

**CO-ACTIVATION DIFFERENCES IN LOWER LIMB MUSCLES BETWEEN
ASYMPTOMATIC CONTROLS AND THOSE WITH VARYING DEGREES OF
KNEE OSTEOARTHRITIS DURING WALKING**

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Short title: Co-activation and knee OA severity

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Abstract

Background: Increased muscle co-activation during gait has been identified as a neuromuscular alteration associated with knee osteoarthritis, however levels of co-activation among different osteoarthritis severity have not been established. The purpose of this study was to determine if differences in co-activation could be detected among asymptomatic controls, those with moderate and those with severe osteoarthritis using a co-activation index and a pattern recognition technique.

Methods: Surface electromyograms from vastus lateralis and medialis, lateral and medial hamstring and gastrocnemius pairs were recorded from 63 asymptomatic, 59 moderate and 48 severe osteoarthritic subjects during self-selected walking. A co-activation index was calculated over the initial stance for four medial and lateral muscle pairs. The four co-activation indices were tested among groups using a one factor ANOVA ($\alpha=0.05$). Gait waveform pattern recognition procedures were applied to yield a principal pattern, scored for each muscle site and subject. A mixed model ANOVA (group-muscle) tested for principal pattern score differences.

Findings: A significant group effect was found ($p<0.05$) for all four co-activation indices. Principal pattern one captured the amplitude and general shape of activity throughout the entire stance phase. ANOVA revealed a significant ($p<0.05$) group by muscle interaction for the principal pattern scores. Significant differences were found among all three groups and between the two osteoarthritic groups for both measures.

Interpretation: The co-activation indices and principal patterns identified that lateral site differences occurred among all three groups with medial site differences between the two osteoarthritic groups. These findings suggest that measures of muscle co-activity provide additional information related to knee osteoarthritis severity.

Key words: knee osteoarthritis severity, gait, electromyography, co-activation index, pattern recognition

Introduction

Osteoarthritis (OA) is the most common form of arthritis (Felson et al., 2000), and the leading cause of pain and disability in the elderly worldwide (Buckwalter et al., 2001). Although associated with older adults, those around 55 years of age are the largest group affected (Buckwalter et al., 2001). This cohort is expected to grow given our aging population and the trend toward increased Body Mass Index (BMI) in our population, a factor linked to the development of OA (Felson et al., 2004). The knee is the joint most commonly affected by OA (Buckwalter et al., 2001) and while total knee replacement surgery is a feasible treatment option many OA sufferers will not be surgical candidates (Buckwalter et al., 2001).

Given the size of this cohort, a need exists for accurate determination of disease progression so that effective treatment options can be prescribed. Currently, radiography is a widely used diagnostic procedure (Altman 1991). Unfortunately, there is a poor association between radiographic scores used to diagnose disease progression and symptoms of OA (Barker et al., 2004; Creamer et al., 2000). This may in part be due to subjectivity in self-reports of function and symptoms, thus identifying objective measures that capture characteristics of disease progression is needed (Barker et al., 2004). Presumably, objective measures associated with how disease progression affects function would lead to more informed treatment decisions and improved management of knee OA.

The present study aimed to explore the potential value of exploiting the changes reported in neuromuscular control strategies during walking for those with knee OA as a basis for assessing disease progression. Although only a few studies have examined muscle activation patterns during walking for those with knee OA, increased muscle co-activation of the knee joint musculature has consistently been reported (Benedetti et al.,

1999; Childs et al., 2004; Hubley-Kozey et al., 2008; Lewek et al., 2004a). The co-activation measures reported include increased amplitude (Benedetti et al., 1999; Childs et al., 2004), prolonged duration (Childs et al., 2004), increased co-contraction indices (Lewek et al., 2004a; Ramsey et al., 2007b) and high magnitude scores from pattern recognition techniques (Hubley-Kozey et al., 2008). To date, there remains no standard method to measure muscle co-activation during gait.

There are numerous methods for quantifying co-activation; however, the definition used in the present study refers to the simultaneous recruitment of synergistic muscles (Sirin and Patla 1987), with synergistic muscles referring to all muscles that participate in producing moments of force around a joint (Nigg et al., 2003). The present study compared two approaches presented in the literature. The first approach was the co-contraction index (Lewek et al., 2004a) which attempts to measure the relative activity of muscle pairs surrounding a joint. This index is calculated over a short time interval corresponding to the initial loading phase. The second approach was a pattern recognition procedure. This approach attempts to measure the similarities in amplitude and shape among muscles by applying the technique to the time normalized EMG waveforms from the muscles surrounding the knee joint (Hubley-Kozey et al., 2008). These two approaches were chosen for comparison because they both result in a degree of data reduction by providing a single value to represent characteristics of the waveform.

Studies of muscle activation during walking and knee OA, have compared asymptomatic controls to those with knee OA (Hubley-Kozey et al., 2006; Lewek et al., 2004a) or presented characteristics for those with knee OA only (Benedetti et al., 1999; Hubley-Kozey et al., 2008). Only one paper using a multivariate approach examined

differences between OA subgroups but did not focus specifically on quantifying co-activity (Astephen et al., 2008a). Therefore, the purpose of this study was to determine if differences in co-activation could be detected among asymptomatic controls, subjects with moderate OA and subjects with severe OA using i) a co-activation index (CCI) calculated during the initial phase of the gait cycle for medial and lateral muscle pairs and ii) a pattern recognition procedure applied to the entire gait cycle EMG waveforms for six muscles surrounding the knee joint. We hypothesized that co-activation of the synergistic muscles would differ among the three groups and that these differences would capture characteristics of disease progression at the joint previously reported such as changes in medial joint loading (Astephen et al., 2008b) and increases in joint space narrowing (Kellgren and Lawrence 1957). The long term goal is to develop objective, non-invasive measures that provide an adjunct to radiographic scores and clinical signs and symptoms that improve the diagnostic classification of those with varying severities of knee OA.

