2-1-2021

Association between changes in knee load and effusion-synovitis: evidence of mechano-inflammation in knee osteoarthritis using high tibial osteotomy as a model

H. F. Atkinson
Western University

T. B. Birmingham
Western University

C. A. Primeau
Western University

J. M. Schulz
Western University

C. T. Appleton
Western University, tom.appleton@sjhc.london.on.ca

See next page for additional authors

Osteoarthritis and Cartilage 29 (2021) 222–229

Osteoarthritis and Cartilage

Association between changes in knee load and effusion-synovitis: evidence of mechano-inflammation in knee osteoarthritis using high tibial osteotomy as a model

H.F. Atkinson [† ‡], T.B. Birmingham [† ‡ *], C.A. Primeau [† ‡], J.M. Schulz [† ‡], C.T. Appleton [‡ §], S.L. Pritchett [§], J.R. Giffin [‡ §]

† *School of Physical Therapy, Faculty of Health Sciences, University of Western Ontario, London, Canada*
‡ *Bone and Joint Institute, University of Western Ontario, London, Canada*
§ *Schulich School of Medicine & Dentistry, University of Western Ontario, London, Canada*

ARTICLE INFO

Article history:
Received 7 June 2020
Accepted 19 November 2020

Keywords:
Gait biomechanics
Synovitis
Inflammation
MRI
Alignment

SUMMARY

Objective: Although mechanically-induced inflammation is an appealing explanation linking different etiologic factors in osteoarthritis (OA), clinical research investigating changes in both biomechanics and joint inflammation is limited. The purpose of this study was to evaluate the association between change in surrogate measures of knee load and knee effusion-synovitis in patients with medial compartment knee OA undergoing high tibial osteotomy (HTO).

Methods: Thirty-six patients with medial compartment knee OA and varus alignment underwent 3D gait analysis and 3T magnetic resonance imaging (MRI) preoperatively and 1 year after medial opening wedge HTO. Primary outcome measures were the change in the external knee adduction moment impulse during walking and change in knee suprapatellar effusion-synovitis volume manually segmented on MRI by one blinded assessor.

Results: Mean (SD) knee adduction moment impulse [24.0 (6.5) Nm•s] and knee effusion-synovitis volume [8976.7 (8016.9) mm^3] suggested substantial preoperative medial knee load and inflammation. 1-year postoperative changes in knee adduction moment impulse [−10.1 Nm•s (95%CI: −12.7, −7.4)], and knee effusion-synovitis volume [−1856 mm^3 (95%CI: −3830, 117)] were positively correlated [$r = 0.60$ (95% CI 0.34, 0.78)]. Simple linear regression suggested a 448 mm^3 (95%CI: 241, 656) reduction in knee effusion-synovitis volume per 1 Nm•s reduction in knee adduction moment impulse. Change in knee adduction moment impulse explained 36% ($R^2 = 0.36$) of the variance of change in knee effusion-synovitis volume.

Conclusions: Reduction in medial knee load is positively associated with reduction in knee inflammation after HTO, suggesting the phenomenon of mechano-inflammation in patients with knee OA.

Introduction

The etiology of osteoarthritis (OA) is complex and includes mechanical, biological and immune processes that affect the health of the entire joint-organ system[1]. The high loads borne by the knee during ambulation make it particularly vulnerable to OA, and the knee joint is the most common site of the disease[2–4]. Although OA is not an autoimmune disease, it frequently manifests signs of inflammation, including synovitis in early and later stages of disease[5]. At the tissue level, synovitis manifests in OA as synovial hyperplasia with or without fibrosis, increased vascularity, inflammatory cell infiltration and joint effusion[6]. Synovial membrane thickening and effusion identified on magnetic resonance imaging (MRI) is termed effusion-synovitis; it is readily demonstrated in the supra-patellar and para-patellar regions and is distinct from MRI signs of inflammation in the infra-patellar (Hoffa's) fat pad ("Hoffa-

