Introduction

Numerous risk factors for knee osteoarthritis (OA) progression and development have been identified from large epidemiological studies, but the relationship among these variables is not well understood. This is largely attributed to the complex, multifactorial nature of the disease process. Numerous mechanical factors have been linked to the progression of knee OA, particularly excessive joint loading and the magnitude of the knee adduction moment during gait, which has been associated with loading in the medial compartment of the knee joint. Recent literature provides a compelling argument for using gait as a model to understand the loading environment of the joint. Dynamic loading occurs with higher frequency during gait than other activities of daily living, and walking is the activity most commonly reported as difficult by those with knee OA. Obesity is another particularly prevalent risk factor for knee OA that has been linked to the mechanical degeneration of the joint. However, the interaction between obesity and joint biomechanics in the progression of knee OA remains unclear.
Knee OA is a progressive disease, with changing biomechanics at different levels of clinical severity\(^{18,19}\). Many biomechanical investigations of knee OA have focused on subjects with severe knee OA\(^{20–22}\), but results of these studies are often confounded with the concomitant changes of the end stages of the disease process and tell us little of the underlying pathomechanics. Investigations of the biomechanics of more mild to moderate levels of disease severity can provide better information on the pathomechanical processes of disease progression. Some recent studies have compared the gait patterns of asymptomatic and moderate knee OA subjects\(^{23–25}\), and between discrete radiographic levels of severity in individuals with moderate OA\(^{7,8}\). However, these studies often focus on individual factors of the disease and rarely consider the potentially important interactions between factors\(^ {26}\). As well, disease severity classification is often based on a discrete, categorical radiographic criterion such as the Kellgren–Lawrence (KL) global radiographic score\(^ {27}\), which is limited in sensitivity to four discrete categories. The KL score is a blunt measure of radiographic severity because each level can describe joints with a range of radiographic changes, and it has been suggested that mild osteophyte formation alone may represent age-related bone modeling as opposed to a disease process\(^ {28}\). A more continuous structural severity rating by an experienced clinician, such as those used extensively in the measurement of clinical pain\(^ {29}\), could provide a more continuous metric of structural disease severity for which to compare mechanical changes.

There is a known discrepancy between the radiographic and symptomatic expression of knee OA\(^ {30,31}\) suggesting that the structural degeneration of the joint and symptomatic progression of the disease are likely associated with different biomechanical factors. While some studies have examined the association between biomechanical factors and radiographic\(^ {32,34}\) and pain severity\(^ {6,32–34}\), there are some conflicting results, particularly regarding the association of the knee adduction moment during gait and pain\(^ {6,32–34}\). As well, few studies have examined the association between neuromuscular control patterns and radiographic and symptomatic severity\(^ {35}\). The purpose of this study was to identify the biomechanical and neuromuscular factors that explain both radiographic and symptomatic (pain) disease severity within a group of individuals clinically diagnosed with mild to moderate, medial-compartment knee OA.

Materials and methods

Subjects

Forty individuals with mild to moderate, clinically diagnosed medial-compartment knee OA were recruited from the waiting list for exploratory knee arthroscopy of the Orthopedic and Sports Medicine Clinic of Nova Scotia. All individuals were diagnosed with knee OA from a clinical assessment that included knee radiographs and a physical exam. Subjects were included in the study if they had clinical and radiographic symptoms of knee OA, but were not a candidate for total knee joint replacement surgery, consistent with our previous work\(^ {35,36}\). KL radiographic scores\(^ {27}\) of these individuals could range from 1 to 4 based on a radiographic assessment, but all participants could walk at least one city block, jog 5 m and walk upstairs one foot after the other. Exclusion criteria included any major trauma or surgery to the lower limb, neuromuscular disorders, other forms of arthritis, gout, history of stroke, and cardiovascular disease. All subjects were over the age of 35 years. Informed consent was obtained for all subjects prior to testing in accordance with the institutional ethics board.