Methods

Three groups were recruited for this study i) asymptomatic controls, ii) those with moderate knee OA and iii) those with severe knee OA. All subjects completed gait analysis procedures at the Dynamics of Human Movement Laboratory, Dalhousie University, Halifax, Nova Scotia, Canada, between 2002 and 2006. Subjects were included if they were able to walk the length of a 6-meter walkway without an ambulatory aid and were over 35 years old. They were excluded if they had any neurological, cardiovascular, respiratory or musculoskeletal conditions other than the

knee OA that would affect their gait or place them at risk of injury by participating.

Subjects provided informed consent approved by the Institution Ethics Board.

Asymptomatic controls recruited from the general community presented with no lower extremity injuries within the past six months and no known lower extremity degenerative pathology (hip, knee, or ankle osteoarthritis). Those with knee OA were recruited from the Capital District Health Authority and Orthopedic and Sports Medicine Clinic of Nova Scotia, Canada. Assignment to the moderate OA and severe OA groups was based on clinical diagnosis by two orthopedic surgeons (MJD, WDS), physical function and the grading of standard anterior-posterior and lateral radiographs. Radiographs were scored using the Kellgren Lawrence (KL) global scoring that assigns a number from 0 (normal) to 4 (severe) based on the presence of osteophytes, joint space narrowing, sclerosis and joint deformity (Kellgren and Lawrence 1957) and the Scott feature based scoring of medial and lateral joint space narrowing (JSN) separately with 0 being normal or no narrowing and 3 severe narrowing or bone on bone (Scott et al., 1993). Two surgeons (MJD, WDS) completed the rating and good reliability was previously reported (McKean et al., 2007). Subjects with mild to moderate knee OA were included with a i) KL grade of 1-3; ii) diagnosis of mild to moderate knee OA; iii) conservative treatment prescribed and iv) the ability to complete three standard functional activities. These activities included i) reciprocally ascend and descend 10 stairs; ii) ability to walk one city block, and 3) jog five meters. KL radiographic criteria has been utilized to classify mild to moderate knee OA (Hubley-Kozey et al., 2006; Landry et al., 2007). The classification of severe knee OA was based on i) KL grade of 3 or 4 (definite JSN); ii) diagnosis of severe end-stage knee OA based on a clinical assessment by an

orthopaedic surgeon; iii) treatment prescribed was a total knee replacement and iv) impaired function with respect to the above mentioned functional activities. Severe OA group completed their gait analysis procedures within one week prior to total knee replacement surgery. The OA groups had predominantly medial compartment involvement (lateral JSN score < medial JSN score). All subjects completed the pain, stiffness and physical function scales of the WOMAC questionnaire, a validated questionnaire for OA research (Bellamy et al., 1988).

Subjects were prepared utilizing standardized protocols for motion capture (Landry et al., 2007) and electromyographical analysis of six lower extremity muscles (Hubley-Kozey et al., 2006). The affected leg for the two OA groups and a randomly selected leg for the asymptomatic group were studied. Skin surface was prepared by shaving and abrading with alcohol wipes and a water solution. Two silver/silver chloride surface electrodes (0.79 mm² contact area, Bortec Inc, Calgary, Canada) were placed 20 mm centre-to-centre in line with the muscle fibers on the prepared skin over the vastus lateralis, vastus medialis, the lateral and medial hamstrings, and the lateral and medial gastrocnemius using standardized placements (Hubley-Kozey et al., 2006). A reference electrode was placed over the mid-tibial shaft. Electrode placements were validated and assessed for cross talk (Shiavi et al., 1987; Winter et al., 1994) by having subjects performing isolated manual muscle tests (Kendall et al., 1993). Skin-electrode impedance was measured and the ratio to the input impedance of the amplifier was less than the 1% as recommended (Winter 1996). EMG signals were amplified using an eight-channel EMG amplifier (Bortec, Inc., Calgary, Alberta, Canada, CMRR: 115dB at

60 Hz, Input Impedance: $\sim 10\text{G}\Omega$, Band-pass filter (10-1000 Hz)) and were digitally converted at 1000Hz

Lower extremity three-dimensional motion and ground reaction forces were captured using two optoelectronic motion analysis sensors (Optotrak 3020™, Northern Digital Inc., Waterloo, ON, Canada) and a single force plate (AMTI™, Advanced Mechanical Technology Incorporation, Newton, MA, USA) aligned to the global coordinates of the motion capture system (Landry et al., 2007). These data determined walking velocity and identified heel strike events for time normalization. The net external knee adduction moment was calculated using inverse dynamics (Costigan et al., 1992; Landry et al., 2007) as the peak knee adduction moment was required for the CCI calculation.

Participants walked along a 6-meter walkway at their self-selected walking velocity while motion, force and EMG data were recorded. A minimum of three trials within five percent of the average speed were recorded. Following the walking trials, subjects lay supine while a bias trial was collected. Subjects then completed a series of eight exercises aimed at eliciting maximal voluntary isometric contractions (MVIC) for the three muscle groups tested. Eight exercises described in detail elsewhere (Hubley-Kozey et al., 2006) were used to amplitude normalize the EMG waveforms during walking. Seven were completed against a Cybex II™ Isokinetic dynamometer (Lumex, NY, USA). Maximal effort contractions were held for three seconds and separated by a 60-second rest period. Subjects were given practice, encouragement and feedback. Both OA and asymptomatic controls have been shown to voluntarily elicited 93% or more of their maximal stimulated quadriceps activity (Lewek et al., 2004b). Amplitudes

normalized to maximal effort contractions served as a physiological reference for comparing the EMG amplitudes among muscle sites (Burden et al., 2003; Kasman et al., 1998).

