Knee osteoarthritis alters peri-articular knee muscle strategies during gait

Aseel Ghazwan1,2,3*, Chris Wilson2,4, Cathy A. Holt1,2, Gemma M. Whatling1,2

1 Cardiff School of Engineering, College of Physical Sciences and Engineering, Cardiff University, Cardiff, United Kingdom, 2 Biomechanics and Bioengineering Research Centre Versus Arthritis, Cardiff University, Cardiff, United Kingdom, 3 Biomedical Engineering Department, College of Engineering, Al-Nahrain University, Baghdad, Iraq, 4 University Hospital of Wales, Cardiff, United Kingdom

* aseel_ghzwan@yahoo.com

Abstract

The primary role of muscles is to move, and control joints. It is therefore important to understand how degenerative joint disease changes this role with the resulting effect on mechanical joint loading. Muscular control strategies can vary depending on strength and coordination which in turn influences joint control and loading. The purpose of this study was to investigate the variation in neuromuscular control mechanisms and joint biomechanics for three subject groups including those with: uni-compartmental knee osteoarthritis (OA), listed for high tibial osteotomy surgery (pre-HTO, n = 10); multi-compartmental knee OA listed for total knee replacement (pre-TKR, n = 9), and non-pathological knees (NP, n = 11). Lower limb kinematics and electromyography (EMG) data for subjects walking at self-selected speed, were input to an EMG-driven musculoskeletal knee model which was scaled and calibrated to each individual to estimate muscle forces. Compared to NP, the peak gastrocnemius muscle force reduced by 30% and 18% for pre-HTO and pre-TKR respectively, and the peak force estimated for hamstring muscle increased by 25% for pre-HTO. Higher quadriceps and hamstring forces suggest that co-contraction with the gastrocnemius could lead to higher joint contact forces. Combined with the excessive loading due to a high external knee adduction moment this may exacerbate joint destruction. An increased lateral muscle co-contraction reflects the progression from NP to uni-compartmental OA (pre-HTO). Pre-TKR patients adopt a different gait pattern to pre-HTO patients. Increased medial muscle co-activation could potentially differentiate between uni- or multi-compartmental OA.

1. Introduction

Mechanical factors play an important role in the development and progression of Osteoarthritis (OA) [1]. The knee joint is recognized as the most commonly affected joint [2] and about 4.71 million people have sought treatment for knee OA [3]. Estimates suggest that the number of people with knee OA will increase from 4.71 million in 2010, to 5.4 million in 2020, reaching 6.4 million by 2035 [3]. Typically, total knee joint loading is influenced by ground reaction, joint contact, muscle, and soft tissue forces. The net moment resulting from the ground
reaction force is counterbalanced by the moments produced by muscles and contact forces. 60–80% of total intrinsic knee load is primarily produced by muscle forces [4, 5] and is distributed through the medial compartment of the tibio-femoral joint [6]. The pattern and magnitude of knee compressive forces are directly affected by the way that individuals activate their muscles. Therefore, assessments of muscle forces and joint moments are essential to fully understand altered loading mechanisms associated with the incidence and progression of OA.

Most gait studies have focussed their investigations on knee kinematics and kinetics [7–10], muscle activations [11–15], and muscle forces [16, 17]. In contrast, a limited number of studies have investigated all these variables together and related them to the compartmental involvement of knee OA [18–20].

External knee adduction moment (EKAM), suggested as a surrogate measure of knee OA severity [21, 22], has been used to evaluate joint loading, with peak EKAM providing a strong predictor of medial knee contact force [23]. However, being a net moment, it does not explicitly account for individual muscle activation patterns as well as muscle co-contractions.

Muscle activation features also play an important role in understanding the effects of longitudinal progression or interventions for knee OA. Hubley-Kozey et al. [24] showed that reliable EMG characteristics can be captured for patients with moderate medial compartment knee OA. Lloyd and Buchanan [15] investigated the activation strategies used by individuals to support adduction/abduction moments and the muscle loading patterns that result from these activation schemes during highly controlled isometric tasks. Wilson et al. [25] associated EMG patterns of the knee periarticular musculature with post-operative tibial implant migration. They found that a prolonged muscle activation pattern for both the lateral gastrocnemius and vastus medialis muscles, during the stance phase, was related to increased posterior migration of the tibial component. Moreover, higher muscle co-contractions have been linked to OA severity [14, 26–28], presumed to be linked with higher muscle forces [29, 30], to compensate for joint instability.

Measuring the forces applied to a joint and estimating how these forces are partitioned with respect to surrounding muscles, ligaments, and articular surfaces is fundamental to understanding joint function, injury, and disease. Muscle forces have been proposed as the primary determinants of joint contact forces [4, 31], with correctly predicted muscle forces assumed to result in sensible estimates of joint contact loads. However, to date, accurate measurement and prediction of individual muscle forces are still a major challenge.

Advances in musculoskeletal knee modelling and computation power have enabled researchers to generate gait simulations in efforts to estimate joint moments, muscle forces (e.g., [32, 33]) and subsequently joint loading, for patient populations that use altered neuromuscular activation patterns (e.g., [32–35]). Among the four prominent methods introduced to estimate muscle forces (EMG-driven model [36], Static optimization [37], computed muscle control [38] and DeVita model [39]), the EMG-driven model is preferred as it accounts for subject specific EMG patterns resulting in improved estimations of muscle forces.

Although biomechanical evaluations of people with OA are frequently performed to identify gait impairments; little attention has been paid to the provision of quantitative information regarding the function of individual muscles. Adouni and Shirazi-Adl [40] developed a gait-data driven musculoskeletal model of the lower extremity to estimate muscle forces and knee joint stresses-strains during the stance phase of the walking cycle in a subject with knee OA and a non-pathologic (NP) subject. The OA patient adopted reduced muscle forces through stance phase, except at mid stance, compared to the NP subject. However, Kumar et al. [41] demonstrated that OA patients had higher hamstring and gastrocnemius muscle forces at both loading response and mid-stance phases of the gait cycle.
This paper contributes to our current understanding of the underlying neuromuscular mechanisms during gait for patients with knee OA prior to HTO and TKR surgery. A question has been posed: Do muscle coordination strategies, adopted by subjects with knee OA, and associated changes in knee function reflect the level of involvement of compartmental knee OA?

2. Methods
Kinematic and kinetic data were collected in the Motion Analysis Laboratory (Cardiff School of Engineering) from thirty subjects, each gave their informed written consent prior to data collection, divided into three groups: eleven subjects with no knee pathology (NP), ten subjects with medial uni-compartmental knee OA and correctable varus deformity listed for high tibial osteotomy (pre-HTO) [42], and nine subjects with multi-compartmental knee OA listed for total knee replacement (pre-TKR). Ethical approval was granted from the Wales Research Ethics Committee 3 (10/MRE09/28) and Cardiff and Vale University Health Board.

