis is elevated antagonistic co-contraction of quadriceps and hamstrings muscles during gait (Zeni et al., 2010), which is believed to result in greater joint loading.

However, subjects with moderate knee osteoarthritis exhibit significantly greater co-activation primarily in the lateral vasti and hamstrings muscles (Heiden et al., 2009; Hortobágyi et al., 2005; Mills et al., 2013) in conjunction with reduced activation in the medial gastrocnemius (Hubley-Kozey et al., 2006). It was speculated that, rather than causing knee osteoarthritis, these local changes in muscle activation could actually be a protective response aimed at decreasing the contact force on the damaged medial knee condyle. This distinction is extremely important because the two interpretations of antagonism suggest diametrically opposed interventions for treatment of knee osteoarthritis.

Previous studies have used musculoskeletal models of varying complexity to compare knee joint loading in healthy and

* Corresponding author. Tel.: +1 613 533 6737; fax: +1 613 533 6789.
E-mail address: brandon@me.queensu.ca (S.C.E. Brandon).

0021-9290/$ - see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jbiomech.2014.01.038

osteoarthritis subjects (Messier et al., 2005; Kumar et al., 2012; Richards and Higginson, 2010; Henriksen et al., 2006). An electromyogram (EMG)-driven model demonstrated that antagonistic co-contraction of quadriceps and hamstrings during gait will increase the medial contact force during gait (Kumar et al., 2012). None of these previous studies has addressed the hypothesis that selective antagonism of lateral muscle groups, independent of other changes in gait, could actually unload the medial condyle where osteoarthritis damage tends to be present.

The purpose of this study was to determine whether the selective lateral activation patterns characteristic of subjects with medial knee osteoarthritis could unload the medial condyle during gait while constraining the kinematics and ground reaction forces to remain unchanged. It is not feasible to experimentally alter neuromuscular patterns without changing kinematics and ground reaction forces; therefore, we used a constrained musculoskeletal modeling approach to address this research question. We hypothesized that despite elevated antagonist co-contraction, selective lateral activation of hamstrings and quadriceps muscles and inhibition of medial gastrocnemius would decrease the medial joint load.

2. Methods

2.1. Data

Lower limb marker trajectories and ground reaction forces (GRF) were collected from the affected limb of eight subjects with moderate medial knee osteoarthritis walking overground at self-selected speeds (Table 1, Astephen et al., 2008). Kinematic data were sampled at 100 Hz using an Optotrak 3D motion analysis system (Northern Digital Inc., Waterloo, ON). Ground reaction forces were sampled synchronously at 1000 Hz using an AMTI force platform (Advanced Mechanical Technology Inc., Watertown, MA). Subjects had no history of knee pain or surgical intervention, KL grades between 1 and 3, and were not candidates for knee replacement surgery. Our objective was to assess "early-stage" individuals who had clinically diagnosed knee osteoarthritis, but whose gaits were not yet severely altered by factors such as pain, immobility, and joint instability. Standard frontal-plane short knee radiographs were obtained to compute varus alignment (Cooke et al., 2007; Moreland et al., 1987). Electromyograms (EMG) were obtained from seven muscles spanning the affected knee: medial and lateral gastrocnemii, medial and lateral vasti, rectus femoris, biceps femoris, and semimembranosus (Hubley-Kozey et al., 2006). Raw EMG signals were full-wave rectified and low pass filtered at 6 Hz using a Butterworth filter, and then amplitude-normalized to the maximal value obtained for each muscle during maximal voluntary isometric contractions (MVIC) on a Cybex (Lumex, NY) dynamometer. The study was approved by the institutional ethics review board.

2.2. Musculoskeletal model

A 3D unilateral lower-limb musculoskeletal model (Arnold et al., 2010), including 7 segments, 11° of freedom, and 44 individual heads of 35 muscles, was uniformly scaled to each subject based on the distance between the lateral knee epicondyle and lateral malleolus markers. This generic lower-limb model computes tibiofemoral joint translations as well as adduction and internal rotation angles as a function of the flexion degree of freedom. However, the variation in knee adduction angle throughout the gait cycle (~2°) is less than the frontal plane angles observed in our subjects (Table 1). Consequently, we uncoupled the adduction degree of freedom from flexion and locked the adduction angle at each subject's standing radiographic angle. Using OpenSim 3.0 (Delp et al., 2007), inverse kinematics, inverse dynamics, and muscle moment arms about the ankle, knee, and hip joints during gait were computed for each subject from the experimental GRF and motion capture data (Table 2). Additionally, we included intermediate joints at medial and lateral knee contact locations which were locked during inverse kinematics, but unlocked during inverse dynamics computations to provide joint loads and muscle moment arms about each contact location. Within the generic model, these contact points were located 25% of the proximal tibial width (Schipplein and Andriacchi, 1991), or roughly 2.5 cm (Iwaki et al., 2000; Yao et al., 2008) medial and lateral to the knee joint center and, assuming spherical femoral condyles (Pandy et al., 1998), 25% of the same distance distal to the knee joint center. Contact locations were fixed in the tibial frame to approximate translation with respect to the femur during knee flexion (Winby et al., 2009). For each subject, the distance from each contact location to the knee joint center was uniformly scaled with the model as described above.

2.3. Muscle Forces

"Baseline" muscle forces during a representative stride for each subject were estimated in Matlab (The Mathworks, Natick, MA) using static optimization to minimize a muscle area-weighted sum of squares of muscle stress at each instant in the gait cycle (Happee and Van der Helm, 1995; Brandon et al., 2011). Muscle forces were constrained to be positive, and to balance the inverse dynamics hip flexion, hip adduction, knee flexion, and ankle flexion moments. These "Baseline" muscle forces, computed using a generic cost function for "normal" gait (Crowninshield and Brand, 1981) are not expected to be representative of OA subjects who exhibit abnormal muscle activity (Hubley-Kozey et al., 2006). Instead, these muscle forces are an estimate of the baseline forces required to replicate the kinematics of these OA subjects.