* Address correspondence and reprint requests to: T.B. Birmingham, School of Physical Therapy Faculty of Health Sciences University of Western Ontario London, ON, N6H 1H1, Canada. Tel.: 1-519-661-2111x84349; Fax: 1-519-661-3866.
E-mail addresses: hatkins5@uwo.ca (H.F. Atkinson), tbirming@uwo.ca (T.B. Birmingham), cprimea@uwo.ca (C.A. Primeau), jschulz2@uwo.ca (J.M. Schulz), tom.appleton@sjhc.london.on.ca (C.T. Appleton), stephany.pritchett@lhsc.on.ca (S.L. Pritchett), rgiffin@uwo.ca (J.R. Giffin).

https://doi.org/10.1016/j.joca.2020.11.007
1063-4584/

synovitis")[7]. Longitudinal cohort studies suggest knee effusion-synovitis is associated with the onset[8,9] and progression[10] of structural OA joint changes, including cartilage damage[11] and bone marrow lesions[12]. Longitudinal studies also suggest knee synovitis is associated with pain[13] and pain sensitization[14] in patients with knee OA. Moreover, limited evidence suggests *change* in knee synovitis in knee OA following corticosteroid injection is associated with change in pain and function[15].

Although mechanopathology can manifest variably in OA, aberrant loading at the knee due to lower limb frontal plane malalignment is common and is strongly associated with future structural damage and symptom progression[3,16,17]. Medial compartment tibiofemoral OA is frequently observed in neutral and varus alignment because the knee adduction moment during walking distributes greater load medially, creating a feed-forward cycle of increased medial loading, medial joint damage and further varus alignment[3]. The external knee moments derived from 3D gait analysis are independently associated with medial knee OA progression[18–21] and increased pain after walking[22,23]. There is also limited evidence suggesting *change* in gait biomechanics is associated with clinically important change in symptoms[24].

Medial opening wedge high tibial osteotomy (HTO) is a lower limb realignment surgery for patients with symptomatic OA primarily affecting the medial tibiofemoral compartment and varus alignment. The procedure aims to correct malalignment and thereby improve distribution of the dynamic loads on the knee. Conceptually, HTO is a biomechanical intervention that targets the underlying mechanical etiology in knee OA. Although the commonly proposed rationale for biomechanical interventions is that changing joint loads alters structural tissues including cartilage and bone, we propose there may also be effects on joint inflammation that are not well understood.

Defining the association between aberrant mechanics and local inflammation (mechano-inflammation) would be a key milestone in improving our overall understanding of the etiology of knee OA. As gait biomechanics and knee synovitis are both modifiable[25,36], an association between these measures would be highly relevant to the development and delivery of clinical interventions for OA. This could include the opportunity to define biological mechanisms of mechano-inflammation, which may inform the discovery of new treatment targets[25]. Although mechano-inflammation is an appealing explanation linking etiological factors, we are unaware of any human studies directly investigating the association of change in knee loading with change in knee inflammation in patients with OA. Therefore, the purpose of this study was to compare measures of dynamic knee loading and knee inflammation before and 1 year after medial opening wedge HTO and evaluate the association between the changes. Specifically, we aimed to test the hypothesis that a reduction in the knee adduction moment impulse measured during walking is positively associated with a reduction in knee effusion-synovitis volume measured on MRI.

Methods

Study design

A subgroup of patients participating in an ongoing prospective cohort study investigating medial opening wedge HTO[24] agreed to additional testing, including gait analyses and MRI (completed on the same day) preoperatively and 1-year postoperatively. Participants also agreed to the use of an osteotomy fixation plate that did not create metal artifact on MRI[26], or to have a more commonly used titanium plate removed before the postoperative visit. The first 36 patients with preoperative and 1-year postoperative gait and MRI data were analyzed. The sample size was chosen to detect a correlation coefficient of $r = 0.45$ or greater (equating to a moderate-to-large effect size) between change in knee load and change in knee effusion-synovitis, with 80% power and $\alpha = 0.05$[27]. All participants provided informed consent. The study was approved by the institution's Research Ethics Board for Health Science Research Involving Human Subjects.

Participants

We recruited patients referred to a tertiary care clinic for consultation with an orthopaedic surgeon regarding unresolved knee pain and/or decreased function. All patients met the American College of Rheumatology clinical classification criteria for knee OA[28]. Additionally, patients had varus alignment of the lower limb (mechanical axis angle $< 0^{\circ}$)[29], with radiographic signs and symptoms of knee OA primarily affecting the medial tibiofemoral compartment. Patients with concomitant radiographic signs of OA in the lateral tibiofemoral and/or patellofemoral compartments were considered suitable candidates for HTO as long as radiographic joint space narrowing and pain were greatest in the medial tibiofemoral compartment.