For all subjects, an experienced orthopedic surgeon assessed anterior posterior and lateral radiographs of the affected knee with (1) the KL global radiographic score\(^ {27}\) and (2) a radiographic visual analog severity (RVAS) score designed to capture a complete picture of the radiographic joint changes (joint space narrowing, osteophytes, sclerosis, joint deformity) on a continuum from 0 to 10. The RVAS employed a 10-centimeter analog scale, and severity was rated along this scale. A high volume knee arthroplasty orthopedic surgeon performed all of the assessments, and rated severity in a relative comparison to all other radiographs assessed in clinical practice. Severity rating took into account all features of common severity scoring systems, such as joint space narrowing, osteophytes, sclerosis, tibial spines etc., in a single measure. The inter-rater reliability of the RVAS and other radiographic features (KL, joint space narrowing, osteophyte grade, subluxation, sclerosis, and chondrocalcination) of 64 different knees (different than the 40 included in this study) with moderate knee OA and eight raters (two orthopedic surgeons, two orthopedic surgeon residents, two radiologists and two rheumatologists) was assessed. Pain severity was defined by the pain subscale (0 [best]–20 [worst]) of the Likert Western Ontario McMaster Osteoarthritis Index (WOMAC)\(^ {37}\).

Gait and electromyography (EMG)

All participants visited the Dynamics of Human Motion laboratory once for gait testing. All walking trials were performed at the participant’s self-selected walking speed. Three-dimensional motion of the lower limb and ground reaction forces during gait was recorded with an Optotrak\(^ {38}\) 3020 motion capture system (Northern Digital, Inc.), and a synchronized AMTI force platform (Advanced Mechanical Technology, Inc., Watertown, MA). Three-marker triads of infrared light emitting diodes were placed on each of the pelvis, thigh, shank and foot, and individual markers were placed on the greater trochanter, lateral epicondyle, lateral malleolus, and shoulder. Eight virtual markers were identified during quiet standing to define anatomical coordinate systems in each lower limb segment\(^ {39}\). Inter-segmental joint kinematics and kinetics were calculated by modeling the pelvis, thigh, shank and foot as rigid bodies, and the pose of each segment at each time point was computed using a least squares optimization routine\(^ {38}\). The sign convention for the angles and moments at each joint followed a previously-defined anatomically based coordinate system\(^ {39}\). Due to the nature of coupled motions at the knee joint, ab/adduction and internal/external rotation angles are significantly prone to any error associated with definition of the flexion/extension axis\(^ {40}\) and are of a similar magnitude to the measurement error associated with kinematic cross-talk and skin motion\(^ {40,41}\). Therefore, only the knee flexion/extension angle and three dimensions of the net resultant knee joint reaction moments were included in the analysis. Moments were calculated using an inverse dynamics biomechanical model\(^ {42}\), expressed as net external moments, and were normalized to body mass (Nm/kg).

EMG from seven muscle sites surrounding the knee (vastus lateralis [VL] and medialis [VM], rectus femoris [RF], biceps femoris [LF], semimembranosus [MH], lateral [LG] and medial [MG] gastrocnemius) was collected at 1000 Hz during the gait trials. Bi-polar electrode placement, type, amplification and filtering have been described previously\(^ {43}\). For normalization and inter-muscular comparison, subjects performed a series of maximal voluntary isometric contractions (MVICs) on a Cyber\(^ {36}\) (Lumex, NY) dynamometer\(^ {36}\). Ensemble average EMG profiles were time and amplitude normalized to 100% of the gait cycle and to MVIC\(^ {36}\).