Motion analysis was performed using nine 120Hz infra-red motion capture units (Qualisys, Gothenburg, Sweden). Qualisys Track Manager (QTM, Qualisys, Gothenburg, Sweden) was used to capture full body motion using reflective markers placed on the trunk, pelvis, and both the upper and lower limbs (modified Cleveland clinic marker set) [7, 43]. Four floor-embedded force platforms (Bertec Corporation) were used to capture the ground reaction force vectors with a sample rate of 1080 Hz. Motion data were processed using the Matlab Motion data elaboration Toolbox for NeuroMusculoSkeletal applications (MOtoNMS) [44].

Muscle electromyographic (EMG) data were collected bilaterally, using a Trigno™ Wireless EMG System (Delsys Incorporated, Natick, MA, USA), for seven muscles: rectus femoris, vastus lateralis, vastus medialis, biceps femoris, semitendinosus, gastrocnemius lateralis, and gastrocnemius medialis. The electrodes were placed longitudinally over the muscle bellies after standard preparation of the skin, according to SENIAM recommendations [45], involving shaving, exfoliation, cleaning of the skin and finally electrode gel was used to reduce the electrode–skin impedance [46].

Participants were asked to perform activities of daily living whilst muscle EMG, ground reaction force and three-dimensional movements were collected using the synchronized movement analysis system. Six trials of level gait at self-selected walking speeds, six trials of ascending/descending a four-step staircase [47], and two trials of standing/sitting were recorded for each subject. The stance phase was determined by the ground reaction force measured from heel strike to toe-off.

Recorded raw EMG data, through stance phase, were analysed in Matlab (version R2013a, Mathworks Inc.). The raw EMG signals were band-pass filtered, to remove the movement artefacts, by a Butterworth 4th order filter at (10_450) Hz, rectified and finally low-pass-filtered with a 4th order Butterworth filter at 6 Hz to create a linear envelope for each muscle. Then linear envelopes for each muscle were normalized to peak values obtained through activities of daily living, as recommended by [48]. Finally, the co-contraction index (CCI) was calculated through stance, by using Eq (1) developed by Rudolph et al. [49], for the following muscle sets: vastus lateralis- gastrocnemius lateralis (VLLG), vastus lateralis-lateral hamstring (VLLH), vastus medialis- gastrocnemius medialis (VMMG), and vastus medialis-medial hamstring (VMMH).

$$\text{CCI} = \sum_{i=1}^{100} \left[ \frac{\text{low EMG}_i}{\text{high EMG}_i} \times (\text{high EMG}_i + \text{low EMG}_i) \right] / 100$$

Gait biomechanics were determined using OpenSim v3.3 [50]. For each participant, the customized generic anatomic model was scaled to the participant’s anthropometry. The final
anatomic model was then used to calculate joint angles, moments and musculo-tendon unit kinematics (lengths and moment arms) for walking trials using OpenSim inverse kinematics (IK), inverse dynamics (ID) and muscle analysis tools, respectively. Gait biomechanics and processed EMGs were then used to calibrate and execute an EMG-driven model, for each subject, to estimate muscle forces by using CEINMS [51]. CEINMS has already been mentioned in depth [51, 52], so it will only be addressed briefly here. The musculo-tendon unit parameters of each individual were adjusted, which is part of the CEINMS framework, i.e., optimizing the musculo-tendon unit parameters to minimize the least square differences between the expected joint moments of the model and the experimentally measured joint moments. Two walks were included in the experimental trials used in the calibration process. The calibration parameter and boundary conditions list is the same as that used in [51]. After calibration, the model worked as an open-loop predictive ways to predict muscle forces and joint moments based on muscle activation and kinematic model.

Muscle forces and joint moments (hip, knee, and ankle) were normalized to each stance phase of the gait cycle. Values at heel strike, peak weight acceptance and peak push off, along with co-contraction indices were averaged across six representative stance phases for each subject, and then averaged across subjects to obtain group means. Heel strike was defined as the value at 0% of the stance phase. Peak weight acceptance was defined as the first 15% of the stance phase. Peak push off was defined as the mean value between 5% on either side of the peak knee extension moment.

Patient-reported outcome measures (PROMs) including Oxford Knee Score [53], Knee Outcome Survey [54], Western Ontario and McMaster Universities Osteoarthritis Index [55], Pain Audit Collection System [56], and Knee Injury And Osteoarthritis Outcome Score [57] were completed to provide a subjective measure of how each patient perceived their knee function.

3. Statistical analysis

The Kolmogorov–Smirnov and Levene tests were used to assess the normality of distribution ($P > 0.05$) and the equality of variances, respectively. One way analysis of variance (ANOVA) model was tested for significant group differences for demographics, walking speed, and patient reported outcome measures (PROMS), where data was normally distributed and homogenous. All significant findings were post hoc tested using Tukey adjusted alpha level to determine pair-wise significant differences.

Kinematic and kinetic data, were compared across the three subject groups, were not normally distributed or homogeneous. Accordingly, a Kruskal Wallis test of nonparametric data was performed. Pairwise comparisons using the Dunn-Bonferroni approach were automatically produced for any dependent variables for which the Kruskal-Wallis test was significant. All statistical analyses were performed using SPSS (version 20, Chicago, IL).

4. Results and discussion

Demographics and PROMS differed across the three subject groups; summarized in Tables 1 and 2. The Oxford Knee Score, Knee Outcome Survey, Western Ontario and McMaster Universities Osteoarthritis Index and Pain Audit Collection System were higher for the pre-TKR compared with the pre-HTO subjects indicating more severe self-reported pain and stiffness and reduced function. Knee Injury And Osteoarthritis Outcome Score was lower for pre-TKR compared to pre-HTO subjects, where lower scores indicate extreme knee problems.

No significant differences, between pre-HTO and pre-TKR groups, were observed in PROMS suggested that these outcome measures were not the most sensitive methods to differentiate between uni- and multi-compartmental knee OA.
Group ensemble-averaged waveforms for quadriceps, hamstring and gastrocnemius muscle forces illustrate that peaks and patterns changed between NP, pre-HTO and pre-TKR groups (Fig 1). The sequence and timing of predicted muscle activity were consistent with a previous study [32], with gastrocnemius generating the largest forces about the knee at push off, for NP subjects. Pre-HTO subjects had elevated quadriceps and lateral hamstring activity compared to the NP subjects.

A reduced range of sagittal plane knee joint angle was observed for OA cohorts (pre-HTO and pre-TKR patients) as compared to NP, Fig 2.