Intervention

Participants underwent unilateral medial opening wedge HTO with internal fixation completed by one of five surgeons. The operative technique aimed to correct varus alignment to approximately neutral to very slight valgus alignment using methods similar to those previously described[24,30]. The tibial osteotomy wedge was fixed using either a polyethyletherketone insert and screws, which did not produce artifact on MRI[26], or a titanium locking plate and cortical and cancellous screws. If a titanium fixation plate and screws were used, they were removed within 1 year after surgery and postoperative imaging was delayed at least 6 weeks after its removal. Early postoperative management included the use of a hinged brace and feather weight-bearing with crutches. Patients gradually increased weight-bearing based on clinical and radiographic evidence of healing of the osteotomy, typically progressing to one crutch within 6 weeks, full weight-bearing within 12 weeks, and cleared to resume pre-operative levels of activity by 6 months postoperative. Patients completed a rehabilitation protocol with exercise progressions and milestones reviewed on postoperative day 1, and 2-, 6-, and 12-week follow-up visits. The rehabilitation protocol focused on range of motion and swelling control from 0 to 2 weeks postoperative, non-weightbearing and limited-weightbearing strengthening and postural control exercises from 2 to 6 weeks postoperative, that were progressed from 6 to 12 weeks postoperative and included gradual return to preoperative activities from 12 to 26 weeks postoperative.

Gait analysis

All participants completed 3D gait analysis using a 10-camera motion capture system (Motion Analysis Corporation, Santa Rosa, CA, USA), a modified Helen–Hayes reflective marker set, and floor-mounted force platforms (AMTI, Watertown, MA, USA), using valid and reliable methods sensitive to change after HTO[31,32]. Patients walked barefoot at a self-selected, comfortable walking pace across the laboratory while kinematic data (sampled at 60 Hz) and kinetic data (sampled at 600 Hz) were recorded for five trials of each limb. We calculated external moments about the knee in the frontal, sagittal and transverse planes using an inverse dynamics model (Orthotrak 6.6.1; Motion Analysis Corporation, Santa Rosa, CA, USA). With the exception of the knee adduction moment impulse,

gait data were normalized to 100% of stance phase. Moments were reported in Nm and also normalized to bodyweight and height (% Bw•Ht). We calculated the mean of five trials for each patient. Given its association with pain[22] and disease progression[20], and its reduction after HTO[24], the knee adduction moment impulse was determined *a priori* as the primary gait outcome measure.

Magnetic resonance imaging

All participants were scanned using a Siemens Magnetom Trio 3.0 T magnet with a dedicated 15-channel Tx/Rx PRISMA knee coil. We used the 3D Dual-Echo Steady State (DESS) pulse sequence with fat suppression and water excitation, which enabled excellent contrast to identify effusion-synovitis. The 3D DESS sequence consists of 160 slices, with a slice thickness of 0.7 mm and 0.37 × 0.46 mm in-plane resolution (acquisition time 10.6 min). Example sagittal and axial slices obtained from the present dataset are presented in Fig. 1.

One reader trained by a musculoskeletal radiologist and a rheumatologist measured suprapatellar effusion-synovitis volume by manual segmentation (3D Slicer, http://www.slicer.org)[33]. Using effusion-synovitis as a surrogate for synovial inflammation, we followed recommendations from previous investigators reporting repeatability and validity of the method[34,35]. We studied the suprapatellar pouch, as it is the most responsive synovial region of interest in the knee joint[13]. The reader segmented borders of effusion-synovitis in the suprapatellar pouch of all knees in the sagittal view, then applied a signal intensity threshold for each image to eliminate hypointense tissue within the synovial volume. Upon completing segmentation in the sagittal view, the imaging plane was converted to the axial view to verify multiplanar accuracy of effusion-synovitis segmentation. Examples of sagittal and axial views of effusion-synovitis are presented in Fig. 1. The reader carried out segmentations on paired images while blinded to timepoint. A separate investigator masked the evidence of HTO surgery on the tibia of both the preoperative and postoperative images and randomized the order of the paired images[26].