Processing

Electromyographic, kinematic and kinetic data were processed using algorithms written in MatLab™ version 7.0 (The Mathworks Inc., Natick, Massachusetts, USA). EMG signals were corrected for subject bias and converted to micro-volts, full wave rectified and low pass filtered (Butterworth 6-Hz, 4th order, low pass filter) (Hubley-Kozey et al., 2008). For amplitude normalization, a 100-ms moving window algorithm identified the maximal amplitude for each muscle across all eight MVIC exercises. This value was used to amplitude normalize the EMG data for the walking trials to a percentage of MVIC. Time normalization differed for the two approaches. For the pattern recognition analysis, the EMG waveforms were time normalized to 101 points using a linear interpolation technique from heel strike to heel strike on the same foot (Hubley-Kozey et al., 2006) (Fig.1A and 1C). For the CCI approach the EMG waveforms were time normalized to 101 data points from 100 ms prior to heel strike to the time when the peak knee adduction moment occurred in the gait cycle as described by Lewek et al. (2004a) (Fig. 1B and 1D right panels).

Analysis

For the pattern recognition procedure the normalized waveforms for all muscles and all subjects were included into one matrix [X=101*1020] (Hubley-Kozey et al.,

2008). The procedure is described in detail elsewhere (Hubley-Kozey et al., 2008), however briefly a cross product matrix was calculated from the original matrix X and standard eigenvector decomposition of this matrix was performed. The orthonormal eigenvectors were derived. For consistency with previous work (Hubley-Kozey et al., 2008), eigenvectors will be referred to as principal patterns (note: when a covariance matrix is factored these eigenvectors are typically referred to as principal components (Jackson 1991)). The principal pattern score (*PP score*) provides a measure of how accurately an individual's gait waveform projected on to the derived principal pattern. A percent trace was calculated to determine how well the patterns represented the original waveform (Hubley-Kozey et al., 2008; Hubley-Kozey et al., 2006). In this study, the principal pattern with the highest percent trace was used as a measure of co-activation as it provided a measure of the general shape and amplitude of the original waveforms. The individual *PP scores* were utilized in statistical analysis to compare the characteristics of the waveforms among groups and among all muscles.

The CCI was computed for the following muscle groupings using the method described by Lewek et al. (2004a) (see equation below); vastus medialis-medial gastrocnemius (VMMG), vastus medialis-medial hamstring (VMMH), vastus lateralis-lateral gastrocnemius (VLLG), and vastus lateralis-lateral hamstring (VLLH). Figure 1 provides an example of the two EMG waveforms with the knee adduction moment superimposed.

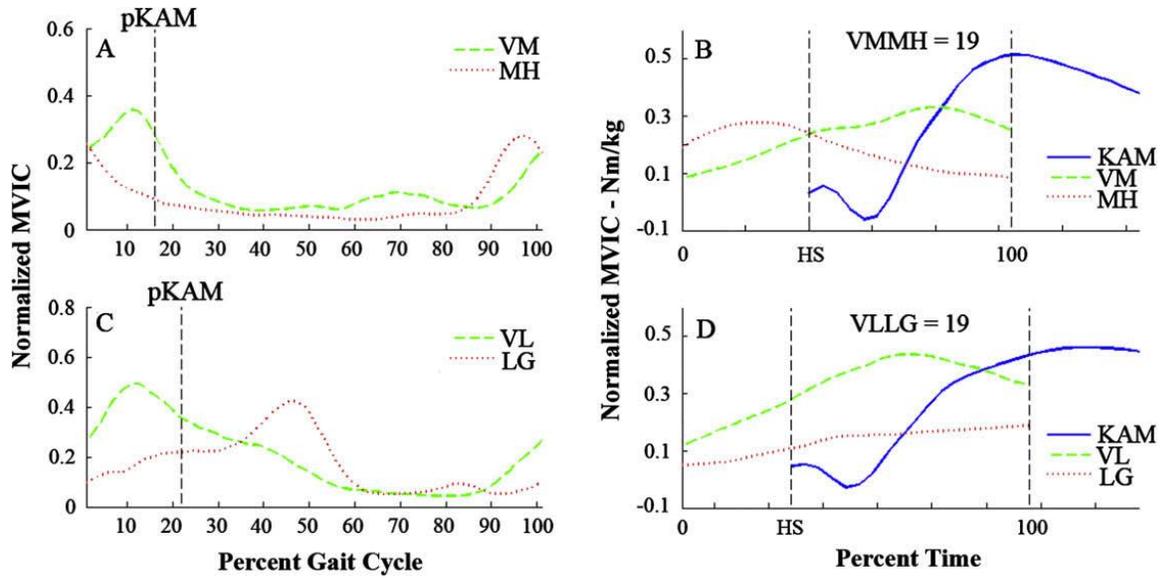


Fig. 1. (A) Example ensemble averaged VM (Vastus Medialis) and MH (Medial Hamstring) electromyogram for an asymptomatic individual and (C) for VL (Vastus Lateralis) and LG (Lateral Gastrocnemius) electromyogram for an individual with severe knee OA. These waveforms are time normalized to one gait cycle from heel contact to heel contact. The vertical line indicates when the peak knee adduction moment (pKAM) occurred. Both left and right columns are amplitudes normalized to percent MVIC. The MVIC normalization is scaled to unity (scaled to 1 = 100% MVIC). For the right panels (B and D) time is normalized from 100 ms prior to heel contact (0% indicated by first vertical line) to the pKAM (100% indicated by the second vertical line) used in the calculation of the CCIs.

$$CCI = \frac{1}{100} \sum_{i=1}^{100} \left[\frac{\text{lowerEMG}_i}{\text{higherEMG}_i} \times (\text{lowerEMG}_i + \text{higherEMG}_i) \right]$$