Table 1. Demographics and clinical data mean (SD) for NP, Pre-HTO, and Pre-TKR subjects.

| Characteristics                  | NP   | Pre-HTO | Pre-TKR | P     | P     | P     |
|----------------------------------|------|---------|---------|-------|-------|-------|
|                                  | n = 11 | n = 10 | n = 9  | NP vs. HTO | NP vs. TKR | HTO vs. TKR |
| Age, years                       | 32.9 (5.2) | 50.3 (6.9) | 66.6 (9.8) | <0.001 † | <0.001 † | <0.001 † |
| Weight, kg                       | 79.5 (12.6) | 87.8 (14.9) | 88.7 (20.3) |       |       |       |
| Height, m²                       | 1.76 (0.04) | 1.73 (0.09) | 1.69 (0.08) |       |       |       |
| Walking speed, m/s               | 1.31 (0.23) | 1.066 (0.16) | 0.81 (0.19) | 0.027 † | <0.001 † | 0.024 † |
| Static varus angles              |       |       |         |       |       |       |
| Medial compartment KL score      |       |       |         |       |       |       |
|                                  | Grade 2: n = 4 | Grade 3: n = 5 | Grade 4: n = 1 |       |       |       |

NP = Non-pathologic subjects.
† Significant differences between groups (P<0.05).
KL = Kellgren and Lawrence (range 0–4 where stage 0 is assigned to a normal, healthy knee and stage 4 to severe knee OA).

Table 2. Patient reported outcome measures (PROMS) mean (SD) for Pre-HTO, and Pre-TKR subjects.

| Characteristics              | Pre-HTO | Pre-TKR | P     |
|------------------------------|---------|---------|-------|
|                              | n = 10  | n = 9   |       |
| OKS                          | 25.8 (10.0) | 29.2 (9.5) | 0.456 |
| KOS                          | 48.8 (15.8) | 49.1 (13.9) | 0.964 |
| WOMAC                        | 38.9 (23.2) | 49.8 (21.5) | 0.303 |
| PACS                         | 39.3 (25.0) | 47.6 (24.1) | 0.475 |
| KOOS Pain                    | 63.1 (24.7) | 54.0 (22.9) | 0.439 |
| KOOS Symptom                 | 65.0 (19.5) | 53.6 (22.2) | 0.266 |
| KOOS ADL                     | 69.4 (24.4) | 59.6 (21.5) | 0.383 |
| KOOS Sport/Rec               | 41.1 (32.7) | 18.8 (23.4) | 0.124 |
| KOOS QOL                     | 43.1 (21.7) | 32.8 (22.1) | 0.336 |

OKS = Oxford Knee Score (range from 12 for least difficulties to 60 for most difficulties).
KOS = Knee Outcome Survey (scale from 0–100 where 100 indicates no disability).
WOMAC = Western Ontario and McMaster University Osteoarthritis Index (high scores indicating high degree of impairment).
PACS = Pain Audit Collection System (scale from 0–10, from least to most difficulty or severity).
KOOS = Knee injury and osteoarthritis outcome score (range 0–100, with zero representing extreme knee problems).
ADL = Activities of daily living.
QOL = Quality of life.

https://doi.org/10.1371/journal.pone.0262798.t001

https://doi.org/10.1371/journal.pone.0262798.t002
3A and 3D, respectively) for the knee OA group. Only the pre-TKR group had a reduced first peak hip adduction moment (Fig 3B). However, both knee OA cohorts had increased EKAM (Fig 3D). Pre-TKR subjects showed a trend of higher mid-stance EKAM (related to knee OA severity) with no clearly defined double peak (Fig 3D).

A summary of the individual muscle forces and joint moment is reported in Tables 3 and 4, respectively, during heel strike (HS), weight acceptance (WA), and push off (PO) phases of stance.

Fig 4 shows the CCI for NP, pre-HTO, and pre-TKR subjects. As expected, patients with knee OA have a higher CCI compared to NP subjects. Some evidence of co-contraction between the quadriceps and hamstrings muscles was found, in particular, for the VLLH in the pre-TKR compared to the NP subjects, which may contribute to a reduction in medial knee contact force.
This study has shown that neuromuscular control and biomechanics differ between non-pathological knees and those with OA. These differences are magnified as the level of compartmental involvement increases. The results have demonstrated that, in line with previous research findings [58], knee OA is a multifactorial disease process that involves many interrelated factors that interact to produce biomechanical changes throughout the disease process. In agreement with literature [10], a reduced range of motion for the sagittal plane knee joint angle was observed for knee OA cohorts as compared to NP, Fig 2. In principle, muscle control and external moments are the key to stance stability. Throughout stance, muscles contract when body alignment creates a moment that is antagonistic to weight bearing stability of the limb and trunk, and the amount of contraction is proportional to the magnitude of the demand torque that must be restrained.

Fig 2. Group ensemble-averaged sagittal plane knee kinematic waveforms (knee flexion), during stance-phase for NP (blue), pre-HTO (green) and pre-TKR (red) subjects. Values represent mean (SD).

https://doi.org/10.1371/journal.pone.0262798.g002

Fig 3. The external joint moment waveforms during stance-phase for NP (blue), pre-HTO (green) and pre-TKR (red) subjects: Hip flexion moment–A, Hip adduction moment–B, Hip rotation moment–C, Knee flexion moment–D, Knee adduction moment–E, knee rotation moment–F, Ankle flexion moment–G. Values represent mean (SD).

https://doi.org/10.1371/journal.pone.0262798.g003
Knee OA is associated with a reduction in gastrocnemius muscle force, whereas quadriceps and hamstring muscles play a significant role in controlling the knee joint. Subjects with knee OA had reduced gastrocnemius muscle forces compared to NP subjects by 30% and 18% for pre-HTO and pre-TKR, respectively. This could happen due to a reduction in knee extension moment (Fig 3D) for these groups; i.e, the role of a plantar flexor–knee extension couple. A plantar flexor–knee extension couple, which was addressed by [59, 60], plays a key role in knee control during gait. According to this phenomenon, under load, the planter flexors, i.e., gastrocnemius, are capable of acting on the tibiofemoral joint to extend the knee by holding back the tibia. Brunner and Rutz [61] suggested that the knee extensors (quadriceps) can control only the first phase of knee extension, during the response to loading. The second phase is

### Table 3. Muscle forces for NP, pre-HTO and pre-TKR subjects at three different events: Heel strike (HS), weight acceptance (WA), and push off (PO) phases of stance.