2.4. OA-type perturbation

It was hypothesized that OA subjects exhibit additional changes in muscle activation that are not consistent with their kinematics. Therefore, joint kinematics and kinetics were held constant while muscle activations were perturbed from the "Baseline" condition to the "OA-type" condition. For each subject, vastus lateralis

Table 2
Peak joint kinematics, joint moments, and ground reaction forces for the eight subjects during level gait at self-selected normal walking speed. These parameters were held constant for both "Baseline" and "OA-type" simulations.

Parameter	Location	Mean (SD)
Kinematics [deg.]		
Pelvic tilt	Late-stance	4.7 (6.6)
Hip flexion	Heel-strike	24.4 (6.6)
	Toe-off	−16.3 (7.4)
Knee flexion	Early-stance	19.6 (8.5)
	Swing	63.2 (4.8)
Ankle dorsiflexion	Late-stance	8.3 (4.7)
External joint moments [Nm/kg]		
Hip flexion	Early-stance	−0.8 (0.2)
	Late-stance	0.6 (0.2)
Hip adduction	Early-stance	0.5 (0.1)
	Late-stance	0.6 (0.1)
Knee flexion	Early-stance	0.6 (0.4)
	Late-stance	−0.4 (0.2)
Knee adduction	Early-stance	0.4 (0.1)
	Late-stance	0.4 (0.1)
Ankle dorsiflexion	Late-stance	1.2 (0.2)
Ground reaction force [N/body weight]		
Anterior	Early-stance	−0.19 (0.04)
	Late-stance	0.18 (0.05)
Vertical	Early-stance	1.09 (0.14)
	Late-stance	1.05 (0.05)
Lateral	Heel-strike	0.06 (0.04)
	Early-stance	−0.06 (0.02)
	Late-stance	−0.05 (0.02)

Table 1
Osteoarthritis subject characteristics. These eight subjects were selected as a subset of the population described in Astephen et al. (2008). Where applicable, data are: mean (standard deviation).

Gender	Kellgren–Lawrence			Height [m]	Weight [kg]	BMI [kg/m^2]	Age [years]	Speed [m/s]	Static varus alignment [deg.]
	1	2	3						
2F, 6M	$N=2$	$N=3$	$N=3$	1.73 (0.12)	93.3 (7.3)	32 (5)	60 (7)	1.3 (0.2)	5 (3)

(VL), biceps femoris (LH) and medial gastrocnemius (MG) activations were conservatively perturbed by adding the "mean principal component difference" (MPCD) between OA and control EMG (Hubley-Kozey et al., 2006) to the model-predicted "Baseline" muscle activations to define their "OA-type" activations (Fig. 1). The MPCD perturbation was calculated for each muscle from the results of Hubley-Kozey et al. (2006) as the difference between mean principal component scores for OA and control groups, multiplied by the significant principal component pattern (Ramsay and Silverman, 1997).

Because these three muscle activation patterns were purposefully perturbed from the "Baseline" equilibrium solution, the sum of the muscle moments at the hip, knee, and ankle for this set of muscle activations would no longer balance the inverse dynamic moments applied to the model. Therefore, activations for the remaining 41 muscles were re-optimized in Matlab (The Mathworks, Natick, MA) to balance the inverse dynamic joint moments, using the same area-weighted stress-squared objective function, subject to the additional constraints that each muscle's activation was greater than or equal to its "Baseline" activation, and that the three perturbed muscles (MG, VL, and LH) must maintain their prescribed patterns of activation.

2.5. Contact model

For both "Baseline" and perturbed "OA-type" conditions, axial medial and lateral tibial contact forces were computed using a frontal-plane moment balance at tibial-fixed medial and lateral contact locations (Winby et al., 2009). If the moment balance at the medial condyle yielded a physiologically impossible tensile lateral contact force, the lateral condyle force was constrained to zero (*i.e.* unloaded) and a lateral collateral ligament force was added to the model at the lateral edge of the tibial plateau to maintain equilibrium (Winby et al., 2009). This contact model computes only the components of the medial and lateral tibiofemoral contact forces that are aligned with the long axis of the tibia. However, it has been shown that the shear components of tibiofemoral contact are comparatively small in magnitude (Kutzner et al., 2010; Shelburne et al., 2006). This musculoskeletal model can be used to predict medial and lateral axial contact loads within 0.3 BW of *in vivo* measured loads and, more importantly, to estimate within 0.1 BW the change in contact loads due to a gait perturbation (Appendix 1).

2.6. Statistics

Peak muscle forces, first and second peak medial, lateral, and total (combined) knee contact forces from "Baseline" and "OA-type" conditions were compared using a one-factor repeated measures ANOVA across the eight osteoarthritis subjects. An asymptomatic control group was not considered because the perturbation design of this study allowed each osteoarthritis subject to serve as their own control.

