advantage of using body weight to apply resistance, eliminating the need for exercise equipment or resistance machines. However, little is known about the muscle forces experienced during common weightbearing exercises and how these compare to everyday movements such as walking. Furthermore, there is a common misconception for patients with knee OA that weightbearing exercise will aggravate their symptoms or hasten structural decline. Accordingly, kineseophobia and pain catastrophising towards exercise is common in knee OA. Conceivably, these fears may be accentuated in high-risk subgroups such as those with varus malalignment, who have greater functional and structural decline than neutrally aligned OA knees. The stigma surrounding weightbearing exercise also extends to clinicians, who can be reluctant to prescribe weightbearing exercises due to a fear of aggravating patient symptoms. The uncertainty towards weightbearing exercise may arise because medial knee OA pathogenesis is likely due, at least in part, to increased medial tibiofemoral compartment loading. The medial tibiofemoral contact forces (MTCF) during walking in people with knee OA and varus malalignment is on average ~2 times bodyweight, yet limited research has evaluated articular knee loads during different weightbearing exercises in people with knee OA. The aim of this cross-sectional study was to use EMG-informed neuromusculoskeletal modelling to test the hypothesis that common weightbearing exercises will generate larger lower-limb muscles forces than walking in people with medial knee osteoarthritis and varus malalignment. A secondary aim was to test the hypothesis that peak MTCF was no higher during these exercises compared to walking.

**Methods:** Twenty-eight participants aged ≥50 years with medial knee OA (Kellgren & Lawrence grade ≥2) and varus malalignment were recruited from the community. Three-dimensional lower-body motion, ground reaction forces and surface electromyograms from 12 lower-limb muscles were acquired during five squat, forward lunge, single-leg heel raise and walking trials, performed at self-selected speeds. These exercises were selected to reflect a different range of weightbearing exercises and positions often used within knee OA programs. The exercises were divided into three phases: (i) ascent/descent from starting pose to end of self-selected range; (ii) a three-second isometric hold; and (iii) ascent/descent back to the initial starting pose. An electromyogram-informed neuromusculoskeletal model with magnetic resonance imaging informed bone geometry and tibiofemoral contact points was used to estimate muscle forces (N) and bodyweight (BW) normalised MTCF. The peak forces for muscle groups (knee extensors, knee flexors, ankle plantar flexors and hip abductors) and peak MTCF during each exercise were compared to walking using a multivariate analysis of variance model. We were primarily interested in the main effect of each exercise condition (squat, lunge, heel raise) compared to walking. In the event of a significant main or interaction effect, post-hoc pairwise comparison (mean difference [95% confidence interval (95% CI)]) with a Bonferroni correction was performed to explore significant effects.

**Results:** The cohort had a mean age of 64, slightly more males than females and was overweight on average. Muscle force and MTCF outcomes for each exercise condition and walking are presented in Table 1. There was a significant main effect ($p<0.001$). Post-hoc tests (mean difference [95%CI]) showed that compared to walking, participants generated higher peak knee extensor and flexor forces during squatting (extensor: 902 N [576, 1227], flexor: 192 N [9.39, 375]) and lunging (extensor: 917 N [604, 1231], flexor: 496 N [198, 794]), and lower peak hip abductor force during squatting (-1975 N [-2841, -1108]) and heel raises (-1217 N [-2131, -303]). Compared to walking, MTCF was lower during squatting (-0.79 BW [-1.04, -0.53]) and heel raises (-0.27 BW [-0.50, -0.04]). No other significant differences were observed.

**Conclusions:** Despite clinical practice guidelines advocating exercise as a core treatment for all people with knee OA based on strong research evidence, there is uncertainty amongst physiotherapists and patients about whether exercise is effective and/or safe for all people with knee OA. Compared to walking, peak knee extensor force was ~3 times higher during squatting and lunging, and peak knee flexor forces were 1.6 and 2.5 times higher, respectively. These are important observations given these muscles stabilise the knee during the loading response of walking, which is where the peak MTCF occurs. Surprisingly, peak ankle plantar flexor and hip abductor force did not exceed the peak forces during walking for any of the exercises. This may highlight a need for alternative and/or more demanding exercises to target these muscle groups. Furthermore, the MTCF was lower during the heel raises and squatting relative to walking, but similar between lunging and walking. Collectively, these novel findings can give clinicians and their patients confidence that squatting and lunging will generate peak knee extensor and knee flexor forces larger than normal walking but do not increase forces within the osteoarthritic joint compartment.