Statistical Analysis

Means and standard deviations were calculated for age, BMI, walking speed, stride length, WOMAC and radiographic scores. For the CCIs and the *PP scores* a Bartlett test for equal variance and a Kolmogorov Smirov test for normality were performed. A mixed model ANOVA tested group and muscle main effects and interactions for the *PP scores* ($\alpha=0.05$). Bonferonni post hoc procedures tested pair-wise differences among groups based on 18 comparisons ($\alpha=0.003$) and among muscles correcting α based on 45 comparisons ($\alpha=0.001$) (Zar 1996). A one-way ANOVA tested for differences between the three groups for the CCI ($\alpha=0.05$). Bonferonni correction ($\alpha=0.0167$) was employed to test for pair-wise differences. Statistical analyses were performed using Minitab™ V.15 (Minitab Inc. State College, PA, USA).

Results

Demographic data for the three groups are in Table 1. Sixty three asymptomatic controls, 59 moderate OA and 48 severe OA subjects completed the gait procedure. After grading the radiographs, 6 moderate OA subjects did not meet the radiographic criteria and were excluded from further analysis leaving 53 in the moderate OA group. Significant differences among the groups for demographic data are indicated in Table 1.

Ensemble average waveforms for the three groups and six muscle sites are in Figure 2. There are qualitative differences among the three groups. Progressive decrease in activation amplitude from the asymptomatic to the severe OA group during late stance was observed for the medial gastrocnemius muscle only. Severe OA had higher amplitudes for the two vasti muscles and the two hamstrings for most of stance phase compared to both the moderate OA and the asymptomatic groups. The moderate OA group had elevated activity for the vastus lateralis and lateral hamstring only compared to the asymptomatic group.

Percent trace for principal pattern one was 70 percent. This pattern captured the amplitude and general shape of the waveforms over the stance phase of the gait cycle (Fig. 3 upper panel). Essentially this pattern captured the prolonged activation during stance with two small bursts one corresponding to the vasti muscles burst in early stance and a second one corresponding to the gastrocnemius burst later in the stance phase. The Kolmogorov Sminov ($p < 0.05$) and the Bartlett's test ($p < 0.05$) were both significant and the data were transformed using a log transformation. The ANOVA revealed a statistically significant group by muscle interaction ($p < 0.05$). Mean *PP scores* for each

muscle and group are in the lower panel of Figure 3. Post hoc differences among groups are indicated on this figure and differences among muscles are indicated in the figure caption. Vastus lateralis and lateral hamstring muscles were significantly different among all three groups ($p < 0.003$) whereas the medial hamstring and vastus medialis were only significantly higher for the severe OA group compared to the other two groups. Post hoc results found distinct differences among the three muscle groupings for the asymptomatic group. The gastrocnemius muscles had higher scores ($p < 0.001$) than the two vasti muscles and the two hamstrings; as well the vastus medialis scores were higher than the two hamstrings. Conversely only medial hamstring was lower ($p < 0.001$) than the other five muscles and lateral hamstring was lower than the medial gastrocnemius muscle for the moderate OA group. Severe OA group had a different pattern with significantly ($p < 0.001$) higher quadriceps and lateral hamstring activity compared to the two gastrocnemius muscles.

Means and standard deviations for the four CCIs are in Figure 4. The indices ranged from approximately 8 for the asymptomatic VMMG to about 40 for the severe VLLH. The Kolmogorov Smirnov ($p < 0.05$) and the Bartlett's test ($p < 0.05$) were both significant and the data were transformed using a log transformation. There was a significant group effect ($p < 0.05$) for all CCIs. Post hoc results are depicted on Figure 4. The asymptomatic and moderate OA groups were significantly ($p < 0.017$) lower than the severe group for all CCIs, but only different from the moderate OA group for the VLLH. The remaining three CCIs were not different between the moderate OA and the asymptomatic group ($p > 0.017$).

Discussion

Descriptive data in Table 1 shows that our knee OA classification resulted in three distinct samples. Severe OA had significant joint involvement based on their KL grades of 3 and 4, and their joint space narrowing compared to reports for a more severe OA samples in the literature (Mundermann et al., 2005). Moderate OA is not well described in the literature with respect to joint space narrowing, KL global grades and WOMAC scores, although Thorp et al. (2006) classified moderate OA based on KL scores of 2 or 3, similar to our classification. The moderate OA group walked 0.1 m/s slower than the asymptomatic controls and 0.3 m/s faster than the severe OA group. Although there is a range of walking velocities presented in the literature our self selected velocities are comparable to values reported for asymptomatic (Lewek et al., 2004a), moderate OA (Mundermann et al., 2005; Thorp et al., 2006) and more severe OA (Benedetti et al., 1999; Kaufman et al., 2001) groups. While walking velocity has been shown to affect EMG amplitude the expected finding would be a decrease in activation with a decrease in walking velocity based on previous studies (Shiavi et al., 1987; Winter et al., 1994). This was not the case since the severe OA group walked slower than the other two groups and had higher EMG amplitudes for quadriceps and hamstrings muscles. A trend for lower medial gastrocnemius activity only was evident from the waveforms in Figure 2.

Table 1
Demographics, stride characteristics, outcome measures and radiographic scores [mean (SD)].