Statistical methods

Principal component analysis (PCA) is a multivariate statistical technique that is an effective tool in the reduction and interpretation of gait waveform\(^ {20}\) and EMG data\(^ {36}\), and can be used to
objectively extract uncorrelated features of variability in gait waveforms. PCA was applied separately to gait and EMG measures: the three dimensions of joint moments at the knee and the knee flexion angle (4 measures), and to the EMG profiles of the seven muscle sites (7 measures). The first three principal components (PC1, PC2, PC3) were extracted from each gait and EMG measure if they cumulatively represented more than 80% of the total variability in the original measure. Subject waveforms were projected onto each principal component (PC) to calculate discrete PC scores. PCs were interpreted using a previously described technique of comparing the fifth and ninety fifth percentiles of PC scores.20

Pearson correlation analyses were used to determine the association between the PCs, body mass index (BMI) and gait speed with radiographic (RVAS) and pain (WOMAC pain) severity (P < 0.05). Multiple regression models of radiographic and pain severity were developed based on the results of the correlation analyses. Variables with significant correlations with each were included in the original multivariate models. If variables did not significantly contribute to the multivariate model (P < 0.05), they were removed. Residual analyses and multicollinearity diagnostics were performed to ensure that no assumptions were violated.

Results

Subject demographics, stride characteristics, WOMAC and radiographic scores are presented in Table I. WOMAC health outcome data were indicative of a mild–moderate symptomatic subject group, and scores were normally distributed covering a range from 0 to 18. The RVAS ranged from very low radiographic severity (0.95) to very high (9.75), also indicating a wide spectrum of radiographic disease severity. A spearman rank correlation coefficient indicated a moderately strong correlation between the RVAS and the KL score (r = 0.64). Interestingly, in the inter-rater reliability analysis of structural severity scores, the simple RVAS showed the highest inter-observer reliability between the eight raters [RVAS intraclass correlation coefficient (ICC) = 0.80]. KL scores had a similar and high ICCs between the eight raters (KL ICC = 0.75). Reliability of medial joint space narrowing was also

<table>
<thead>
<tr>
<th>Table I</th>
<th>Subject demographics, WOMAC and radiographic scores</th>
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<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.4 (9.49)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.73 (0.11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>91.0 (16.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.4 (4.5)</td>
</tr>
<tr>
<td>Sex distribution</td>
<td>Female: n = 13; Male: n = 27</td>
</tr>
<tr>
<td>Stride characteristics</td>
<td></td>
</tr>
<tr>
<td>Speed (m/s)</td>
<td>1.24 (0.19)</td>
</tr>
<tr>
<td>Stride length (m)</td>
<td>1.38 (0.15)</td>
</tr>
<tr>
<td>Stance time (s)</td>
<td>0.72 (0.08)</td>
</tr>
<tr>
<td>Stance percent (%)</td>
<td>64.17 (1.45)</td>
</tr>
<tr>
<td>WOMAC</td>
<td></td>
</tr>
<tr>
<td>Pain (/20)</td>
<td>7.23 (3.68)</td>
</tr>
<tr>
<td>Stiffness (/8)</td>
<td>3.53 (1.74)</td>
</tr>
<tr>
<td>Function (/68)</td>
<td>21.65 (12.60)</td>
</tr>
<tr>
<td>Total (/96)</td>
<td>32.40 (16.89)</td>
</tr>
<tr>
<td>RVAS</td>
<td>4.65 (2.24)</td>
</tr>
<tr>
<td>KL score distribution</td>
<td>0: n = 0; 1: n = 1; 2: n = 23; 3: n = 12; 4: n = 4</td>
</tr>
</tbody>
</table>

Fig. 1. Knee adduction moment PC1. (a) The knee adduction moment waveforms during gait for all subjects are shown. (b) PC1 of the knee adduction moment represented a higher overall magnitude of the moment during stance. (c) High radiographic severity (RVAS) was significantly correlated with higher knee adduction moment PC1 scores (i.e., higher moment magnitudes during stance). (d) Representative high and low PC1 (ninety fifth and fifth percentiles) subject waveforms are shown to illustrate the interpretation of the pattern associated with PC1.
high (ICC = 0.79), and good reliability was observed for medial and lateral femorotibial osteophytes (ICC = 0.70 and 0.68), and patellofemoral osteophytes (ICC = 0.61). Moderate reliability was observed with tibial erosions (ICC = 0.53), lateral femoral joint space narrowing (ICC = 0.52), lateral sclerosis (ICC = 0.47), and tibial spine osteophytes (ICC = 0.45). Poor correlation was seen with medial sclerosis, chondrocalcinosis, and medial and lateral subchondral sclerosis (ICC < 0.40).