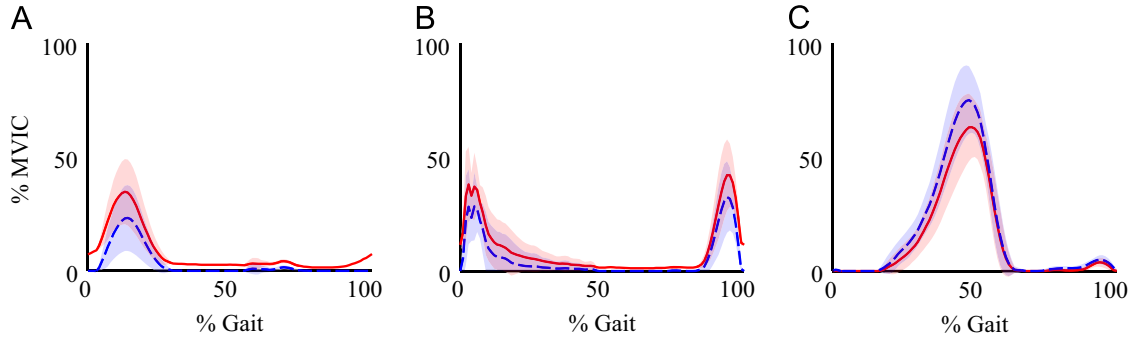

Fig. 1. Mean activation ± standard deviation (shaded) across eight subjects for "Baseline" (dashed, blue) and "OA-type" (solid, red) conditions: (A) Vastus lateralis (VL), (B) Biceps femoris (LH), and (C) Medial gastrocnemius (MG). "Baseline" activation patterns were computed using the static optimization model. "OA-type" activation patterns were computed by adding the mean principal component difference between OA and healthy control subjects (MPCD, computed from results of Hubley-Kozey et al. (2006)) to the "Baseline" activations. These three muscles were perturbed to simulate "OA-type" EMG patterns because they have been shown to be activated differently by OA and healthy control subjects (Hubley-Kozey et al., 2006). The muscle activation patterns for this static optimization model correlate well with experimental EMG (Appendix 1). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

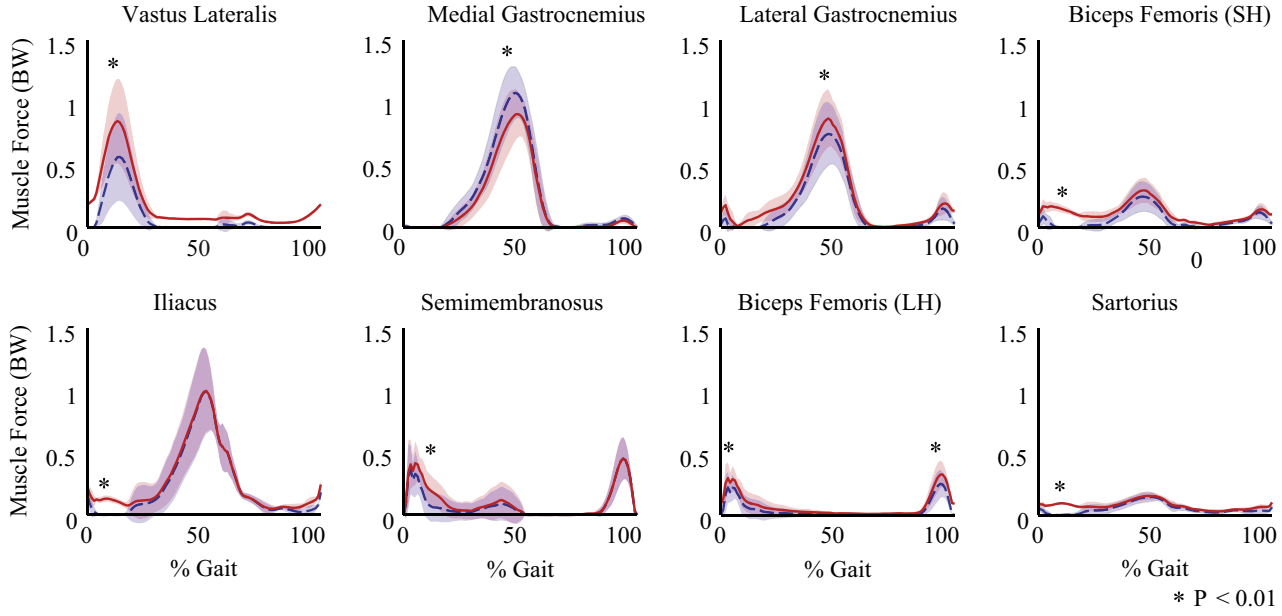

Fig. 2. Mean muscle forces ± standard deviation (shaded) for eight subjects, ranked in order of %RMS difference between "Baseline" (blue, dashed) and perturbed "OA-type" (red, solid) conditions. Vastus lateralis, medial gastrocnemius, and biceps femoris (LH) were directly prescribed by the "OA-type" perturbation; all other changes in muscle forces occurred to maintain dynamic equilibrium at each joint, while minimizing the overall cost in optimization. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Results

3.1. OA-type muscle forces

Across the eight subjects, the mean change in muscle force due to the "OA-type" activation perturbation was largest for the vastus lateralis and medial gastrocnemius muscles, which were two of the directly perturbed muscles (Fig. 2). The remaining 41 non-prescribed muscles responded to the "OA-type" perturbation indirectly in order to maintain equilibrium at each of the lower-limb joints. Listed in order of decreasing root mean square (RMS) change, the remaining muscles most affected by the perturbation were the lateral gastrocnemius, biceps femoris (SH), illiacus, semimembranosus, and sartorius (Fig. 2). All other muscle forces were virtually unaffected by the "OA-type" perturbation.

3.2. Contact forces

With a significance level of $P=0.05$, the repeated-measures study design provided the statistical power to detect a 0.1 times body-weight (BW) change in medial, lateral, or total knee contact force. The effect of the "OA-type" activation perturbation on tibiofemoral contact loads differed between the medial and lateral condyles. For the medial condyle, the "OA-type" perturbation caused a significant increase in contact force early in stance (2.1 to 2.4 BW; $P<0.01$); this shifted the peak medial contact force of 2.4 BW from late-stance in the "Baseline" condition to early-stance in the "OA-type" condition, but did not change the overall peak magnitude (Fig. 3A; Table 3). However, loading on the lateral condyle increased for both peaks (Fig. 3B; Table 3). The greatest change in the total knee contact force occurred in early stance, where the peak increased from 2.5 to 3.2 BW due to the "OA-type" perturbation ($P<0.01$).