| Variables | Group | Muscle Force (BW) |
|-----------|-------|------------------|
|           | NP (n = 11) | Pre-HTO (n = 10) | Pre-TKR (n = 9) |
| Heel Strike | Biceps Femoris Long Head | 1.59 | 0.255 | 0.208 |
|           | Biceps Femoris Short Head | 0.114 | 0.274 | 0.153 |
|           | Semimembranosus | 0.482 | 0.422 | 0.429 |
|           | Semitendinosus | 0.087 | 0.063c | 0.102 |
|           | Lateral Gastrocnemius | 0.149 | 0.178 | 0.222 |
|           | Medial Gastrocnemius | 0.154 | 0.3 | 0.351 |
|           | Rectus Femoris | 0.017 | 0.022 | 0.053 |
|           | Vastus Intermedius | 0.015ah | 0.036c | 0.096 |
|           | Vastus Lateralis | 0.018 | 0.044 | 0.086 |
|           | Vastus Medialis | 0.03bc | 0.03c | 0.106 |
| Weight Acceptance | Biceps Femoris Long Head | 0.16 | 0.261 | 0.224 |
|           | Biceps Femoris Short Head | 0.119b | 0.32 | 0.232 |
|           | Semimembranosus | 0.484 | 0.422 | 0.445 |
|           | Semitendinosus | 0.088 | 0.064c | 0.107 |
|           | Lateral Gastrocnemius | 0.15 | 0.178 | 0.24 |
|           | Medial Gastrocnemius | 0.166 | 0.3 | 0.351 |
|           | Rectus Femoris | 0.147 | 0.156 | 0.182 |
|           | Vastus Intermedius | 0.216 | 0.201 | 0.272 |
|           | Vastus Lateralis | 0.249 | 0.286 | 0.278 |
|           | Vastus Medialis | 0.204 | 0.159 | 0.286 |
| Push off | Biceps Femoris Long Head | 0.006ah | 0.072 | 0.081 |
|           | Biceps Femoris Short Head | 0.027ah | 0.172 | 0.166 |
|           | Semimembranosus | 0.015 | 0.038 | 0.072 |
|           | Semitendinosus | 0.009ah | 0.017 | 0.03 |
|           | Lateral Gastrocnemius | 0.417 | 0.43 | 0.508 |
|           | Medial Gastrocnemius | 1.04 | 0.626 | 0.763 |
|           | Rectus Femoris | 0.059ah | 0.189 | 0.2 |
|           | Vastus Intermedius | 0.026ah | 0.087 | 0.177 |
|           | Vastus Lateralis | 0.029ah | 0.122 | 0.172 |
|           | Vastus Medialis | 0.02b | 0.06c | 0.118 |

*a* significant between NP and pre-HTO. (Kruskal–Wallis).

*b* significant between NP and pre-TKR.

*c* significant between pre-HTO and pre-TKR.

https://doi.org/10.1371/journal.pone.0262798.t003

Knee OA is associated with a reduction in gastrocnemius muscle force, whereas quadriceps and hamstring muscles play a significant role in controlling the knee joint. Subjects with knee OA had reduced gastrocnemius muscle forces compared to NP subjects by 30% and 18% for pre-HTO and pre-TKR, respectively. This could happen due to a reduction in knee extension moment (Fig 3D) for these groups; i.e, the role of a plantar flexor–knee extension couple. A plantar flexor–knee extension couple, which was addressed by [59, 60], plays a key role in knee control during gait. According to this phenomenon, under load, the planter flexors, i.e., gastrocnemius, are capable of acting on the tibiofemoral joint to extend the knee by holding back the tibia. Brunner and Rutz [61] suggested that the knee extensors (quadriceps) can control only the first phase of knee extension, during the response to loading. The second phase is
controlled by the planter flexors. During this time interval, both knee OA groups had a reduced gastrocnemius muscle force compared to NP. In line with this finding, the results of

### Table 4. Knee, hip, and ankle kinetics for NP, pre-HTO and pre-TKR subjects at three different events: heel strike (HS), weight acceptance (WA), and push off (PO) phases of stance.

| Variables | Joint kinetic [BW.H] | NP (n = 11) | Pre-HTO (n = 10) | Pre-TKR (n = 9) |
|-----------|----------------------|-------------|------------------|----------------|
| **Heel Strike** | | | | |
| Knee flexion (+) / extension (–) | −0.23 | 0.22 | 0.42 |
| Knee adduction | 0.08 | 0.05 | 0.04 |
| Knee internal (+) / external (–) rotation | 0.01 | −0.02 | −0.02 |
| Hip flexion | 0.30<sup>b</sup> | 1.16<sup>c</sup> | 2.58 |
| Hip adduction | −0.40 | −0.30 | −0.19 |
| Hip internal (+) / external rotation (–) | −0.01<sup>a</sup> | 0.01<sup>a</sup> | 0.03 |
| Ankle plantarflexion (+) / dorsiflexion (–) | 0.09 | 0.06 | 0.14 |
| **Weight Acceptance** | | | | |
| Knee flexion (+) / extension (–) | −1.36 | −0.98 | −0.87 |
| Knee adduction | 1.01<sup>a</sup> | 2.06 | 1.11 |
| Knee internal (+) / external (–) rotation | 0.04 | 0.08<sup>c</sup> | 0.14 |
| Hip flexion | 4.03<sup>a</sup> | 4.37<sup>c</sup> | 3.87 |
| Hip adduction | 0.12 | 0.16 | −0.06 |
| Hip internal (+) / external rotation (–) | −0.06<sup>a</sup> | 0.14 | −0.25 |
| Ankle plantarflexion (+) / dorsiflexion (–) | 0.62 | 0.58 | 0.40 |
| **Push off** | | | | |
| Knee flexion (+) / extension (–) | −2.46<sup>ab</sup> | −1.09 | −0.40 |
| Knee adduction | 1.21<sup>a</sup> | 3.29 | 2.09 |
| Knee internal (+) / external (–) rotation | 0.67 | 1.04 | 0.78 |
| Hip flexion | 0.30<sup>a</sup> | −0.76 | −0.70 |
| Hip adduction | −3.97 | −4.37 | −3.42 |
| Hip internal (+) / external rotation (–) | −0.49<sup>ab</sup> | 0.05 | −0.01 |
| Ankle plantarflexion (+) / dorsiflexion (–) | −7.86 | −7.28 | −7.34 |

<sup>a</sup> significant between NP and pre-HTO.
<sup>b</sup> significant between NP and pre-TKR.
<sup>c</sup> significant between pre-HTO and pre-TKR.

https://doi.org/10.1371/journal.pone.0262798.t004

---

**Fig 4. Co-contraction index during stance-phase for NP subjects–n = 11, pre-HTO subjects–n = 10, pre-TKR subjects–n = 9.** Values represent mean (SD), (*) means the difference is significant (P< 0.05).

https://doi.org/10.1371/journal.pone.0262798.g004
this study have shown that patients with knee OA had reduced knee extension moments during late stance. Therefore, less gastrocnemius muscle force was developed in the knee OA (compared to NP group), to control the knee extension moment during late stance. The gastrocnemius is a biarticular muscle, crossing over the knee and ankle joints. Under load, the activity of the gastrocnemius can be adjusted according to this arrangement. Due to the lever arm situation at the knee under load, the gastrocnemius muscle is a powerful knee flexor when the knee is flexed. However, if its strength is needed at the ankle, simultaneous contraction of the vasti locks the knee and shifts the gastrocnemius’ strength to the ankle [62], i.e., the net effect is to extend the knee.