## V-33
## PREDICTING CHANGE IN KNEE CARTILAGE FROM INTERACTIONS OF CUMULATIVE LOADING WITH CARTILAGE TURNOVER BIOMARKERS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

N.K. Ivanochko [1], A.A. Gatti [2], P.W. Stratford [3], **M.R. Maly** [1]. [1] *Univ. of Waterloo, Waterloo, ON, Canada;* [2] *Stanford Univ., Stanford, CA;* [3] *McMaster Univ., Hamilton, ON, Canada*

**Purpose:** In people with established knee OA, exposure to high dynamic loading is associated with worsening knee cartilage morphology. Yet, habitual runners, who experience high loading rates do not show an increased risk of developing OA. This apparent contradiction likely requires that we identify factors that modify the relationship between loading and knee joint health. The purpose of our work was to evaluate potential factors that influence the relationship between cumulative loading to affect cartilage knee outcomes. Our primary objective was to investigate the relationship between cumulative load and two-year changes in cartilage thickness and mean transverse relaxation time (T2). A secondary objective was to examine whether baseline cartilage turnover biomarker concentration predicted changes in cartilage outcomes.

**Methods:** Data from the FNIH OA Biomarkers Consortium Project of the longitudinal Osteoarthritis Initiative (OAI) study was used for this

| | Mean (SD) | | | | Mean difference (95% confidence interval) | | |
|---|---|---|---|---|---|---|---|
| | Squat (n=28) | Lunge (n=28) | Heel raise (n=28) | Walking (n=28) | Squat minus walking | Lunge minus walking | Heel raise minus walking |
| Peak muscle force (N) | | | | | | | |
| Knee extensors | 1409 (529) | 1420 (521) | 437 (367) | 487 (253) | 902 (576,1227) | 917 (604, 1231) | -46.1 (-274, 182) |
| Knee flexors | 531 (316) | 836 (521) | 417 (372) | 342 (149) | 192 (9.39, 375) | 496 (198, 794) | 90.0 (-119, 298) |
| Ankle plantar flexors | 762 (619) | 1002 (641) | 1073 (546) | 1219 (829) | -399 (-913, 114) | -156 (-648, 336) | -85.8 (-533, 362) |
| Hip abductors | 842 (376) | 2536 (1114) | 1600 (902) | 2817 (1610) | -1975 (-2841, -1108) | -281 (-1178, 616) | -1217 (-2131, -303) |
| Tibiofemoral contact force (BW) | | | | | | | |
| Peak medial | 1.32 (0.41) | 2.12 (0.45) | 1.83 (0.43) | 2.09 (0.42) | -0.79 (-1.04, -0.53) | -0.01 (-0.25, 0.24) | -0.27 (-0.50, -0.04) |

Table 1

Osteoarthritis and Cartilage

Peak muscle and medial tibiofemoral contact force for exercise conditions and walking

secondary analysis (n=412 participants). Only participants with a Kellgren-Lawrence grading $\leq 3$ were included. Cartilage morphology and composition measures were calculated from scans acquired at the 24-month and 48-month visits using a validated convolutional neural network (NeuralSeg). The outcome measures of interest were change in cartilage thickness and T2. Four regions of interest were identified: lateral and medial weight-bearing femur, and lateral and medial tibia. Cumulative loading was defined using two loading measures: (A) Total score from the Physical Activity Scale for the Elderly (PASE), to represent loading repetition in daily life; and (B) body mass index (BMI) to reflect loading magnitude. The interaction term between PASE*BMI was also used in the analysis to represent cumulative loading. Biochemical biomarkers investigated were serum cartilage oligometric matrix protein (COMP) and serum Coll2-1 NO2 at baseline, to reflect cartilage degradation, type II collagen degradation and inflammation. An interaction between the cumulative loading interaction term and each biochemical biomarker was also included (e.g. PASE*BMI*COMP). Multiple linear regression models (adjusted for baseline measures of age, KL grade, cartilage measures, KOOS-Pain, and Charlson Comorbidity Index) were used to evaluate the relationship between cumulative loading and biochemical biomarkers on two-year changes in cartilage outcomes. Potential predictors were added in a forward fashion. If a significant interaction occurred, its constituent predictors were retained in the model, whether significant or not.