To assess intra-rater reliability, the reader repeated segmentation of each preoperative and postoperative knee approximately 30 days after the first reading, in random order with all images being assigned new identification labels. To assess inter-rater reliability, a second rater segmented 10 pre-operative and 10 post-operative knees, selected at random.

Statistical analyses

Baseline demographic and clinical characteristics for the sample were described using means and standard deviations for continuous data and frequencies and percentages for categorical data. We assessed the intra-rater and inter-rater reliability of the effusion-synovitis measurements by calculating separate intraclass correlation coefficients ($ICC_{2,1}$) for the preoperative and postoperative images. We calculated mean changes and 95% confidence intervals (CI) for all biomechanical variables and for effusion-synovitis. We plotted individual patient 1-year change scores (postoperative minus preoperative value) for knee adduction moment impulse vs. knee effusion-synovitis volume, including the linear line of best fit with mean 95% CIs. Given the proposed effects of changing knee load on changes in knee inflammation, simple linear regression of the change scores was then used to evaluate the association between the change in surrogate measures of knee load (predictor) and the change in knee effusion-synovitis volume (outcome) from baseline to 1-year after HTO. We then evaluated the association between the change in knee adduction moment impulse and the change in effusion-synovitis volume through a multivariate regression model while adjusting for the effect of baseline covariates including mass (kilograms), height (meters), age and radiographic disease severity (Kellgren & Lawrence grade [$\leq$2 vs 3]). As sensitivity analyses, we repeated the regression models substituting the predictor of interest (knee adduction moment impulse) with the 1st or 2nd peak knee adduction moment. To test regression model assumptions, we visually inspected component-plus-residual plots for linearity, residual plots (e.g., Kernel density plot) for normality and residual-versus-predictor plots for homoscedasticity. Data were linear with normally distributed and homoscedastic residuals. We used Stata 16 statistical software (StataCorp LLC, College Station, TX).

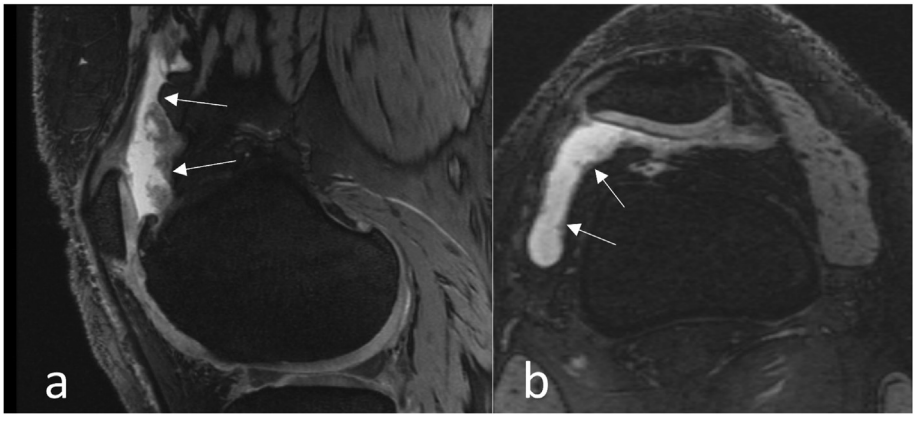

Fig. 1 Sagittal (a) and axial (b) views of 3D DESS sequences with white arrows indicating effusion-synovitis (hyperintense tissue posterior and superior and lateral to the patella) in a left knee, prior to segmentation.

Results

Intra-rater and inter-rater reliability of effusion-synovitis measurements were excellent for both preoperative and postoperative knees (lower ends of 95% CI of all ICC > 0.80) and was consistent with a previous study[35]. The participants' baseline characteristics are reported in Table I. Consistent with previous research in HTO, the majority of recruited patients were middle-aged males, overweight or obese, with varus alignment. Most patients had Kellgren and Lawrence grades 2 or 3.