The model predicted lateral condylar unloading for four of the eight subjects for the "Baseline" condition, and three of eight subjects after the "OA-type" perturbation. Therefore, the lateral "ligament" force was recruited to maintain equilibrium for some or all of the period from 10% to 40% of the gait cycle. For the baseline condition, the mean peak "ligament" force across all eight subjects was 65N, while for the "OA-type" condition the mean peak force was just 27 N. The maximum ligament force for any subject was 374 N for the "Baseline" condition, and 173 N for the "OA-type" condition.

3.3. Sensitivity to baseline muscle forces

These results motivated a follow-up question: would the effect of the "OA-type" perturbation on knee contact loads change if the "Baseline" muscle forces were different? To address this question, we computed for each subject a new set of muscle forces, "Baseline_stress5", which minimized the sum of stress in each muscle raised to the fifth power. We then applied the same "OA-type" perturbation to the "Baseline_stress5" forces to estimate "OA-type_stress5" muscle and knee contact forces (Fig. 4), and compared these results to our original "Baseline" and "OA-type" contact forces using a two-factor repeated measures ANOVA. There was no evidence of an interaction effect for any of the peak contact forces ($P>0.05$); the "OA-type" perturbation caused a significant ($P<0.01$) increase in medial, lateral, and total contact loads regardless of the choice of baseline muscle forces (Fig. 4).

4. Discussion

Contrary to our hypothesis, the "OA-type" perturbation did not decrease the medial knee contact force. However, the perturbation increased the medial contact force only slightly during early stance (Fig. 3A, 15–30% gait cycle, Table 3), and the overall peak (the greater of the first or second peak) medial contact force was unchanged. The lateral knee contact force, in comparison, was greater throughout the gait cycle, and the increase on the lateral condyle due to the "OA-type" perturbation was greater than on the medial (Fig. 3B, Table 3). Thus, these analyses do not support our hypothesis that OA subjects selectively activate lateral muscles, beyond any changes required by their gait kinematics, in an attempt to unload the medial knee condyle. Alternatively, it appears that selective lateral activation could be an effective strategy for subjects with medial osteoarthritis to increase overall joint stiffness (Schmitt and Rudolph, 2008) without large increases in contact force on the damaged medial compartment.

Table 3
Changes in discrete measurements of knee contact forces due to "OA-type" activation perturbation.

	Baseline	OA-Type	*P*-value
Lateral condyle			
Peak 1 [BW]	0.9 (0.3)	1.3 (0.3)	< 0.01
Peak 2 [BW]	0.8 (0.2)	1.0 (0.2)	< 0.01
Medial condyle			
Peak 1 [BW]	2.1 (0.5)	2.4 (0.4)	< 0.01
Peak 2 [BW]	2.4 (0.6)	2.3 (0.5)	< 0.01
Total contact load			
Peak 1 [BW]	2.5 (0.7)	3.2 (0.7)	< 0.01
Peak 2 [BW]	3.2 (0.4)	3.3 (0.4)	< 0.05

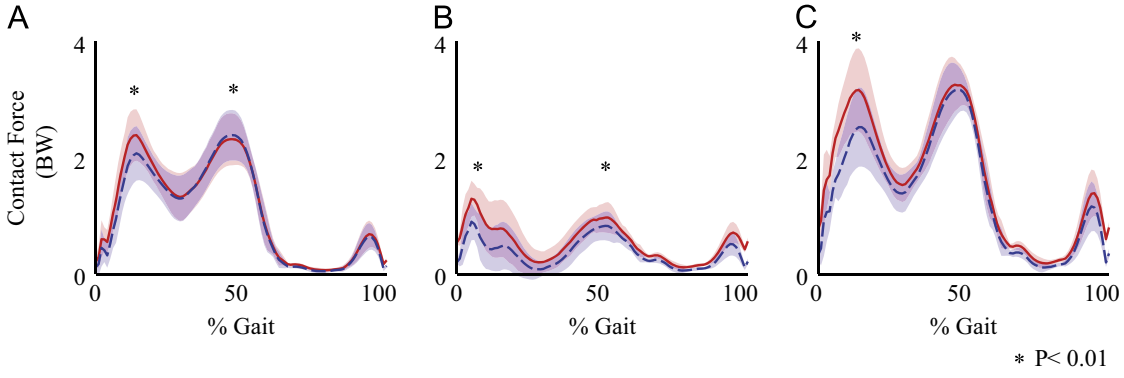

Fig. 3. Mean ± standard deviation (shaded) (A) medial, (B) lateral and ((C) total, sum) axial knee contact force during normal gait in eight subjects with moderate knee osteoarthritis. Forces predicted for "Baseline" condition (blue, dashed) were lower than those predicted after applying an "OA-type" activation perturbation (red, solid) to vastus lateralis, biceps femoris (LH), and medial gastrocnemius. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