Our finding of increased quadriceps and hamstrings muscle forces in the knee OA groups is supported by an earlier study [63], where these muscle groups appear to be capable of supporting up to 100% of the applied adduction/abduction moment, where it is high in knee OA patients (Fig 3E), because of their abdution and/or adduction moment arm. The quadriceps play a major role in controlling the knee, as shortly after heel strike it acts to prevent excessive or rapid knee flexion. knee OA subjects used substantially higher quadriceps and hamstring muscle force than NP subjects, presumably in an attempt to support the joint against an excessive knee adduction moment, Fig 3E. The peak force estimated for hamstring muscle increased by 25%, for pre-HTO compared to NP.

In the NP stance phase, there are at least three crucial sub-phases. First is the initial heel contact (HS) when the line of action of the ground reaction force (GRF) passes posterior to the ankle centre, producing a plantar-flexion moment at the ankle. This moment is countered by the activation of ankle dorsiflexor muscles; this was the case for all groups. Considering the importance of leg stability during this phase, compensations aimed at extending the knee include premature activity of the gastrocnemius [62], avoiding knee flexion during loading response, with co-contraction of the knee extensors and hamstring muscles during knee flexion. Pre- TKR cohort shows a higher activity of the gastrocnemius compared to the other groups, Fig 1. At the knee joint, the ground reaction force passes anterior to the knee axis creating an extension moment, which is eccentrically controlled by the hamstring muscles to avoid hyper-extension of the knee and slow the forward movement of the leg. The results of this study show that at initial HS, there is an excessive knee flexion for the knee OA groups compared to the NP group, (18±5, 9±4, 5±3 degrees for Pre-TKR, Pre-HTO, and NP, respectively), leading to the GRF passing posterior to knee centre of rotation, creating a flexion moment rather than extension moment at the knee, (0.22, 0.42) %BW H for pre-HTO and pre-TKR, respectively, Fig 3D. The GRF passes anterior to hip rotation centre creating a flexion moment, where the Pre- TKR cohort shows a significantly higher flexion moment compared to the pre-HTO and NP groups.

Second, is the weight acceptance (WA) phase where the ankle dorsiflexors eccentrically contract towards foot flat. The knee extensors contract, to correct the position of the knee before it accepts further loading into single leg stance. Peak quadriceps action occurs during loading response, when the GRF vector is behind the joint axis. As the vector moves forward of the knee axis, an extension moment is created at the knee, and this muscle group relaxes. The gastrocnemius muscle group contracts to control knee extension at this stage, due to the planter flexor–knee extension couple. Higher muscle forces occur during WA when the EKAM is high and the knee extends in single limb support. In this study the knee OA subjects (pre-HTO and pre-TKR), used substantially higher lateral hamstring and vastus lateralis muscle forces during WA phase compared to NP (Table 3). Further still, these were higher for pre-HTO subjects than for pre-TKR subjects. This finding further supports the notion that selective activation of lateral muscles is likely a pain and symptom management strategy in this population to unload the medial compartment of the knee.
Third, is the push-off (PO) phase, where the leg is accelerated forward by the gastrocnemius creating a rapid ankle plantar flexion to push off and with associated activity at the hip flexor (rectus femoris). During this phase, generally for NP gait, there is a maximal knee extension moment, a second peak knee adduction moment, and a peak dorsiflexion moment. In this study both knee OA groups had reduced the terminal knee extension moments ($P < 0.05$) and ankle dorsiflexion moment (Fig 3G), compared to NP. This seems to be partially a compensatory action for the poorer physical capacity and the subjective knee pain experienced by this population. This, in addition to a reduced gastrocnemius force (Fig 1B and 1C and Table 3), implies that subjects with knee OA inadvertently used greater hip flexors (rectus femoris) muscle force to propel the body forward, i.e., 0.2, 0.18, and 0.06 (BW) for pre-TKR, pre-HTO and NP subjects, respectively. When comparing quadriceps muscle forces; vastus lateralis and vastus inter-medialis produced higher force in the pre-TKR subjects than NP ($P < 0.05$) and pre-HTO subjects, and in the pre-HTO subjects compared to the NP subjects ($P < 0.05$).

In the frontal plane, the hip adduction moment is generally found to be high in knee OA patients compared to NP. However, the pre-TKR cohort exhibited a different adduction pattern compared to the NP and pre-HTO cohorts. In both the NP and pre-HTO subjects, frontal plane moments had two distinct peaks. The first peak was higher for the pre-HTO compared to the NP group. This is attributed to altered alignment of the tibiofemoral joint (knee varus), which would create a valgus alignment at the hip.

The same trend was seen in the EKAM, where a significant increase ($P < 0.05$) was observed for the pre-HTO subject group (2.06, 3.29) %BW’H compared to the NP (1.01, 1.21) %BW’H at weight acceptance and push-off, respectively. A remarkable increase in the first peak of EKAM for NP, in comparison to the second peak, was mainly due to the increase in the quadriceps force resisting the external knee flexion moment during this time interval. In contrast, the moderate increase of the second peak in the pre-HTO cohort, in comparison to the first peak, was due to the increase in both quadriceps and hamstring muscle forces during this time interval as compared to NP. The double peak could not be identified in pre-TKR patients.

In the transverse plane, the hip is significantly more internally rotated for the pre-HTO subjects group compared to the NP subject group ($P < 0.05$), during weight acceptance and push off.

Higher symmetrical quadriceps and hamstring forces suggest that their co-contraction with the gastrocnemius muscles could lead to higher joint contact forces that, combined with the excessive loading due to high EKAM, would exacerbate joint destruction. Nonetheless, the knee OA groups used greater vastus lateralis muscle force compared to the NP subjects, which may imply that people with knee OA inadvertently increase the activity of vastus lateralis as a compensatory strategy to reduce medial joint compression and subsequent pain. For the knee OA subject groups, a reduced dorsiflexion moment and lower gastrocnemius co-contraction suggest that gastrocnemius overload may not be the primary cause of joint degeneration. If this is the case; attention should be focussed on the counterbalancing role of the quadriceps and hamstrings during dynamic movements to control knee biomechanics.

Pre-TKR patients (Fig 4), have significantly ($P < 0.05$) higher CCI compared to NP subjects. Interestingly, this study shows that gastrocnemii indices are doubled in the pre-HTO group as compared to NP subjects. For the pre-TKR group, in addition to the gastrocnemii role that is associated with a two-fold increase in the CCI, the hamstring muscles also have the potential to control the knee joint. The hamstring indices increased by almost four-fold on the lateral side and three-fold on the medial side, as compared to NP individuals. There was also a significant increase in VLLH for the pre-TKR group, which may contribute to a reduction in the medial contact force. The lateral indices indicated an almost two-fold increase ($P < 0.05$), for
the pre-HTO group compared to NP subjects. Therefore, increased lateral muscle co-contraction reflects the non-pathological knee’s progression to uni-compartmental OA with varus deformity. No significant differences were found between pre-HTO and pre-TKR lateral indices.