Group	N	BMI (kg/m ²)	Age (y)	Stride length (m)	Walking velocity (m/s)	WOMAC			Radiographic scores		
						Pain	Stiffness	Function	TF-Med	TF-Lat	KL global
ASYM	63	25.1 ^a (4.0)	49.2 ^a (9.7)	1.44 ^b (0.13)	1.37 ^a (0.18)	0.3 ^a (1.2)	0.3 ^a (0.9)	1.2 ^a (4.4)	-	-	-
MOA	56	30.8 (5.5)	58.0 ^b (8.7)	1.41 ^b (0.15)	1.27 ^b (0.20)	7.1 ^b (3.3)	3.6 ^b (1.5)	22.2 ^b (11.6)	1.5 ^b (0.7)	0.2 ^b (0.4)	2.3 ^b (0.7)
SOA	48	31.8 (5.3)	63.7 (8.2)	1.20 (0.18)	0.97 (0.23)	10.0 (6.2)	4.4 (1.5)	34.3 (11.5)	2.3 (0.7)	1.0 (0.6)	3.2 (0.5)

ASYM = asymptomatic controls, MOA = moderate OA and SOA = severe OA, BMI = body mass index, WOMAC = Western Ontario and McMaster University Index with the pain, stiffness and function subscales, Scott features: TF-Med = medial tibiofemoral joint space narrowing, TF-Lat = lateral tibiofemoral joint space narrowing and KL Global = Kellgren Lawrence global rating scale.

^a Significant differences: Different from MOA and SOA.

^b Significant differences: Different from SOA.

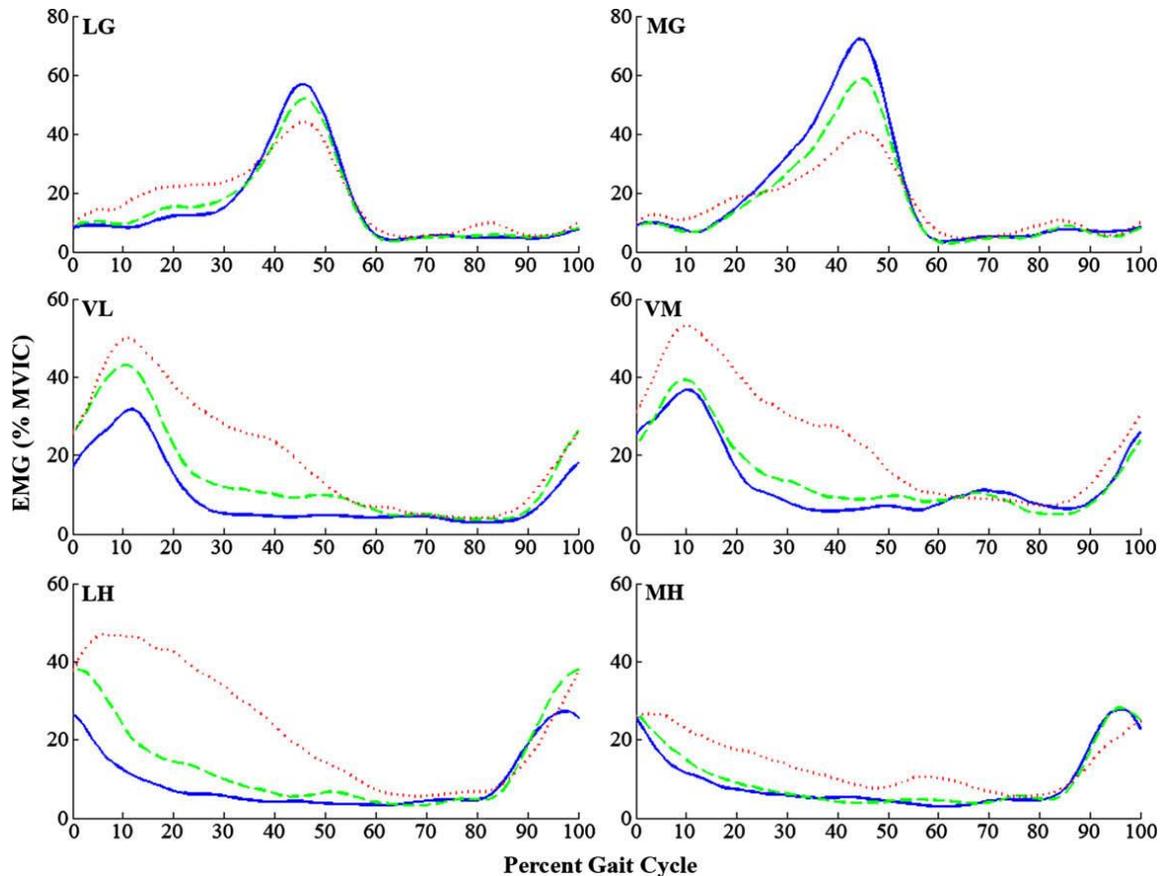


Fig. 2. Ensemble averaged electromyogram amplitude normalized to percent MVIC for each muscle included in the analysis. Asymptomatic (solid), Moderate knee OA (dashed) and Severe knee OA (dotted). LG = lateral gastrocnemius, MG = medial gastrocnemius, VL = vastus lateralis, VM = vastus medialis, LH = lateral hamstring and MH = medial hamstring.

Both the CCI and the *PP* scores differed among the groups, with the differences on the lateral sites related to a progressive increase from asymptomatic, to moderate through to severe knee OA, whereas the differences on the medial sites were specific to differentiating the moderate from severe OA. Thus, muscle activation characteristics and in particular these two measures of co-activity could be a valuable adjunct in classifying different severities of knee OA given the poor association between radiographic scores and symptoms (Barker et al., 2004; Creamer et al., 2000).

Principal patterns

Principal pattern one captured a pattern of constant activity throughout stance with a small burst capturing the quadriceps pattern during early stance and a second small

burst capturing the gastrocnemius activity prior to toe off. This pattern was similar to the principal pattern reported for severe OA (Hubley-Kozey et al., 2008). The main difference was the principal pattern for severe OA only had no second burst of activity (Hubley-Kozey et al., 2008). This is because the gastrocnemius muscle amplitude was generally reduced in the presence of OA (Hubley-Kozey et al., 2008) consistent with Figure 2, whereas the asymptomatic group had prominent medial gastrocnemius activity (Figure 2).