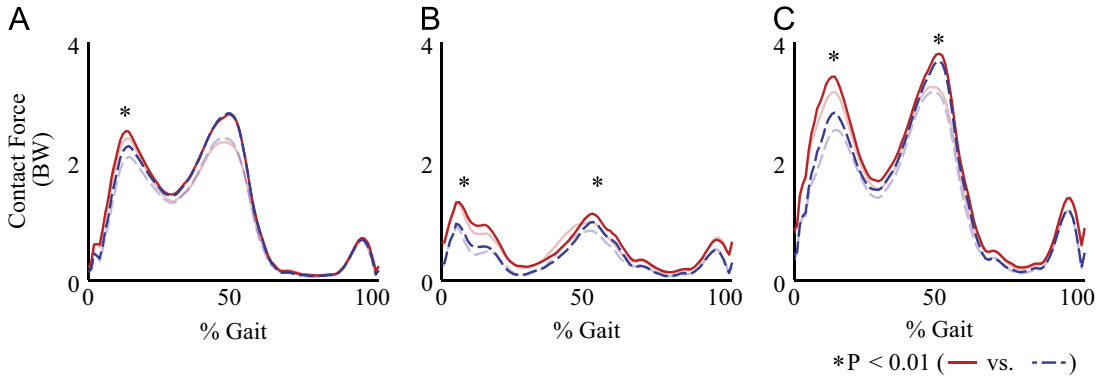

Fig. 4. Mean contact forces predicted for follow-up simulation conditions "Baseline_stress5" (dashed, blue) and "OA-type_stress5" (solid, red) are superimposed over original "Baseline" and "OA-type" results from Fig. 3. (A) Medial, (B) lateral and (C, sum) total axial knee contact force predictions were greater when using the stress5 objective criterion than using the original weighted stress2 criterion. The "OA-type" perturbation significantly increased first peak medial load, and both first and second peaks for lateral and total loads under the follow-up "_stress5" condition. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

This study tested the hypothesis that a pattern of selective lateral knee muscle activation, as seen in OA subjects, could reduce medial knee contact forces independent of changes in kinematics and kinetics. We are not aware of any studies where gait kinematics were constrained and differences in muscle coordination were recorded; such a study would be difficult, if not impossible, to experimentally perform. However, differences in neuromuscular control of knee muscles, without corresponding changes in joint kinetics, have been observed during isokinetic activities, particularly in subjects with patellar pain (Christou, 2004; Owings and Grabiner, 2002). Given that joint pain is also a primary symptom of knee osteoarthritis (Maly et al., 2006), it is reasonable to hypothesize that an osteoarthritis population might, similarly, alter their muscle coordination without corresponding changes in gait kinematics and kinetics.

In this study, we predicted "Baseline" muscle forces to match experimental gait data from subjects with moderate knee osteoarthritis. There are small, but significant, differences in gait kinematics and kinetics between healthy control and moderate OA subjects (Astephen et al., 2008; Kaufman et al., 2001), which may have predisposed our "Baseline" forces towards "OA-type" co-contraction (Richards and Higginson, 2010). However, preferential activation of lateral muscles, as seen in OA subjects, is energetically non-optimal (Crowninshield and Brand, 1981), and would not be predicted by our static optimization function. Additionally, our "Baseline" contact force estimates fall within the 2–3.5 BW range typically reported from *in vivo* measurements (Kutzner et al., 2010; Fregly et al., 2012a, 2012b), and are considerably lower than other recent modeling predictions greater than 4 BW (Winby et al., 2009; Richards and Higginson, 2010). Finally, we were primarily interested in the effect of the "OA-type" perturbation; our follow-up simulation (Fig. 4) demonstrated that the "OA-type" perturbation increased first peak medial and both peak lateral contact forces, regardless of the choice for "Baseline" muscle forces.

We validated our model by comparing model predictions of muscle activations and joint contact forces with EMG measurements and synchronized *in vivo* knee force measurements for a single subject with an instrumented joint implant (Appendix 1, Fregly et al., 2012a, 2012b). Our model's peak medial load prediction error of 0.3 BW was similar to another recent validated modeling study (Lin et al., 2010), although this error is also similar in magnitude to the effect sizes measured *in vivo* for subjects walking with and without assistive knee braces (Kutzner et al., 2011). However, when we examined the model's ability to predict, blinded, changes in joint loading due to gait perturbations, we found that the model consistently predicted the correct direction of perturbation, and was accurate within 0.03 BW for all loads except first peak lateral (error 0.3 BW) and total (error 0.2 BW) loads (Appendix 1, Table 4). Thus, we designed a study where the outcome measure was not an absolute prediction of medial contact force, but rather a perturbation in contact force between model conditions.

Table 4
Mean (SD) blind predictions of contact force for a single subject with an instrumented tibial implant from the second grand challenge to predict knee loading, across four normal walking trials and five "trunk sway" trials.

Location		Normal gait [BW]		Trunk sway gait [BW]		Delta (Trunk sway – normal)	
		in vivo	Predicted	*in vivo*	Predicted	*In vivo*	Predicted
Medial	Peak 1	0.9 (0.1)	0.6 (0.1)	1.4 (0.2)	1.1 (0.2)	0.5	0.5
	Peak 2	1.3 (0.2)	1.0 (0.0)	1.2 (0.2)	0.9 (0.1)	−0.1	−0.1
Lateral	Peak 1	1.3 (0.1)	0.9 (0.1)	1.7 (0.2)	1.6 (0.3)	0.4	0.7
	Peak 2	0.9 (0.0)	1.0 (0.1)	0.8 (0.2)	0.9 (0.1)	−0.1	−0.1
Total	Peak 1	2.2 (0.3)	1.5 (0.2)	3.1 (0.4)	2.6 (0.5)	0.9	1.1
	Peak 2	2.2 (0.2)	2.0 (0.1)	1.9 (0.2)	1.8 (0.2)	−0.2	−0.2

To better understand changes in knee loading, we investigated the direct contribution of knee-spanning muscles to medial and lateral joint loads. In accordance with previous studies, (Sritharan et al., 2012; Winby et al., 2009) hamstrings dominated early-stance loading, followed by quadriceps at the first peak and gastrocnemius at the second peak contact forces. In this study, the early-stance increase in medial contact load between "Baseline" and "OA-type" conditions was primarily due to increased vastus lateralis, sartorius, and semimembranosus forces (Table 3, Fig. 2). Similarly, vastus lateralis and biceps femoris (short and long heads) were primarily responsible for the early-stance increase in lateral contact force. Elevated vastus lateralis activation from the "OA-type" perturbation caused a net increase in the early-stance internal knee extension moment which was countered by biceps femoris (SH), semimembranosus, and sartorius muscles in proportion with their cost in the optimization function. If the biceps femoris (LH) perturbation had been sufficient to balance the increased vastus lateralis knee extension moment, or if biceps femoris (SH) activation had also been perturbed, it is possible that semimembranosus and sartorius need not have been recruited and there might have been no change, or even a decrease, in first peak medial contact force. However, such a large increase solely in biceps femoris (LH) force would not correspond with EMG observations (Hubley-Kozey et al., 2006; Mills et al., 2013) or optimal muscle endurance (Crowninshield and Brand, 1981). During late-stance, there was an increase in lateral gastrocnemius force which caused the increase in lateral knee contact loads, while the slight decrease in medial gastrocnemius force was not enough to generate a substantial change in medial contact force (Table 3; Fig. 2).