The mean time (standard deviation) from preoperative to postoperative assessments was 13.3 (1.2) months. Mean changes for all measures are reported in Table II. Mean knee effusion-synovitis volume, knee adduction moment impulse and first and second peak knee adduction moments decreased from baseline to 1 year after HTO. Individual patient changes in knee adduction moment impulse and knee effusion-volume are plotted in Fig. 2. Change in knee adduction moment impulse was positively associated with change in knee effusion-synovitis volume [$r = 0.60$ (0.34, 0.78)] (Table III). Simple linear regression suggested an approximate 448 mm^3 (95%CI 241, 656) reduction in knee effusion-synovitis volume for every 1 Nm•s reduction in knee adduction moment impulse (Table III). The change in knee adduction moment impulse explained 36% of the variance in change in knee effusion-synovitis volume over time ($R^2 = 0.36$). Reductions in 1st peak knee adduction moment and 2nd peak knee adduction moment were also associated with a reduction in knee effusion-synovitis volume, explaining 29% and 21% of the variance in change in knee effusion-synovitis volume, respectively (Table III). Additional results are provided in Appendix A (Supplemental Table 1) with knee moment measures normalized to bodyweight and height (%Bw•Ht). In the multivariate model, change in knee adduction moment impulse remained associated with change in knee effusion-synovitis volume (unstandardized $\beta = 466$ [95%CI 239, 693]) while adjusting for the effects of baseline mass, height, age and disease severity (Table IV). Similarly, both the 1st and 2nd peak knee adduction moment were associated with knee effusion-synovitis volume while adjusting for the effects of baseline mass, height, age and disease severity (Appendix A – Supplemental Tables 2 and 3).

Discussion

The present findings suggest an association ($r = 0.60$) exists between the change in medial knee load and the change in knee effusion-synovitis in patients with medial knee OA 1 year after undergoing HTO. These results provide evidence supporting the existence of a dynamic process of mechano-inflammation in knee OA. The findings also support the need for future work investigating inflammation as a potential mediator between

	Full patient sample ($n = 36$)	Larger change in knee load after HTO§ ($n = 18$)	Smaller change in knee load after HTO§ ($n = 18$)
Age, years	53.6 (6.1)	53.2 (6.1)	54.0 (6.2)
Sex, no. (%)			
Male	29 (80.6)	15 (83.3)	14 (77.8)
Female	7 (19.4)	3 (16.7)	4 (22.2)
Body mass index (kg/m^2), mean (SD)	29.8 (4.2)	30.2 (3.7)	29.7 (5.2)
Height, (m)	1.8 (0.1)	1.8 (0.1)	1.7 (0.1)
Mass, (kg)	93.0 (17.6)	97.6 (18.0)	89.4 (17.0)
Mechanical axis angle, degrees*	−6.5 (2.4)	−7.3 (2.7)	−5.7 (1.9)
Kellgren & Lawrence Grade, no. (%)†			
0	–	–	–
1	4 (11.1)	–	4 (22.2)
2	11 (30.6)	5 (27.8)	6 (33.3)
3	21 (58.3)	13 (72.2)	8 (44.4)
4	–	–	–
OARSI Joint Space Narrowing Grade, no. (%)‡			
Medial			
0	–	–	–
1	11 (30.6)	4 (22.2)	7 (38.9)
2	13 (36.1)	5 (27.8)	8 (44.4)
3	12 (33.3)	9 (50.0)	3 (16.7)
Lateral			
0	29 (80.6)	13 (72.2)	16 (88.9)
1	7 (19.4)	5 (27.8)	2 (11.1)
2	–	–	–
3	–	–	–

*Values are reported as means with standard deviations unless otherwise specified.

* A negative mechanical axis value indicates varus alignment.

† The Kellgren & Lawrence (KL) grade evaluates the degree of radiographic osteoarthritis severity. A grade 1 indicates doubtful joint space narrowing and possible osteophytic lipping; grade 2 indicates possible joint space narrowing and definite osteophytes; grade 3 indicates definite joint space narrowing, multiple moderate osteophytes, some sclerosis and possible deformity of the bone contour.

‡ The OARSI Joint Space Narrowing grade, a semi-quantitative subjective scoring system, specifically evaluates the joint space between the femur and the tibia on a scale of 0 (normal joint space) to 3 (total loss of joint space).

§ Change in knee load was represented by the change in knee adduction moment impulse observed 1 year after HTO. For descriptive purposes, the full sample was split based on the median change to derive two exposure groups.