The group by muscle interaction confirms co-activation strategies distinctive to each diagnostic group as illustrated in Figure 3. Medial site scores for the vasti and hamstring muscles were higher for the severe OA group only whereas the lateral hamstring and vastus lateralis were higher for both OA groups compared to asymptomatic controls and the two OA groups differed from each other. Therefore severe the OA group had quadriceps and hamstring waveforms that resembled the principal pattern whereas the asymptomatic groups did not. *PP scores* with the same amplitude among muscles within a subject group illustrate that those muscles had a similar overall level of co-activation during stance phase. *PP score* magnitude indicates whether the co-activity was high or low. Differences in *PP scores* among muscles for the asymptomatic group illustrates that while there was co-activity within medial and lateral muscle pairings each of the three muscle grouping had a different score. Thus there was not a general level of coactivity for the 6 muscles. In contrast for all three muscle groupings the moderate OA group (Figure 3) had similar *PP scores* (excluding the medial hamstring) indicative of similar co-activity. The severe group had similar scores (Figure 3) among the two vasti and the lateral hamstring and since these were higher than the

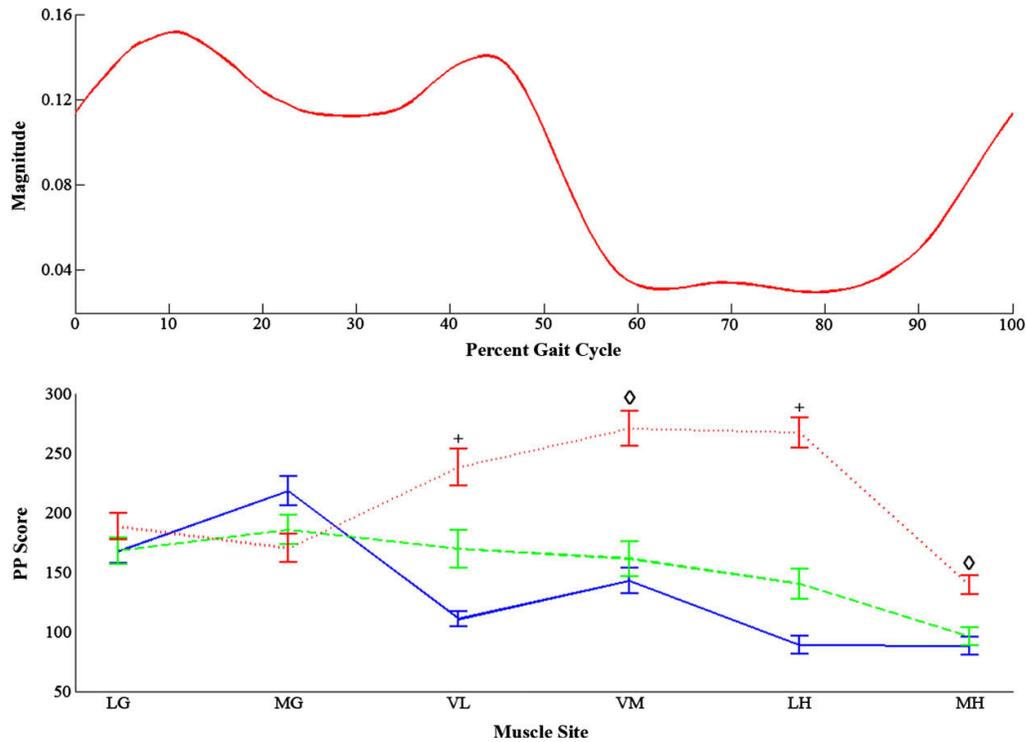


Fig. 3. Principal pattern 1 explained 70% of the variance in the waveform data. The upper panel displays the first principal pattern and the lower panel displays the interaction plot of the associated PP scores (mean (SE)) for each muscle and group assignment. Asymptomatic (solid), moderate knee OA (dashed), and severe knee OA (dotted). There was a significant group by muscle interaction ($\alpha = 0.05$). + indicates that all three groups are significantly different and e indicates that the severe knee OA group differed from the asymptomatic and moderate knee OA groups (18 comparisons, $P < 0.003$). The muscle differences for the asymptomatic group are: LG > VL, LH, MH; MG > VL, VM, LH, MH and VM > LH, MH; for the moderate OA group are: LG, MG, VL, VM, LH > MH; for the severe OA group are: LG > MH; MG > MH; VL, VM, LH > MH (45 comparisons, $P < 0.001$).