When the "OA-type" perturbation was applied, with the exception of a prescribed decrease for medial gastrocnemius, all other muscle activations were constrained to be greater than or equal to their "Baseline" values. Osteoarthritis subjects exhibit elevated, not decreased, muscle activation in quadriceps and hamstrings (Astephen et al., 2008; Hortobágyi et al., 2005; Hubley-Kozey et al., 2006; Mills et al., 2013); therefore, this lower-bound on "OA-type" muscle activations was required to create a realistic "OA-type" perturbation and to ensure that the greatest change in muscle forces were attributed to the directly perturbed muscles: vastus lateralis, medial gastrocnemius, and biceps femoris (LH) (Fig. 2). It is important to consider that these results are based on a single, general, model of the musculoskeletal geometry that was uniformly scaled to the stature of each subject (Arnold et al., 2010). With respect to each individual, the model certainly includes errors in musculoskeletal geometry and relative muscle strength which could have biased the solution (Cleather and Bull, 2012; Fregly et al., 2012b; Wagner et al., 2013). There is a need to develop a greater understanding of the effect of modeling parameters and constraints, and to validate these models with *in vivo* measurements.

Muscles that do not span the knee can affect knee joint loading because they can accelerate other limb segments, thereby altering the ground reaction force and the knee contact loads through dynamic coupling (Chen, 2006; Hamner et al., 2010; Neptune and McGowan, 2011; Sritharan et al., 2012). Sritharan et al. (2012) showed that during gait, the contribution of non-knee-spanning muscles is primarily *via* changes in the ground reaction force. Because our model perturbation constrained body kinematics and external loads to be constant, we found a change in only one non-knee-spanning muscle: iliacus (Fig. 2). However, iliacus has not been shown to be a primary contributor to medial or lateral knee loads during gait (Sritharan et al., 2012), and since the ground reaction force was constant, this non-knee-spanning muscle is unlikely to have altered knee loading. Future studies could investigate the combined effect of altered kinematics, ground reaction forces, and "OA-type" muscle activation on medial condylar loading in osteoarthritis subjects.

It is often assumed that static optimization models cannot account for antagonist muscle co-contraction, which is elevated in knee osteoarthritis subjects. In fact, Ait-Haddou et al. (2000) showed that models, such as the one in this study, that include biarticular muscles and are constrained to balance inverse dynamics loads across multiple joints will predict some antagonist co-contraction. Richards and Higginson (2010) predicted co-contraction changes with increasing osteoarthritis severity using OpenSim's computed muscle control algorithm, which includes static optimization to distribute muscle forces (Thelen and Anderson, 2006). Our model, likewise, predicted antagonist co-contraction at the knee which was elevated due to the "OA-type" perturbation (Fig. 2).

The literature is divided between studies that have (Hurwitz et al., 1998; Kumar et al., 2012; Shelburne et al., 2006) and have not (Sritharan et al., 2012; Winby et al., 2009) predicted lateral condylar unloading and ligament recruitment. Our model predicted lateral unloading at some point in the first 40% of the gait cycle for four of the eight subjects in the "Baseline" condition, and three subjects in the "OA-type" condition. Selective "OA-type" lateral activation shifted condylar loading to the lateral compartment (Fig. 3) and reduced the maximum "ligament" force from 374 N to just 173 N, perhaps reflecting the important role of lateral muscle co-contraction in stabilizing the knee adduction moment during gait (Winby et al., 2009). Across all subjects and trials, the maximum predicted "ligament" force of 374 N was considerably lower than a reported mean lateral collateral ligament failure strength of 750 N (Maynard et al., 1996), although higher than we would expect during normal gait.

The mediolateral contact force distribution at the knee is sensitive to the contact locations. During the stance phase of gait when the knee is flexed less than 30°, the medial and lateral contact points translate roughly 3 mm in the anterior-posterior and mediolateral directions (Hamai et al., 2009; Iwaki et al., 2000; Kozanek et al., 2009). While such translations are not inconsequential, we performed a sensitivity analysis ± 5 mm for each contact location and found less than 5% changes in estimated joint loads. Similarly, Winby et al. (2009) and Sritharan et al. (2012) perturbed contact locations up to 10 mm, and found less than 10% changes in joint loads. In this study, the contact locations were constant between "Baseline" and "OA-type" perturbations, therefore the changes in contact loads that were detected between conditions are likely true effects, even if our contact location assumption introduced a systematic offset.

The strength of the present study is its isolation of a specific factor (muscle activation) and its effects on knee joint loading. Our hypothesis that OA subjects alter muscle activation without corresponding changes in kinematics and kinetics could not be tested experimentally; however, we used a musculoskeletal model to predict that selective activation of lateral knee muscles, as found in subjects with medial knee OA, would not independently reduce medial knee contact loads. The early-stance increase in medial contact load due to the "OA-type" perturbation could implicate this selective activation strategy as a cause of knee osteoarthritis. However, the largest increase in the contact load was found at the lateral condyle. Therefore, it is possible that selective lateral muscle activation is a compensation aimed at increasing joint stability with minimal change in medial load, rather than simply decreasing medial joint load. This study provides further evidence that the role of muscles cannot be ignored in the pathogenesis of knee osteoarthritis, and that musculoskeletal simulation may be essential for developing suitable clinical interventions.