Table I Baseline characteristics (***n*** = 36)

	Baseline (mean ± SD)	1-year (mean ± SD)	Mean change (95%CI)
Knee Effusion-Synovitis Volume (mm^3)	8976.7 ± 8016.9	7120.5 ± 6968.2	−1856.1 (−3829.5, 117.3)
Adduction Moment Impulse (Nm•s)	24.0 ± 6.5	13.9 ± 7.1	−10.1 (−12.7, −7.4)
1st Peak Adduction Moment (Nm)	47.3 ± 11.9	26.3 ± 11.5	−20.9 (−25.6, −16.2)
2nd Peak Adduction Moment (Nm)	48.2 ± 12.3	31.5 ± 17.5	−16.7 (−22.8, −10.6)
Peak Flexion Moment (Nm)	17.0 ± 19.4	23.0 ± 15.7	6.0 (0.5, 11.4)
Peak Extension Moment (Nm)	−37.7 ± 19.7	−37.1 ± 16.7	0.5 (−6.5, 7.6)
Peak External Rotation Moment (Nm)	0.1 ± 0.7	0.6 ± 1.1	0.4 (0.1, 0.8)
Peak Internal Rotation Moment (Nm)	−18.8 ± 5.2	−12.9 ± 5.7	6.0 (4.1, 7.9)
Mechanical Axis Angle (°)	−6.51 ± 2.5	0.62 ± 3.0	7.13 (5.90, 8.47)
Body Mass Index (kg/m^2)	30.0 ± 4.5	30.3 ± 5.2	0.3 (−0.2, 0.7)

Bw = bodyweight, Ht = height, SD = standard deviation, CI = confidence intervals.

Table II Changes in knee effusion-synovitis volume, gait biomechanics, mechanical axis angle and body mass index from baseline to 1-year after HTO (***n*** = 36)

Osteoarthritis and Cartilage

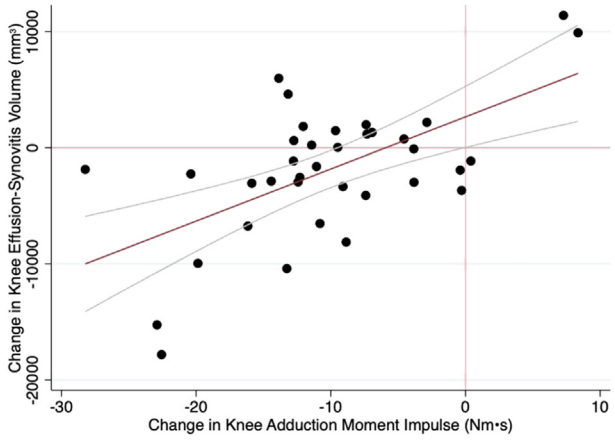

Fig. 2 The association between 1-year changes in knee load (adduction moment impulse) and knee inflammation (effusion-synovitis volume). The line of best fit is black with mean 95% confidence intervals in grey.

Osteoarthritis and Cartilage

mechanopathology and OA progression, as well as a potential mediator between biomechanical interventions and treatment outcomes.

It is important to emphasize that while the present results provide evidence of mechano-inflammation, we cannot be certain that the changes were caused by HTO. It is theoretically possible that the observed changes in load and inflammation were the result of co-interventions, episodic changes in disease status, other unknown sources, or simply regression to the mean. Regardless of their cause, the present results strongly suggest an association exists between changes in joint load and changes in joint inflammation. Our regression analysis suggested 36% of the variance in change in knee effusion-synovitis was explained by the change in knee adduction moment impulse; for each 1-unit reduction in knee adduction moment impulse (Nm•s) there was a 448 mm^3 reduction in knee effusion-synovitis. The regression analyses were also consistent when replacing the knee adduction moment impulse with other surrogate measures of medial compartment load during walking (i.e., first and second peak knee adduction moment; Table III).

The observed magnitudes of change in these surrogate measures of knee load and inflammation should be considered carefully. The mean reductions in knee adduction moment impulse (−10.1 Nm•s) and effusion-synovitis (−1856 mm^3) were large, yet the individual patient responses varied considerably (Fig. 2). The causes of variability in the observed changes should be a focus of future research, including the effects of baseline disease activity and distinct OA phenotypes. Also, as the change in knee adduction moment impulse explained 36% of the variation in change in effusion-synovitis, there is clearly a need and opportunity to identify additional factors influencing the observed change in this form of inflammation.