**Results:** Mean (SD) age at baseline was 63.7 (8.7) years; 57% were female, KL grade 1 (n=42), KL grade 2 (n=204), KL grade 3 (n=166). Mean (SD) baseline values for predictors included the following: PASE score 153 (78), BMI 30.3 (4.5) kg/m$^2$, and serum COMP concentration 771.4 (283.4) ng/mL. Neither cumulative loading nor biochemical biomarkers were associated with changes in cartilage thickness over two years in any region. Cumulative load and cartilage turnover contributed to models explaining two-year change in knee cartilage T2 (Table 1). PASE contributed to a model explaining medial femur T2 change. The PASE*BMI interaction term contributed to medial tibia T2 change. Lastly, the PASE* BMI*COMP interaction term contributed to change in T2 in the lateral tibia.

**Conclusions:** Cumulative loading and biochemical biomarkers concentration were unrelated to two-year change in cartilage thickness. Previous work has found cumulative loading to be a predictor of loss of cartilage volume, but not cartilage thickness. However, cumulative loading and its interaction with cartilage degradation were weakly related with two-year change in T2 in the knee. The magnitudes of these relationships are of questionable clinical significance. Future work should explore the role of cumulative loading in cartilage quality and knee health.

**Table 1** Relationship of measures of cumulative load and cartilage turnover with two-year change in T2 relaxation time (n=412 participants). Cumulative load was reflected by the Physical Activity Scale for the Elderly (PASE) and Body Mass Index (BMI). Cartilage turnover was reflected by serum cartilage oligometric matrix protein (COMP). Covariates included age, Kellgren-Lawrence grade, T2 relaxation time, KOOS-Pain, and Charlson Comorbidity Index at baseline. Within the covariate model, baseline T2 relaxation time was the strongest predictor of changes in cartilage quality in the regions of interest. Reported *p* values are for the overall model.

| | Predictors | Unstandardized β Coefficient | 95% CI | $R^2$ | *p* value |
|---|---|---|---|---|---|
| Medial Femur | Covariates only | | | 0.102 | **< 0.001** |
| | Covariates + PASE | −0.003848 | −0.006, −0.001 | 0.121 | **< 0.001** |
| Lateral Femur | Covariates only | | | 0.094 | **< 0.001** |
| Medial Tibia | Covariates only | | | 0.113 | **< 0.001** |
| | Covariates + PASE*BMI | −0.000114 | −0.000209, −0.000020 | 0.121 | **< 0.001** |
| Lateral Tibia | Covariates only | | | 0.149 | **< 0.001** |
| | Covariates + PASE*BMI*COMP | $-9.37 \times 10^{-8}$ | $-1.73 \times 10^{-7}$, $-1.48 \times 10^{-8}$ | 0.158 | **< 0.001** |

## V-34
## ANGIOGENESIS AND ENDOTHELIAL DYSFUNCTION: SYNOVIAL VASCULAR PATHOLOGY IS ASSOCIATED WITH SURROGATE MEASURES OF KNEE LOAD DURING WALKING

**M.M. Carter**, T.B. Birmingham, H.T. Philpott, J.R. Giffin, B.A. Lanting, C.T. Appleton. *Western Univ., London, ON, Canada*

**Purpose:** Synovial inflammation (synovitis) and aberrant joint loading are important, related risk factors for knee osteoarthritis (OA) incidence and progression. OA-related synovitis is associated with vascular pathology, including neovascularization and perivascular edema. We recently demonstrated that synovial perivascular edema, a key feature of physiologic tissue stress, is associated with aberrant joint loading during walking. However, the mechanisms by which abnormal joint loading induces synovial perivascular edema are unknown. Identifying mechanisms of vascular dysfunction in OA synovium may lead to treatments that mitigate the pathological effects of physiologic joint stress caused by biomechanical loading. The objective of this study was to investigate candidate mechanisms between surrogate measures of dynamic knee load during gait and synovial perivascular edema, including increases in synovial angiogenesis and/or angiogenic factors that cause endothelial stress/dysfunction such as placental growth factor (PlGF) and endoglin.