Significant difference ($P<0.05$) was identified for the medial side index, VMMH, between the two OA groups, Fig 4. In agreement with [6], patients with uni-compartmental OA and varus deformity (pre-HTO) have increased lateral CCIs, which may help to unload the medial compartment. This increase is also evident for multi-compartmental OA (pre-TKR). Since increased medial muscle co-contraction has the potential to differentiate between uni-compartment and multi-compartment OA (Pre-HTO and pre-TKR patients), this could inform treatment management.

The results of this study should be viewed within the context of some limitations. The small sample size potentially lowers statistical power. However, a comparison of the joint angles, moments, and muscle activity from our simulation with the results from previous studies with larger populations demonstrated that our subjects displayed gait patterns that were typical. In addition, EMGs were recorded from just seven muscles bilaterally for use in the model to represent 10 muscles crossing the knee joint; some muscles in the model represented a combination of multiple muscles with similar functions, and this may affect the evaluation of magnitude for knee muscle forces. Finally, while musculoskeletal model parameters are adjusted for each individual, the model does not account for musculoskeletal size variations and alterations in muscle architecture. Variables such as maximum isometric force, optimum fibre length, and tendon slack length were modified to account for each subject’s weakened musculature.

5. Conclusion
Knee OA is associated with a reduction in gastrocnemius muscle force, whereas quadriceps and hamstring muscles play a significant role in controlling the knee joint, with altered coordination and increased forces with increasing age and involvement of knee compartment.

Moreover, pre-TKR patients adopt a gait pattern that differs from that of pre-HTO patients, attempting to unload the affected joint structures during walking, possibly by changing muscle coordination as well as moments at the adjacent ankle and/or hip. The increase of the lateral muscle co-contraction reflects the progression from NP to uni-compartmental OA and varus deformity (pre-HTO). Whereas, the increase of medial muscle co-activation could potentially differentiate between uni-compartmental or multi-compartmental OA.

Acknowledgments
The authors would like to thank Dr Sarah Forrest for assistance with recruitment and data collection.

Author Contributions
Formal analysis: Aseel Ghazwan.
Investigation: Aseel Ghazwan.
Methodology: Aseel Ghazwan, Chris Wilson, Gemma M. Whatling.
Supervision: Cathy A. Holt, Gemma M. Whatling.
Writing – original draft: Aseel Ghazwan.
Writing – review & editing: Cathy A. Holt, Gemma M. Whatling.
References

1. Andriacchi TP, Mündermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. Current opinion in rheumatology. 2006 Sep 1; 18(5):514–8. https://doi.org/10.1097/01.bor.0000240365.16842.4e PMID: 16896293

2. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1995 Aug; 38(8):1134–41.

3. ARUK. 2013. Osteoarthritis in General Practice—Data and perspectives. Arthritis Research UK [Online]. Available: http://www.arthritisresearchuk.org/policyandpublic-affairs/reports-and-resources/reports.aspx [Accessed 23/03/2015].

4. Sasaki K, Neptune RR. Individual muscle contributions to the axial knee joint contact force during normal walking. Journal of biomechanics. 2010 Oct 19; 43(14):2780–4. https://doi.org/10.1016/j.jbiomech.2010.06.011 PMID: 20655046

5. Taylor WR, Heller MO, Bergmann G, Duda GN. Tibio-femoral loading during human gait and stair climbing. Journal of Orthopaedic Research. 2004 May; 22(3):625–32. https://doi.org/10.1002/jor.2003.09.003 PMID: 15099644

6. Andriacchi TP. Dynamics of knee malalignment. The Orthopedic clinics of North America. 1994 Jul; 25(3):395. PMID: 8028883

7. Whalting GM, Biggs PR, Elson DW, Metcalfe A, Wilson C, Holt C. High tibial osteotomy results in improved frontal plane knee moments, gait patterns and patient-reported outcomes. Knee Surgery, Sports Traumatology, Arthroscopy. 2020 Sep; 28(9):2872–82. https://doi.org/10.1007/s00167-019-05644-7 PMID: 31384981

8. Sparks V, Whalting GM, Biggs P, Khatib N, Al-Amri M, Williams D, et al. Comparison of gait, functional activities, and patient-reported outcome measures in patients with knee osteoarthritis and healthy adults using 3D motion analysis and activity monitoring: an exploratory case-control analysis. Orthopedic Research and Reviews. 2019; 11:129. https://doi.org/10.2147/ORR.S199107 PMID: 31572022

9. Zeni JA, Higginson JS. Knee osteoarthritis affects the distribution of joint moments during gait. The Knee. 2011 Jun 1; 18(3):156–9. https://doi.org/10.1016/j.knee.2010.04.003 PMID: 20510618

10. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. Journal of orthopaedic research. 2008 Mar; 26(3):332–41. https://doi.org/10.1002/jor.20496 PMID: 17960658

11. Hodges PW, van den Hoorn W, Wrigley TV, Hinman RS, Bowles KA, Cicuttini F, et al. Increased duration of co-contraction of medial knee muscles is associated with greater progression of knee osteoarthritis. Manual Therapy. 2016 Feb 1; 21:151–8. https://doi.org/10.1016/j.math.2015.07.004 PMID: 26254263

12. Kumar D, Rudolph KS, Manal KT. EMG-driven modeling approach to muscle force and joint load estimations: Case study in knee osteoarthritis. Journal of Orthopaedic Research. 2012 Mar; 30(3):377–83. https://doi.org/10.1002/jor.21544 PMID: 21901754

13. Zeni JA, Rudolph K, Higginson JS. Alterations in quadriceps and hamstrings coordination in persons with medial compartment knee osteoarthritis. Journal of Electromyography and Kinesiology. 2010 Feb 1; 20(1):148–54. https://doi.org/10.1016/j.jelekin.2008.12.003 PMID: 19223023

14. Schmitt LC, Rudolph KS. Influences on knee movement strategies during walking in persons with medial knee osteoarthritis. Arthritis Care & Research. 2007 Aug 15; 57(6):1018–26. https://doi.org/10.1002/art.22889 PMID: 17665469

15. Lloyd DG, Buchanan TS. Strategies of muscular support of varus and valgus isometric loads at the human knee. Journal of biomechanics. 2001 Oct 1; 34(10):1257–67. https://doi.org/10.1016/s0021-9290(01)00995-1 PMID: 11522305

16. Shull PB, Huang Y, Schlotman T, Reinbolt JA. Muscle force modification strategies are not consistent for gait retraining to reduce the knee adduction moment in individuals with knee osteoarthritis. Journal of biomechanics. 2015 Sep 1; 48(12):3163–9. https://doi.org/10.1016/j.jbiomech.2015.07.006 PMID: 26209875