Most studies investigating knee inflammation as a treatment target have evaluated the change in synovitis as a result of pharmacological interventions. For example, 3 weeks after knee intra-articular corticosteroid injection, the mean decrease in synovial tissue volume was 1071 mm^3, and mean decrease in synovial fluid volume was 853 mm^3, measured using contrast-enhanced MRI[15]. Importantly, patients classified as responders according to the OARSI criteria experienced changes in synovial tissue volume of −1474 mm^3 and synovial fluid volume of −1045 mm^3 and provide some indication of what a clinically meaningful change in synovitis may be. We observed a large mean reduction in effusion-synovitis (1856 mm^3) 1 year after an intervention intended to improve knee biomechanics rather than directly targeting inflammation. However, we did not investigate the association of change in effusion-synovitis with symptoms. Although our data suggest the load-altering effects of HTO may provide benefits in part through a reduction in mechano-inflammation, larger studies are needed to assess the clinical importance and potential mechanisms related to the present findings.

Previous studies that assessed knee synovitis on MRI using semi-quantitative measures after weight change are also relevant. In patients with knee OA having lost ≥20% of their bodyweight with either bariatric surgery or dietary intervention, no difference was observed in synovitis between baseline and 1-year follow-up[36]. Similarly, no difference in synovitis was observed between women

Outcome:	Knee effusion-synovitis volume (mm^3)	
Predictors:	Unstandardized β (95% CI)	Pearson Correlation Coefficient (95% CI)
Adduction moment impulse (Nm•s)	448 (241, 656)	0.60 (0.34, 0.78)
1st Peak Adduction Moment (Nm)	221 (97, 345)	0.53 (0.24, 0.78)
2nd Peak Adduction Moment (Nm)	151 (45, 258)	0.46 (0.15, 0.68)
Peak Flexion Moment (Nm)	−9.9 (−142, 122)	−0.03 (−0.35, 0.30)
Peak Extension Moment (Nm)	28 (−73, 129)	−0.10 (−0.24, 0.41)
Peak External Rotation Moment (Nm)	1040 (−781, 2862)	0.20 (−0.14, 0.49)
Peak Internal Rotation Moment (Nm)	−291 (−652, 70)	−0.27 (−0.55, 0.06)
Mechanical Axis Angle (degrees)	−434 (−924, 56)	−0.30 (−0.57, 0.03)

Abbreviations: CI = confidence intervals; m = meter; N = Newton; s = second.

Table III Association between change in knee moments during walking and change in knee effusion-synovitis volume. Results from simple linear regression analyses are shown (***n*** = 36)

Osteoarthritis and Cartilage

Variable	β coefficient	95% Confidence Intervals
Knee Adduction Impulse (Nm*s)	466	239 to 693
Mass (kg)	19	−109 to 146
Height (cm)	98	−160 to 356
Age	3	−277 to 283
Radiographic severity (Kellgren & Lawrence [KL] grade)		
Grade ≤ 2	Reference	Reference
Grade 3	−466	−4098 to 3137
Intercept	−15937	−59016 to 27,141

Multivariate linear regression analysis.

Table IV Multivariate regression model estimating the association between the change in knee adduction impulse (Nm*s) and the change in knee effusion-synovitis volume (mm^3) while adjusting for patient demographics (Model 1)

Osteoarthritis and Cartilage

with knee OA who's bodyweight either remained stable, or decreased by 10 kg over the course of a year, with a group that gained 10 kg experiencing an increase in synovitis[37]. Also, in patients with knee OA having lost >5% bodyweight over 8 weeks, there was no association between weight loss and changes in synovitis[38]. As weight-loss lessens load on the knee and improves symptoms, it is unclear why changes in synovitis were not observed. Differences in synovitis measurement methods, patient characteristics and the interventions may all contribute to the different results.