**Methods:** Patients (n = 98) undergoing total knee arthroplasty or high tibial osteotomy for symptomatic, radiographic knee OA were included in this cross-sectional study. Study participants underwent 3D gait analysis within 12 weeks prior to surgery. Inverse dynamics were used to calculate external knee moments in the sagittal, frontal, and transverse planes. Lateral, supra-patellar synovial tissue biopsies and synovial fluid were obtained intra-operatively. Synovial tissue underwent detailed histopathological measurement to quantify microvessel density (MVD) and the density of microvessels with perivascular edema (edemic MVD) per synovial tissue area (vessels/mm$^2$). Synovial fluid concentrations of endoglin and PlGF were measured by multiplex assay. We used multivariate linear regression models adjusting for age, sex, BMI, and gait speed to investigate associations between external knee moments with synovial MVD and/or edemic MVD, and with synovial fluid endoglin and PlGF concentrations in a sub-group of patients (n = 80) with adequate, high-quality synovial fluid available for factor measurement. Statistical models were constructed using Graphpad Prism 9 (Version 9.2.0) Results include unstandardized β coefficients with 95% confidence intervals (CIs).

**Results:** Our cohort was composed of a roughly equal number of male and female patients with predominately late-stage knee OA (Table 1). The 1$^{st}$ peak knee adduction moment (KAM) (β= 0.54 vessels/mm$^2$ [95%CI 0.24, 0.84]), KAM impulse (β= 0.74 vessels/mm$^2$ [95%CI 0.34, 1.13]) and peak internal rotation moment (β= 1.08 vessels/mm$^2$ [95%CI 0.14, 2.02]) were associated with increased edemic MVD (Table 2). The KAM impulse was also associated with increased synovial MVD (β= 0.70 vessels/mm$^2$ [95%CI 0.02, 1.39]) (Table 2). The associations between edemic MVD and 1$^{st}$ peak KAM (β= 0.44 vessels/mm$^2$ [95%CI 0.17, 0.70]), KAM impulse (β= 0.55 vessels/mm$^2$ [95%CI 0.19, 0.91]) and peak internal rotation moment (β= 0.98 vessels/mm$^2$ [95%CI 0.16, 1.80]) were reduced, but remained when adjusting for synovial MVD, indicating partial mediation (Table 2). The KAM impulse was associated with increased synovial fluid endoglin (β= 2.49 pg/ml [95%CI 0.18, 4.79]) and PlGF (β= 1.49 pg/ml [95%CI 0.46, 2.53]) concentrations (Table 3).

**Conclusions:** We found that proxy measures of dynamic knee load during gait are associated with synovial vascular pathology in patients with late-stage knee OA. This study used quantitative measures of synovial microvessels and confirms our earlier finding of an association between dynamic knee load and the presence of synovial perivascular edema. Further, these new data suggest that increased angiogenesis and synovial fluid levels of angiogenic factors that cause endothelial dysfunction are potential mechanisms leading to perivascular edema associated with dynamic knee load. Together, these data support the general hypothesis that biomechanical loading of structural joint tissues leads to cross-talk with the synovium in patients with knee OA, and links mechanical loading to synovial vascular pathology.

**Table 1**
**Patient Baseline Demographics and Clinical Characteristics**

| Characteristic | Total Cohort (*n* = 98) |
|---|---|
| Sex, *n* (%) | |
| Male | 55 (56) |
| Female | 43 (44) |
| Age, years | 66.6 ± 8.6 (41, 85) |
| BMI, kg/m$^2$ | 32.7 ± 5.3 (21.1, 47.2) |
| Mechanical Axis Angle, degrees | -7.3 ± 5.5 (-18.3, 10.1) |
| KOOS Pain | 47.4 ± 15.1 (11.0, 89.0) |
| Kellgren and Lawrence Grade, *n* (%)[1] | |
| 1 | - |
| 2 | 2 (2) |
| 3 | 37 (38) |
| 4 | 59 (60) |

Mean ± SD (minimum, maximum) or n (%)

BMI = body mass index, mm = millimeter, kg = kilogram, m = meter, KOOS = Knee Injury and Osteoarthritis Outcome Score

[1]Kellgren & Lawrence grade corresponds to radiographic osteoarthritis severity. Grade 1 = doubtful joint space narrowing and possible osteophytic lipping; grade 2 = possible joint space narrowing and definite osteophytes; grade 3 = definite joint space narrowing, multiple moderate osteophytes, some sclerosis and possible deformity of the bone contour; grade 4 = large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony deformity.