17. Brandon SC, Miller RH, Thelen DG, Deluzio KJ. Selective lateral muscle activation in moderate medial knee osteoarthritis subjects does not unload medial knee condyle. Journal of biomechanics. 2014 Apr 11; 47(6):1409–15. https://doi.org/10.1016/j.jbiomech.2014.01.038 PMID: 24581816

18. Rutherford DJ, Hubley-Kozey CL, Stanish WD, Dunbar MJ. Neuromuscular alterations exist with knee osteoarthritis presence and severity despite walking velocity similarities. Clinical Biomechanics. 2011 May 1; 26(4):377–83. https://doi.org/10.1016/j.clinbiomech.2010.11.018 PMID: 21185628
19. Richards C, Higginson JS. Knee contact force in subjects with symmetrical OA grades: differences between OA severities. Journal of biomechanics. 2010 Sep 17; 43(13):2595–600. https://doi.org/10.1016/j.jbiomech.2010.05.006 PMID: 20627301

20. Zeni JA Jr, Higginson JS. Differences in gait parameters between healthy subjects and persons with moderate and severe knee osteoarthritis: a result of altered walking speed?. Clinical biomechanics. 2009 May 1; 24(4):372–8. https://doi.org/10.1016/j.clinbiomech.2009.02.001 PMID: 19285768

21. Sharma L, Hurwitz DE, Thonar EJ, Sum JA, Lenz ME, Dunlop DD, et al. Knee adduction moment, serum hyaluronan level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis & Rheumatism. 1998 Jul; 41(7):1233–40.

22. Mündermann A, Dyrby CO, Hurwitz DE, Sharma L, Andriacchi TP. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 2004 Apr; 50(4):1172–8. https://doi.org/10.1002/art.15077299

23. Zhao D, Banks SA, Mitchell KH, D’Lima DD, Colwell CW Jr, Fregly BJ. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. Journal of orthopaedic research. 2007 Jun; 25(6):789–97. https://doi.org/10.1016/j.jor.200379 PMID: 17343285

24. Hubley-Korey CL, Robbins SM, Rutherford DJ, Stanish WD. Reliability of surface electromyographic recordings during walking in individuals with knee osteoarthritis. Journal of Electromyography and Kinesiology. 2013 Apr 1; 23(2):334–41. https://doi.org/10.1016/j.jelekin.2012.12.002 PMID: 23352396

25. Wilson DA, Hubley-Kozer CL, Wilson JL, Dunbar MJ. Pre-operative muscle activation patterns during walking are associated with TKA tibial implant migration. Clinical biomechanics. 2012 Nov 1; 27(9):936–42. https://doi.org/10.1016/j.clinbiomech.2012.06.012 PMID: 22858133

26. Hubley-Kozer CL, Hill NA, Rutherford DJ, Munar DJ, Stanish WD. Co-activation differences in lower limb muscles between asymptomatic controls and those with varying degrees of knee osteoarthritis during walking. Clinical biomechanics. 2009 Jun 1; 24(5):407–14. https://doi.org/10.1016/j.clinbiomech.2009.02.005 PMID: 19303179

27. Metcalfe AJ, Stellwart C, Postans N, Dodds AL, Holt CA, Roberts AP. The effect of osteoarthritis of the knee on the biomechanics of other joints in the lower limbs. The bone & joint journal. 2013 Mar; 95(3):348–53. https://doi.org/10.1302/0301-620X.95B3.30850 PMID: 23450019

28. Ramsey DK, Snyder-Mackler L, Lewek M, Newcomb W, Rudolph KS. Effect of anatomic realignment on muscle function during gait in patients with medial compartment knee osteoarthritis. Arthritis Care & Research. 2007 Apr 15; 57(3):389–97. https://doi.org/10.1002/art.20068 PMID: 17394224

29. Winby CR, Lloyd DG, Besier TF, Kirk TB. Muscle and external load contribution to knee joint contact forces during normal gait. Journal of biomechanics. 2009 Oct 16; 42(14):2294–300. https://doi.org/10.1016/j.jbiomech.2009.06.018 PMID: 19647257

30. Schmitt LC, Rudolph KS. Muscle stabilization strategies in people with medial knee osteoarthritis: the effect of instability. Journal of Orthopaedic Research. 2008 Sep; 26(9):1180–5. https://doi.org/10.1002/jor.20619 PMID: 18404657

31. Herzog W, Longino D, Clark A. The role of muscles in joint adaptation and degeneration. Langenbeck’s Archives of Surgery. 2003 Oct 1; 388(5):305–15. https://doi.org/10.1007/s00423-003-0402-6 PMID: 14504930

32. Winby CR, Lloyd DG, Besier TF, Kirk TB. Muscle and external load contribution to knee joint contact loads during normal gait. Journal of biomechanics. 2009 Oct 16; 42(14):2294–300. https://doi.org/10.1016/j.jbiomech.2009.06.018 PMID: 19647257

33. Lloyd DG, Besier TF. An EMG-driven musculoskeletal model to estimate muscle forces and knee joint moments in vivo. Journal of biomechanics. 2003 Jun 1; 36(6):765–76. https://doi.org/10.1016/s0021-9290(03)00010-1 PMID: 12742444

34. Manal K, Buchanan TS. An electromyogram-driven musculoskeletal model of the knee to predict in vivo joint contact forces during normal and novel gait patterns. Journal of biomechanical engineering. 2013 Feb 1; 135(2). https://doi.org/10.1115/1.4023457 PMID: 23445059

35. Besier TF, Fredericson M, Gold GE, Beaupré GS, Delp SL. Knee muscle forces during walking and running in patellofemoral pain patients and pain-free controls. Journal of biomechanics. 2009 May 11; 42(7):896–905. https://doi.org/10.1016/j.jbiomech.2009.01.032 PMID: 19268945

36. White SC, Winter DA. Predicting muscle forces in gait from EMG signals and musculotendon kinematics. Journal of Electromyography and Kinesiology. 1992 Jan 1; 2(4):217–31. https://doi.org/10.1016/1050-6411(92)90025-E PMID: 20719615

37. Seireg A, Arvikan RJ. The prediction of muscular load sharing and joint forces in the lower extremities during walking. Journal of biomechanics. 1975 Mar 1; 8(2):89–102. https://doi.org/10.1016/0021-9290(75)90089-5 PMID: 1150683
38. Thelen DG, Anderson FC. Using computed muscle control to generate forward dynamic simulations of human walking from experimental data. Journal of biomechanics. 2006 Jan 1; 39(6):1107–15. https://doi.org/10.1016/j.jbiomech.2005.02.010 PMID: 16023125

39. DeVita P, Hortobagyi T. Functional knee brace alters predicted knee muscle and joint forces in people with ACL reconstruction during walking. Journal of applied biomechanics. 2001 Nov 1; 17(4):297–311.