Correlations

Moderate, statistically significant correlations were found between radiographic severity (RVAS) and the first principal component, PC1, of the knee adduction moment (r² = 0.21, P = 0.003) and PC1 of the knee flexion angle (r² = 0.11, P = 0.03). PC1 of the knee adduction moment represented the overall magnitude of the moment during the stance phase of the gait cycle [Fig. 1(a)], with higher knee adduction moments associated with higher RVAS [Fig. 1(b)]. PC1 of the knee flexion angle represented the overall magnitude of the angle over the entire gait cycle (i.e., stance and swing phases) [Fig. 2(a)], with lower knee flexion angles associated with higher RVAS [Fig. 2(b)].

Statistically significant correlations were found between pain severity (WOMAC pain), and average gait speed (r² = 0.28, P < 0.0001), PC2 of the lateral gastrocnemius (r² = 0.16, P = 0.009), PC2 of the medial hamstring (r² = 0.10, P = 0.04), and PC2 of the VM (r² = 0.14, P = 0.02). Removing two outlier values with VM PC2 values greater than two standard deviations from the mean resulted in a non-statistically significant correlation (r² = 0.014, P = 0.47). Higher pain scores were associated with lower average walking speeds during gait. PC2 of the lateral gastrocnemius muscle was interpreted as the difference between early stance and late stance activation of the muscle [Fig. 3]. Higher pain scores were associated with lower lateral gastrocnemius PC2 scores, or with less difference between early and late stance lateral gastrocnemius activity (i.e., more constant activation, but with a lower late stance peak) [Fig. 3]. PC2 of the medial hamstring was interpreted as the magnitude of activation in early stance and at toe-off [Fig. 4]. High pain scores were associated with higher medial hamstring PC scores, or with a higher activation of the muscle in very early stance and at toe-off.

Multiple linear regression models of radiographic and pain severity were explored that initially included all factors with statistically significant univariate correlations with each (RVAS: knee adduction moment PC1, knee flexion angle PC1; WOMAC Pain: speed, lateral gastrocnemius PC2, medial hamstring PC2). Although BMI was not significantly correlated with either the RVAS or pain (r² = 0.04, P = 0.23; r² = 0.004, P = 0.7 respectively), its inclusion in the multivariate models was also explored because of its known importance to disease severity. In the RVAS multivariate model, only the knee adduction moment PC1 and BMI were significant terms in the model (P = 0.004 and P < 0.0001 respectively). The knee flexion angle PC1 term was therefore removed from the model (P = 0.14). The final RVAS model that included the knee adduction moment and BMI was significant (P < 0.0001) with an R² value of 27.1% (Table II). BMI and the knee adduction moment PC1 were not statistically correlated (r² = 0.008, P = 0.58). Condition indices for the model were all less than 1.5, indicating no significant amount of multicollinearity and residual and influence diagnostics indicated no violation of multiple regression model assumptions or influential observations. The only significant term in the WOMAC pain multivariate model was speed (R² = 28.2%; P < 0.0001) (Table II).

Fig. 2. Knee flexion angle PC1. (a) The knee flexion angle waveforms during gait for all subjects are shown. (b) PC1 of the knee flexion angle represented a higher overall magnitude of the angle during the gait cycle. (c) High radiographic severity (RVAS) was significantly associated with lower knee flexion angle PC1 scores (i.e., lower knee flexion angles during gait). (d) Representative high and low PC1 (ninety-fifth and fifth percentiles) subject waveforms are shown to illustrate the interpretation of the pattern associated with PC1.
Discussion