Conflict of interest statement

The authors have no conflict of interest to declare.

Acknowledgments

RHM and SCEB were funded by the NSERC-CREATE program.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jbiomech.2014.01.038.

References

Ait-Haddou, R., Binding, P., Herzog, W., 2000. Theoretical considerations on cocontraction of sets of agonistic and antagonistic muscles. J. Biomech. 33, 1105–1111.

Anderson, F.C., Pandy, M.G., 2001. Dynamic optimization of human walking. J. Biomech. Eng. 123, 381–390.

Arnold, E.M., Ward, S.R., Lieber, R.L., Delp, S.L., 2010. A model of the lower limb for analysis of human movement. Ann. Biomed. Eng. 38, 269–279.

Astephen, J.L., Deluzio, K.J., Caldwell, G.E., Dunbar, M.J., 2008. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. J. Orthop. Res. 26, 332–341.

Baliunas, A.J., Hurwitz, D.E., Ryals, A.B., Karrar, A., Case, J.P., Block, J.A., Andriacchi, T. P., 2002. Increased knee joint loads during walking are present in subjects with knee osteoarthritis. Osteoarthr.Cartil. 10, 573–579.

Bennell, K.L., Bowles, K., Wang, Y., Cicuttini, F., Davies-Tuck, M., Hinman, R.S., 2011. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann. Rheum. Dis. 70, 1770–1774.

Bennell, K.L., Hunt, M.A., Wrigley, T. V, Lim, B.W., Hinman, R.S., 2008. Role of muscle in the genesis and management of knee osteoarthritis. Rheum. Dis. Clin. North Am. 34, 731–754.

Brandon, S.C.E., Thelen, D.G., Deluzio, K.J., 2011. A Weighted Objective Function Reduces Estimates of Medial and Lateral Knee Joint Contact Loads During Gait. In: ASME 2011 Summer Bioengineering Conference.