40. Adouni M, Shirazi-Adl A. Evaluation of knee joint muscle forces and tissue stresses-strains during gait in severe OA versus normal subjects. Journal of orthopaedic research. 2014 Jan; 32(1):69–78. https://doi.org/10.1002/jor.22472 PMID: 24038150

41. Kumar D, Rudolph K, Manal K. Muscle forces during walking in medial knee osteoarthritis, 55th Annual Meeting of the Orthopaedic Research Society, Poster No. 1990.

42. Brinkman JM, Lobenhoffer P, Agneskirchner JD, Staubli AE, Wymenga AB, Van Heerwaarden RJ. Osteotomies around the knee: patient selection, stability of fixation and bone healing in high tibial osteotomies. The Journal of bone and joint surgery. British volume. 2008 Dec; 90(12):1548–57. https://doi.org/10.1302/0302-620X.90B12.21198 PMID: 19043123

43. Reinbolt JA, Schutte JF, Fregly BJ, Koh BI, Haftka RT, George AD, et al. Determination of patient-specific multi-joint kinematic models through two-level optimization. Journal of biomechanics. 2005 Mar 1; 38(3):621–6. https://doi.org/10.1016/j.jbiomech.2004.03.031 PMID: 15652563

44. Mantoan A, Pizzolato C, Sartori M, Sawacha Z, Cobelli C, Reggiani M. MoToN MS: A MATLAB toolbox to process motion data for neuromusculoskeletal modeling and simulation. Source code for biology and medicine. 2015 Dec 1; 10(1):12. https://doi.org/10.1186/s13029-015-0044-4 PMID: 26579208

45. Hermens HJ, Freriks B, Disselhorst-Klug C, Rau G. Development of recommendations for SEMG sensors and sensor placement procedures. Journal of electromyography and Kinesiology. 2000 Oct 1; 10(5):361–74. https://doi.org/10.1016/s1050-6411(00)00027-4 PMID: 11018445

46. Doorenbosch CA, Harlaar J. Accuracy of a practicable EMG to force model for knee muscles. Neurosurgery. 2000 Sep 16; 3(1):78–81. https://doi.org/10.1093/neuros/60.06.055 PMID: 15342138

47. Whaling GM, Evans SL, Holt CA. Introducing a new staircase design to quantify healthy knee function during stair ascent and descent. Computer methods in biomechanics and biomedical engineering. 2010 Jun 1; 13(3):371–8. https://doi.org/10.1016/j.neulet.2009.05.024 PMID: 19802753

48. Ghazwan A, Forrest SM, Holt CA, Whaling GM. Can activities of daily living contribute to EMG normalization for gait analysis?. PLoS One. 2017 Apr 3; 12(4):e0174670. https://doi.org/10.1371/journal.pone.0174670 PMID: 28369104

49. Rudolph KS, Axe MJ, Snyder-Mackler L. Dynamic stability after ACL injury: who can hop?. Knee Surgery, Sports Traumatology, Arthroscopy. 2000 Sep 1; 8(5):262–9. https://doi.org/10.1007/s001670000130 PMID: 11061293

50. Delp SL, Anderson FC, Arnold AS, Loan P, Habib A, John CT, et al. OpenSim: open-source software to create and analyze dynamic simulations of movement. IEEE transactions on biomedical engineering. 2007 Oct 22; 54(11):1940–50. https://doi.org/10.1109/TBME.2007.901024 PMID: 18018689

51. Pizzolato C, Lloyd DG, Sartori M, Ceseracciu E, Besier TF, Fregly BJ, et al. CEINMS: A toolbox to investigate the influence of different neural control solutions on the prediction of muscle excitation and joint moments during dynamic motor tasks. Journal of biomechanics. 2015 Nov 5; 48(14):3929–36. https://doi.org/10.1016/j.jbiomech.2015.09.021 PMID: 26522621

52. Konrath JM, Saxby DJ, Killen BA, Pizzolato C, Vertullo CJ, Barrett RS, et al. Muscle contributions to medial tibiofemoral compartment contact loading following ACL reconstruction using semitendinosus and gracilis tendon grafts. PLoS One. 2017 Apr 19; 12(4):e0176016. https://doi.org/10.1371/journal.pone.0176016 PMID: 28423061

53. Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. The Journal of bone and joint surgery. British volume. 1998 Jan; 80(1):63–9. https://doi.org/10.1093/jbjs/80.1.63 PMID: 9460955

54. Irrgang JJ, Snyder-Mackler L, Wainner RS, Fu FH, HARNER CD. Development of a patient-reported measure of function of the knee. JBJS. 1998 Aug 1; 80(8):1132–45.

55. Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. InSeminars in arthritis and rheumatism 1989 May 1 (Vol. 18, No. 4, pp. 14–17). WB Saunders. https://doi.org/10.1016/0049-0172(89)90010-3 PMID: 2786253

56. Griffiths DP, Mitchell Noon J, Campbell FA, Price CM. Clinical governance and chronic pain: towards a practical solution. Anaesthesia. 2003 Mar; 58(3):243–8. https://doi.org/10.1016/j.anae.2004.03.0088 PMID: 12603454

57. Roos EM, Roos HP, Lohmander LS, Ek达尔 C, Beynon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)—development of a self-administered outcome measure. Journal of Orthopaedic &
58. Man GS, Mologhianu G. Osteoarthritis pathogenesis–a complex process that involves the entire joint. Journal of medicine and life. 2014 Mar 15; 7(1):37. PMID: 24653755

59. Zajac FE, Gordon ME. Determining muscle’s force and action in multi-articular movement. Exercise and sport sciences reviews. 1989 Jan 1; 17(1):187–230. PMID: 2676547

60. Gage JR, Novacheck TF. An update on the treatment of gait problems in cerebral palsy. Journal of Pediatric Orthopaedics Part B. 2001 Oct 1; 10(4):265–74. PMID: 11727367

61. Brunner R, Rutz E. Biomechanics and muscle function during gait. Journal of children's orthopaedics. 2013 Nov 1; 7(5):367–71. https://doi.org/10.1007/s11832-013-0508-5 PMID: 24432096

62. Brunner R, Romkes J. Abnormal EMG muscle activity during gait in patients without neurological disorders. Gait Posture. 2008; 27(3):399–407. https://doi.org/10.1016/j.gaitpost.2007.05.009 PMID: 18023352

63. Lloyd DG, Buchanan TS, Besier TF. Neuromuscular biomechanical modeling to understand knee ligament loading. Medicine & Science in Sports & exercise: Official Journal of the American College of Sports Medicine. 2005; 37(11):1939–47. https://doi.org/10.1249/01.mss.0000176676.49584.ba PMID: 16286865