There is a known discrepancy between the radiographic and symptomatic expression of knee OA. Our results further suggest that there is also a discrepancy between the biomechanical and neuromuscular factors associated with a composite measure of radiographic and pain severity in this mild to moderate OA group. Interestingly, no biomechanical (knee joint kinematics and kinetics) factors during gait were significantly associated with pain severity in this moderate OA population. This is in conflict to some previous studies that have associated pain with lower knee range of motion during gait and with higher peak adduction moments during gait, which may be reflective of the more moderate level of disease severity in our population. While our results did not support Schnitzer et al.’s finding of an increase in knee adduction moments with reduced pain (using medication), they did support their result of an increase in gait speed with the use of the pain reducing medication. In our study, pain severity was only significantly associated with gait speed and neuromuscular activation patterns. It has been suggested that changing walking speed is a method to change the mechanical environment of the knee. Our results indicated that such a mechanism may be related to symptoms of pain associated with the disease and suggest that a change in gait speed may be the only significant biomechanical response to the pain associated with moderate clinical levels of knee OA. These results also imply that changes in knee joint dynamics associated with moderate levels of knee OA are likely not confounded by compensations associated with pain.

This was the first study to investigate and report a significant association between pain severity and neuromuscular patterns of the knee musculature during gait. A few studies have compared neuromuscular patterns between controls and individuals with moderate and more severe levels of knee OA. However, none has examined the association between neuromuscular patterns during gait and radiographic and pain severity of the disease separately, and none has used a composite measure of radiographic severity. We found no significant associations between neuromuscular patterns and our composite measure of radiographic disease severity, but found significant (moderate) associations between the pattern of the lateral gastrocnemius and medial hamstring muscles and pain severity. Higher pain was associated with more constant activation of the lateral gastrocnemius muscle throughout the stance phase of gait. In a comparison of this moderate OA group to control neuromuscular patterns, there was no lateral gastrocnemius difference between the groups, but the OA group had lower MG activation in late stance. Our current results suggest that within this population of individuals with moderate OA, those with higher pain additionally activate their lateral gastrocnemius muscle more constantly throughout stance, which may be a mechanism to counteract high medial-compartment joint loading during this portion of the gait cycle. We also found that those with higher pain severity had higher activity of the medial hamstring muscle in early and late stance. Compared to controls, this moderate OA group had higher and more prolonged activity of the lateral hamstrings during stance, and these results further suggest that those with increased pain additionally walk with more activity in their medial hamstring muscles during stance, which may be indicative of higher co-activity of these muscles in a guarding mechanism to increase joint stiffness and reduce the pain, and possibly to counterbalance joint...
This result supports the studies of more severe knee OA levels that have also reported prolonged medial hamstring activity compared to controls.\textsuperscript{35,43}

Radiographic disease severity was associated with higher knee adduction moment magnitudes during stance and with lower knee flexion angles over the gait cycle. While our previous research has reported reduced knee flexion angles during gait in a severe knee OA group compared to a moderate OA group,\textsuperscript{18,19} this was the first report of an association between reduced knee flexion angles and radiographic disease severity on a continuum within a moderate OA population. The knee adduction moment is the gait variable most commonly associated with knee OA severity and progression\textsuperscript{5,7} and its potential importance to the development and progression of medial-compartment knee OA has been supported by studies that have related higher knee adduction moments to higher medial-compartment forces.\textsuperscript{9,10} Most previous analyses, however, have looked at discrete levels of radiographic severity and have examined peak values of the knee adduction moment waveform during gait. This was the first study to associate the knee adduction moment magnitude with a composite measure of radiographic severity. As well, peak moments capture only the loading situation in a particular instant in the gait cycle. The first principal component of the knee adduction moment, on the other hand, captured an overall magnitude of the moment over the entire stance phase and provided additional sensitivity to pattern changes during gait. In a previous study on the same population, this stance magnitude of the moment captured with the first principal component was higher in the moderate OA group compared to control; however, peak values of the moment did not show a difference between the moderate OA and control groups.\textsuperscript{25} Furthermore, the problem of comparing peak adduction moments without controlling for speed has been raised by others,\textsuperscript{24,45} and the first principal component of the adduction moment has shown to be insensitive to speed changes, unlike the peak moment.\textsuperscript{25}