Chen, G., 2006. Induced acceleration contributions to locomotion dynamics are not physically well defined. Gait. Posture 23, 37–44.
Christou, E.A., 2004. Patellar taping increases vastus medialis oblique activity in the presence of patellofemoral pain. J. Electromyogr. Kinesiol. 14, 495–504.
Cleather, D.J., Bull, A.M.J., 2012. The development of lower limb musculoskeletal models with clinical relevance is dependent upon the fidelity of the mathematical description of the lower limb. Part 2: patient-specific geometry. Proc. Inst. Mech. Eng. H 226, 133–145.
Cooke, T.D. V, Sled, E. a, Scudamore, R.A., 2007. Frontal plane knee alignment: a call for standardized measurement. J. Rheumatol. 34, 1796–1801.
Crowninshield, R.D., Brand, R.A., 1981. A physiologically based criterion of muscle force prediction in locomotion. J. Biomech. 14, 793–801.
Delp, S.L., Anderson, F.C., Arnold, A.S., Loan, P., Habib, A., John, C.T., Guendelman, E., Thelen, D.G., 2007. OpenSim: open-source software to create and analyze dynamic simulations of movement. IEEE Trans. Biomed. Eng 54, 1940–1950.
Felson, D.T., 2009. Developments in the clinical understanding of osteoarthritis. Arthritis Res. Ther. 11, 203.
Fregly, B.J., Besier, T.F., Lloyd, D.G., Delp, S.L., Banks, S.A., Pandy, M.G., D'Lima, D.D., 2012a. Grand challenge competition to predict *in vivo* knee loads. J. Orthop. Res. 30, 503–513.
Fregly, B.J., Boninger, M.L., Reinkensmeyer, D.J., 2012b. Personalized neuromusculoskeletal modeling to improve treatment of mobility impairments: a perspective from European research sites. J. Neuroeng. Rehabil. 9, 18.
Hamai, S., Moro-Oka, T.A., Miura, H., Shimoto, T., Higaki, H., Fregly, B.J., Iwamoto, Y., Banks, S.A., 2009. Knee kinematics in medial osteoarthritis during *in vivo* weight-bearing activities. J. Orthop. Res. 27, 1555–1561.
Hamner, S.R., Seth, A., Delp, S.L., 2010. Muscle contributions to propulsion and support during running. J. Biomech. 43, 2709–2716.
Happee, R., Van der Helm, F.C., 1995. The control of shoulder muscles during goal directed movements, an inverse dynamic analysis. J. Biomech. 28, 1179–1191.
Heiden, T.L., Lloyd, D.G., Ackland, T.R., 2009. Knee joint kinematics, kinetics and muscle co-contraction in knee osteoarthritis patient gait. Clin. Biomech. (Bristol, Avon) 24, 833–841.
Holt, K.G., Hamill, J., Andres, R.O., 1991. Predicting the minimal energy costs of human walking. Med. Sci. Sports Exerc. 23, 491–498.
Hortobágyi, T., Westerkamp, L., Beam, S., Moody, J., Garry, J., Holbert, D., DeVita, P., 2005. Altered hamstring-quadriceps muscle balance in patients with knee osteoarthritis. Clin. Biomech. (Bristol, Avon) 20, 97–104.
Hubley-Kozey, C.L., Deluzio, K.J., Landry, C.S.N., McNutt, J., Stanish, W.D., 2006. Neuromuscular alterations during walking in those with moderate knee osteoarthritis. J. Electromyogr. Kinesiol. 16, 365–378.
Hurwitz, D.E., Sumner, D.R., Andriacchi, T.P., Sugar, D.A., 1998. Dynamic knee loads during gait predict proximal tibial bone distribution. J. Biomech. 31, 423–430.
Iwaki, H., Pinskerova, V., Freeman, M.A., 2000. Tibiofemoral movement 1: the shapes and relative movements of the femur and tibia in the unloaded cadaver knee. J. Bone Jt. Surg. Br. 82, 1189–1195.
Kaufman, K.R., Hughes, C., Morrey, B.F., Morrey, M., An, K.N., 2001. Gait characteristics of patients with knee osteoarthritis. J. Biomech. 34, 907–915.
Kozanek, M., Hosseini, A., Liu, F., Van, V, de, Gill, T.J., Rubash, H.E., Li, G., 2009. Tibiofemoral kinematics and condylar motion during the stance phase of gait. J. Biomech. 42, 1877–1884.
Kumar, D., Rudolph, K.S., Manal, K.T., 2012. EMG-driven modeling approach to muscle force and joint load estimations: case study in knee osteoarthritis. J. Orthop. Res. 30, 377–383.
Kutzner, I., Küther, S., Heinlein, B., Dymke, J., Bender, A., Halder, A.M., Bergmann, G., 2011. The effect of valgus braces on medial compartment load of the knee joint – *in vivo* load measurements in three subjects. J. Biomech. 44, 1354–1360.
Kutzner, I., Heinlein, B., Graichen, F., Bender, A., Rohlmann, A., Halder, A., Beier, A., Bergmann, G., 2010. Loading of the knee joint during activities of daily living measured in vivo in five subjects. J. Biomech. 43, 2164–2173.
Lin, Y.-C.C., Walter, J.P., Banks, S.A., Pandy, M.G., Fregly, B.J., 2010. Simultaneous prediction of muscle and contact forces in the knee during gait. J. Biomech. 43, 945–952.
Maly, M.R., Costigan, P.a, Olney, S.J., 2006. Determinants of self-report outcome measures in people with knee osteoarthritis. Arch. Phys. Med. Rehabil. 87, 96–104.
Maynard, M.J., Wickiewicz, T.L., Warren, R.F., 1996. The popliteofibular ligament: rediscovery of a key element in posterolateral stability. Am. J. Sports Med. 24, 311–316.
Mills, K., Hunt, M.A., Leigh, R., Ferber, R., 2013. A systematic review and meta-analysis of lower limb neuromuscular alterations associated with knee osteoarthritis during level walking. Clin. Biomech. (Bristol, Avon) 28, 713–724.
Miyazaki, T., Wada, M., Kawahara, H., Sato, M., Baba, H., Shimada, S., 2002. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann. Rheum. Dis. 61, 617–622.
Moreland, J.R., Bassett, L.W., Hanker, G.J., 1987. Radiographic analysis of the axial alignment of the lower extremity. J. Bone Jt. Surg. Am. 69, 745–749.
Mundermann, A., Dyrby, C.O., Andriacchi, T.P., 2005. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum. 52, 2835–2844.
Neptune, R.R., McGowan, C.P., 2011. Muscle contributions to whole-body sagittal plane angular momentum during walking. J. Biomech. 44, 6–12.
Owings, T.M., Grabiner, M.D., 2002. Motor control of the vastus medialis oblique and vastus lateralis muscles is disrupted during eccentric contractions in subjects with patellofemoral pain. Am. J. Sports Med. 30, 483–487.
Pandy, M.G., Sasaki, K., Kim, S., 1998. A three-dimensional musculoskeletal model of the human knee joint. Part 1: theoretical construct. Comput. Biomech. Biomed.Eng. 1, 87–108.
Ramsay, J.O., Silverman, B.W., 1997. Functional Data Analysis. Springer, New York
Richards, C., Higginson, J.S., 2010. Knee contact force in subjects with symmetrical OA grades: differences between OA severities. J. Biomech. 43, 2595–2600.
Schipplein, O.D., Andriacchi, T.P., 1991. Interaction between active and passive knee stabilizers during level walking. J. Orthop. Res. 9, 113–119.
Schmitt, L.C., Rudolph, K.S., 2008. Muscle stabilization strategies in people with medial knee osteoarthritis: the effect of instability. J. Orthop. Res. 26, 1180–5.
Shelburne, K.B., Torry, M.R., Pandy, M.G., 2006. Contributions of muscles, ligaments, and the ground-reaction force to tibiofemoral joint loading during normal gait. J. Orthop. Res. 24, 1983–1990.
Sritharan, P., Lin, Y.C., Pandy, M.G., 2012. Muscles that do not cross the knee contribute to the knee adduction moment and tibiofemoral compartment loading during gait. J. Orthop. Res. 30, 1586–1595.
Thelen, D.G., Anderson, F.C., 2006. Using computed muscle control to generate forward dynamic simulations of human walking from experimental data. J. Biomech. 39, 1107–1115.
Umberger, B.R., Martin, P.E., 2007. Mechanical power and efficiency of level walking with different stride rates. J. Exp. Biol. 210, 3255–3265.
Wagner, D.W., Stepanyan, V., Shippen, J.M., Demers, M.S., Gibbons, R.S., Andrews, B. J., Creasey, G.H., Beaupre, G.S., 2013. Consistency among musculoskeletal models: caveat utilitor. Ann. Biomed. Eng. 41, 1787–1799.
Winby, C.R., Lloyd, D.G., Besier, T.F., Kirk, T.B., 2009. Muscle and external load contribution to knee joint contact loads during normal gait. J. Biomech. 42, 2294–2300.
Yao, J., Salo, A.D., Lee, J., Lerner, A.L., 2008. Sensitivity of tibio-menisco-femoral joint contact behavior to variations in knee kinematics. J. Biomech. 41, 390–398.
Zeni, J.A., Rudolph, K., Higginson, J.S., 2010. Alterations in quadriceps and hamstrings coordination in persons with medial compartment knee osteoarthritis. J. Electromyogr. Kinesiol. 20, 148–154.