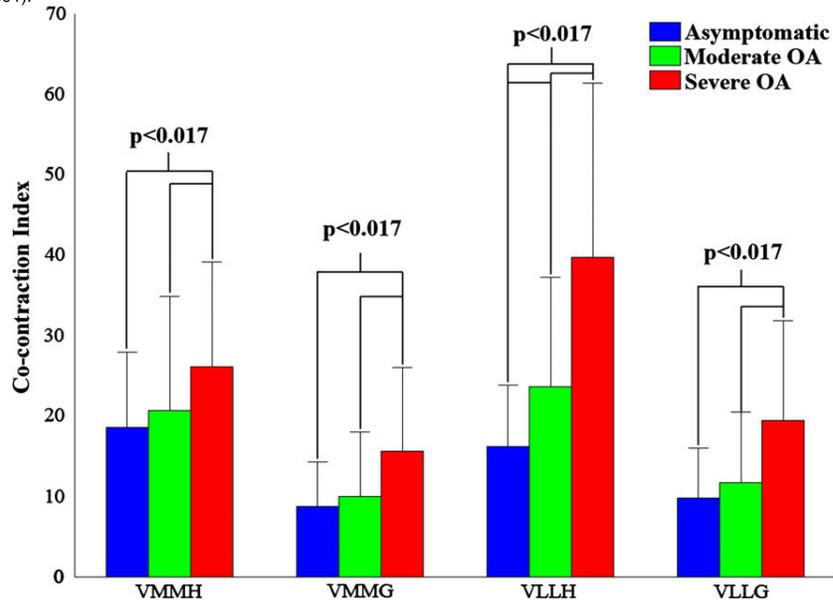


Fig. 4. Mean and standard deviation for the co-contraction index (CCI) magnitude for each muscle grouping and group assignment. There was a significant group main effect for all CCIs ($P < 0.05$). Post hoc results are illustrated on the graph with horizontal lines indicating significant differences between pairs (three comparisons, $P < 0.017$). VMMH = CCI for the VM and MH muscles, VMMG = CCI for the VM and MG muscles, VLLH = CCI for the VL and LH muscles, VLLG = CCI for the VL and LG muscles.

moderate OA group, they reflect a high degree of co-activity for these muscles. The *PP scores* support a strategy of selective lateral site co-activity for the moderate OA group and a general co-activity of the quadriceps and hamstrings with increased OA severity. Muscle activation strategies used to complete the walking task were different among the asymptomatic and two OA groups and were captured in the *PP scores*.

While one principal pattern captured a large majority of the variation in the waveforms, there is considerable variability not explained. This variability is in the shape characteristics of the waveforms. For example in Figure 2 there was a progressive decrease in medial gastrocnemius amplitudes at late stance between the asymptomatic and the OA groups; however, this characteristic was not completely depicted by principal pattern one. Higher ordered principal patterns are needed to capture the differences in waveform characteristics among muscles as previously reported for the severe knee OA group (Hubley-Kozey et al., 2008). This is a limitation of using the score from the highest principal pattern only. Nevertheless, the principal pattern in this study provides a single score for each muscle that captures the fundamental nature of co-activation during the stance phase of the gait cycle and this score can be compared among muscles.

Co-contraction Index

The CCI provides a measure of the relative activation of muscle pairs over the phase of the gait cycle from late swing to the peak knee adduction moment (primarily the loading phase). The CCIs for the asymptomatic group are similar to the literature (Lewek et al., 2004a; Ramsey et al., 2007b) with minor variations. Our moderate OA group are similar to two OA groups reported by Ramsey (2007a; 2007b) based on their clinical criteria and descriptive data. Minor differences in CCIs from Ramsey's (2007a; 2007b)

work most likely reflect the variation in OA severity in their two samples and their samples were small (16 and 15). They did not use the combination of criteria in the present study and while JSN was reported in one study (Ramsey et al., 2007a) no KL scores or walking velocities were reported making direct comparisons difficult. Lewek et al. (2004a) included OA subjects that were not surgical candidates but were moving toward severe knee OA based on their medial joint space narrowing criteria and instability, therefore a direct comparison of our CCI findings to their OA groups is not exact. Our moderate OA CCIs were lower than Lewek's (2004a) for all CCIs except the VMMH in which ours was slightly higher (18.5 versus 15.6). This is the first study to report CCIs for a severe OA and our VLLH and VMMH were much higher, although the VMMG and the VLLG were comparable to reports for less severe groups (Lewek et al., 2004a; Ramsey et al., 2007b).

In the current study, only VLLH CCI was different among all three groups (Figure 4). This is a direct result of higher vastus lateralis and lateral hamstring activation in individuals with progressively increasing knee OA severity (Figure 2). This finding is consistent with the *PP scores*. There was no difference in the VMMH CCI between the asymptomatic and the moderate OA group which is in contrast to Lewek et al. (2004a) but also consistent with the *PP score*. Ramsey (2007b) reported a difference in VMMG between asymptomatic controls and OA subjects scheduled for a high tibial osteotomy, however the asymptomatic group was only different from the severe OA for the VMMG CCI in the present study. A reasonable explanation as previously mentioned, is that our moderate OA group was less severe than both studies (Lewek et al., 2004a; Ramsey et al., 2007b).

The mechanisms involved in the generation of the CCI are not specific since the increase in VMMG for the severe OA group was based on increases in the vastus medialis activity as there were no clear differences in medial gastrocnemius activation among groups for early stance (see Figure 2). In fact, the amplitude of medial gastrocnemius decreased over the entire stance phase with increasing disease severity. While a single value is reported for the CCI, this value can be achieved by an almost infinite number of combinations of activation for the two muscles involved. This is illustrated in Figure 1, which shows that the CCI for the two muscle pairs was 19 whereas the two waveforms used in this calculation had very different combinations of muscle activity. In the upper panel, the vastus medialis and medial hamstring traded off; the medial hamstring showed high amplitude during the pre-heel contact phase where the vastus medialis was higher during the stance phase. The VLLG CCI was the result of low lateral gastrocnemius activity, and high vastus lateralis activation throughout the corresponding time period (Fig. 1). Also, this figure illustrates that the VMMH CCI calculation for the asymptomatic individual included data from 100 ms before heel strike to 15% of the gait cycle where the VLLG CCI calculation for the individual with severe OA included data from 100 ms before heel strike to 20% of the gait cycle.

Overall the CCI provided an indication of activation amplitudes of muscle pairs just prior to and during the initial loading phase of the gait cycle. Overall the CCI provided an indication of activation amplitudes of muscle pairs just prior to and during the initial loading phase of the gait cycle. Interpretation of the CCI, as calculated in this study, requires knowledge of where the peak knee adduction moment occurs within the gait cycle for all subjects. Also, it is clear from Fig. 2 that the relationship differs among

muscles throughout the entire gait cycle, including mid-stance when subjects are in single leg support. CCI could be calculated at different time intervals to estimate co-activity if the time interval is short, but interpretation is affected by knowing the variation in waveforms expected during that time period. Essentially, to interpret the CCI one needs to examine the waveforms.