Obesity is one of the most well established risk factors for knee OA.\textsuperscript{14,46} The interaction between body weight and the knee OA disease process appears to be both metabolic\textsuperscript{47,48} and mechanical in nature, but the mechanism for its role in knee OA progression is still very poorly understood. Obesity has emerged as an interacting factor between biomechanics and knee OA in a previous study by our group,\textsuperscript{17} and the results of the present study support its potential importance to radiographic severity of knee OA in combination with the knee adduction moment. BMI tends to be higher in individuals with knee OA compared to control, but has not shown to increase between increasing discrete levels of disease severity.\textsuperscript{18} In this study, BMI was also not significantly associated with knee OA radiographic severity on its own; however its

<table>
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<th>Variable</th>
<th>Correlation with response ($r^2$)</th>
<th>Coefficient (std. error)</th>
<th>$P$ value</th>
<th>Cumulative model $R^2$</th>
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<tbody>
<tr>
<td>RVAS regression model</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Knee adduction moment PC1</td>
<td>0.21</td>
<td>1.10 (0.3)</td>
<td>0.001</td>
<td>21%</td>
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<tr>
<td>BMI</td>
<td>0.04</td>
<td>0.15 (0.1)</td>
<td>&lt;0.0001</td>
<td>27%</td>
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<td>Symptomatic severity (WOMAC pain) regression model</td>
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<tr>
<td>Constant</td>
<td>–</td>
<td>19.9 (3.3)</td>
<td>&lt;0.0001</td>
<td>–</td>
</tr>
<tr>
<td>Gait speed</td>
<td>0.28</td>
<td>-10.2 (2.6)</td>
<td>&lt;0.0001</td>
<td>28%</td>
</tr>
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</table>

Table II

Radiographic and symptomatic linear regression results. Significant factors in each regression model are shown with their individual correlation with the response, coefficient in the regression model, $P$ value of significance of inclusion in the model, and the cumulative $R^2$ of the model with their inclusion.
potential importance to radiographic severity was evident in a multivariate model with the knee adduction moment, highlighting the likely multivariate nature of disease process.

This study provides support for the discrepancy between radiographic and pain severity of knee OA, and shows different associations of each with biomechanical and neuromuscular factors. Only biomechanical factors appear to be associated with the combined measure of radiographic knee OA severity, and only neuromuscular factors and gait speed were associated with pain severity. The potential importance of the combination of the knee adduction moment and BMI also provides evidence that the role of mechanical factors in the radiographic progression of knee OA is likely multivariate in nature, and points to the need to consider further interactions between risk factors in our investigations of knee OA. However, whether the mechanical factors associated with radiographic knee OA disease severity in this study are involved in disease initiation and progression or are a reflection or consequence of an already deteriorating joint cannot be determined from the current study. Biomechanical and neuromuscular factors should be studied simultaneously in larger, longitudinal studies, with consideration of the multidimensional combination of risk factors presented by an individual. Most conservative biomechanical treatment strategies for knee OA, such as the valgus heel wedge and knee ‘unloading’ braces, are aimed at changing the loading on the medial compartment of the knee by changing the dynamic knee adduction moment. The results of this study would support the development of conservative treatment strategies that aim to simultaneously change biomechanical factors in combination with the knee adduction moment, as it explains only 20% of the variability in radiographic severity on its own. These results also suggest that, within a moderate OA population, the confounding of pain on biomechanical measures is not a significant concern, but that consideration of pain levels may be required in interpreting neuromuscular pattern changes during gait in those with moderate knee OA.

**Author contributions**

JAW: gait analysis, statistical analysis, and preparation of manuscript. KD: study design, collection and analysis of gait data, and preparation of manuscript. CHK: study design, collection and analysis of EMG data, and preparation of manuscript. GC: results interpretation and preparation of manuscript. MD: radiographic evaluation and interpretation of results.

**Conflict of interest**
The authors have no conflict of interest.

**Acknowledgements**

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