Both approaches reduced the waveform data to 4 values for the CCI and 6 values for the principal patterns. Our results from both approaches support that in early stages of OA, the neuromuscular strategy is focused on increasing lateral site co-activity that perhaps helps unload the medial compartment (Andriacchi 1994). In later stages of progression, the increase in medial site co-activity may be in response to the increase in medial joint space narrowing and instability (Lewek et al., 2004a). Higher overall activity would not be expected based on the decreased knee flexion moments and angles previously reported for increased OA severity (Aststephen et al., 2008a) making the instability explanation a plausible one since the severe group had significant joint space narrowing based on their radiographic features. Another explanation for the increased co-activity for the OA groups relates to muscular strength. While quadriceps strength deficits have been reported with OA (Ramsey et al., 2007b) no differences were found between moderate OA and asymptomatic subjects for quadriceps, hamstring and plantar flexor strength (Hublely-Kozey et al., 2006) although reduced muscle strength was reported for severe OA for all three muscle groups (Hublely-Kozey et al., 2008). Therefore a general strength difference would not explain the specific differences with respect to medial and lateral muscle sites nor between the asymptomatic and moderate

OA groups. However it could explain the higher medial hamstring co-activity in severe OA.

Clinical implication

The CCI and *PP scores* provide information on early stance co-activity and co-activity over the entire gait cycle respectively. This provides additional evidence on which to make clinical management decisions and to assess the effect of interventions. In an attempt to minimize smearing of the three distinct groups, individuals were classified based on radiographic features, function and clinical classification. There is still potential for overlap among the groups given that we did not have radiographic scores for our asymptomatic group and we had individuals in both OA groups with KL scores of 3. However, based on a large, relatively well defined sample we demonstrated the utility of the two approaches. Although both have inherent limitations, the results have direct clinical implications. The co-activation differences with severity can be used to guide conservative management. For example valgus unloader braces and lateral heel wedges (Buckwalter et al., 2001) aimed at the medial-lateral joint loading imbalance may be more effective in the moderate OA that display high lateral co-activation and normal medial co-activation. In contrast bracing aimed to improve overall joint stability may be more effective for those with more severe knee OA who have a general increase in co-activity. Extremely high CCI or *PP scores* could provide evidence for triaging surgical patients. Effectiveness of interventions can be evaluated based on these measures and Ramsey's group reported that unloader braces decreased both VMMH and VLLH CCIs (Ramsey et al., 2007a) whereas high tibial osteotomies reduced the VMMG only (Ramsey et al., 2007b).

In conclusion, the CCI and principal pattern approaches captured differences in co-activity among all three subject groups and most importantly, between the two OA groups. There was general agreement between the two approaches. Specifically, the lateral site muscle increases were reflective of progression along the continuum from asymptomatic to severe OA, whereas the medial muscle site measures differentiated OA severity between the two OA groups. These findings support the use of both approaches to provide information related to muscle co-activity and severity of knee OA.

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Conflict of Interest

There are no conflicts of interests.

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Figure Captions

Figure 1. A) Example ensemble averaged VM (Vastus Medialis) and MH (Medial Hamstring) electromyogram for an asymptomatic individual and C) for VL (Vastus Lateralis) and LG (Lateral Gastrocnemius) electromyogram for an individual with severe knee OA. These waveforms are time normalized to one gait cycle from heel contact to heel contact. The vertical line indicates when the peak knee adduction moment (pKAM) occurred. Both left and right columns are amplitudes normalized to percent MVIC. The MVIC normalization is scaled to unity (scaled to 1=100 % MVIC). For the right panels B and D) time is normalized from 100 ms prior to heel contact (0% indicated by first vertical line) to the pKAM (100% indicated by the second vertical line) used in the calculation of the CCIs.

Figure 2. Ensemble averaged electromyogram amplitude normalized to percent MVIC for each muscle included in the analysis. Asymptomatic (Solid), Moderate knee OA (dashed) and Severe knee OA (dotted). LG = Lateral Gastrocnemius, MG = Medial Gastrocnemius, VL = Vastus Lateralis, VM = Vastus Medialis, LH = Lateral Hamstring and MH = Medial Hamstring.

Figure 3. Principal pattern 1 explained 70% of the variance in the waveform data. The upper panel displays the first principal pattern and the lower panel displays the Interaction plot of the associated *PP scores* (mean (SE)) for each muscle and group assignment. Asymptomatic (Solid), Moderate knee OA (dashed), and Severe knee OA (dotted). There was a significant group by muscle interaction ($\alpha=0.05$). + indicates that all three groups are significantly different and \diamond indicates that the Severe knee OA group differed from the Asymptomatic and Moderate knee OA groups (18 comparisons, $p<0.003$). The muscle differences for the Asymptomatic group are: LG>VL, LH, MH; MG > VL, VM, LH, MH and VM>LH, MH; for the Moderate OA group are: LG, MG, VL, VM, LH > MH; MG>LH and for the Severe OA group are: LG > MH; MG < VL, VM, LH and VL, VM, LH > MH (45 comparisons, $p<0.001$).

Figure 4. Mean and standard deviation for the co-contraction index (CCI) magnitude for each muscle grouping and group assignment. There was a significant group main effect for all CCIs ($p<0.05$). Post hoc results are illustrated on the graph with horizontal lines indicating significant differences between pairs (3 comparisons, $p<0.017$). VMMH = CCI for the VM and MH muscles, VMMG = CCI for the VM and MG muscles, VLLH = CCI for the VL and LH muscles, VLLG = CCI for the VL and LG muscles.

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