To our knowledge, this is the first study to directly investigate the association between measured changes in joint loading and joint inflammation in patients with OA. The present results are consistent, however, with changes in synovial fluid markers of inflammation observed after 6 weeks of knee joint distraction surgery[39]. Both studies observed changes in knee inflammation after interventions that alter knee joint loads and both studies contribute to our understanding of mechano-inflammation in OA. Knee inflammation is likely stimulated in part by mechanical and enzymatic disruption of articular cartilage, releasing cartilage matrix degradation products including enzymatic cleavage fragments into the joint space[40,41]. Matrix degradation products may trigger a cascade of inflammation (e.g., binding to Toll-like receptors on synovial macrophages and fibroblasts), recruitment of inflammatory cells from the periphery, and production of additional inflammatory cytokines and proteases that may perpetuate cartilage degradation[11,42]. Studies that demonstrate reductions in knee inflammation after mechanical interventions suggest these mechano-inflammatory processes can be modified and may help to inform the development and delivery of clinical interventions for OA. This could include the opportunity to define biological mechanisms of mechano-inflammation along with the discovery of new, more specific treatment targets[25].

Limitations in this study include the lack of other MRI markers of knee inflammation, such as bone marrow lesions and other regions of interest such as the infra-patellar fat pad ("Hoffa-synovitis"). Contrast-enhanced MRI methods may have provided additional information with respect to synovial thickening and vascularization, which may have provided an even better assessment of the inflammatory state of synovial tissue[43] and its association with joint loading. Repeated manual segmentation of MRI features is the current gold standard for quantitative MRI assessment in knee joints but can be subject to reader biases and measurement error. The validated MRI blinding method[26] and very high intra-rater and inter-rater reliability coefficients suggest we limited those possibilities. The external knee moments during walking are surrogate measures of the actual loads on the joint and may not detect the true extent of biomechanical changes. Consideration of those limitations should be weighed against the substantial association observed between the present reliable and valid surrogate measures of knee load and knee inflammation. The present sample included mostly males with medial compartment knee OA; it is unclear whether the observed association differs between males and females or with other forms of OA. While the present results provide compelling evidence supporting the existence of mechano-inflammation in patients with knee OA, and that this may be a modifiable process, the clinical importance of the observed

association between changes in knee loading and effusion-synovitis requires future research.

Contributions

Conception and design: Atkinson, Birmingham, Schulz, Appleton, Giffin.

Collection and assembly of data: Atkinson, Birmingham, Primeau, Schulz, Appleton, Pritchett, Giffin.

Analysis and interpretation of the data: Atkinson, Birmingham, Primeau, Schulz, Appleton, Pritchett, Giffin.

Drafting and approval of the article: Atkinson, Birmingham, Primeau, Schulz, Appleton, Pritchett, Giffin.

Competing interests

None.

Funding

This study was supported in part by the Canada Research Chairs Program (Birmingham), the Canadian Institutes of Health Research, the Arthritis Society of Canada, the Canada First Research Excellence Funds BrainsCAN program, and the Western University Bone & Joint Institute Collaborative Training Program in Musculoskeletal Health Research (Atkinson, Primeau, Schulz). Funding agencies had no involvement in data analysis or interpretation.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2020.11.007.

References

1. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012;64(6):1697–707, https://doi.org/10.1002/art.34453.
2. Vos T, Allen C, Arora M, Barber RM, Brown A, Carter A, *et al*. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1545–602, https://doi.org/10.1016/S0140-6736(16)31678-6.
3. Felson DT. Osteoarthritis as a disease of mechanics. Osteoarthritis Cartilage 2013;21(1):10–5, https://doi.org/10.1016/j.joca.2012.09.012.
4. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis Lancet 2019;393(10182):1745–59, https://doi.org/10.1016/S0140-6736(19)30417-9.
5. Benito MJ, Veale DJ, FitzGerald O, Van Den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. Ann Rheum Dis 2005;64(9):1263–7, https://doi.org/10.1136/ard.2004.025270.
6. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 2010;6(11):625–35, https://doi.org/10.1038/nrrheum.2010.159.
7. Kay J, Bardin T. Joint effusion - an overview | ScienceDirect topics. In: Rheumatology 2015:1420–31, https://www.sciencedirect.com/topics/medicine-and-dentistry/joint-effusion. Accessed February 26, 2020.
8. Felson DT, Niu J, Neogi T, Goggis J, Nevitt MC, Roemer F, *et al*. Synovitis and the risk of knee osteoarthritis: the MOST Study. Osteoarthritis Cartilage 2016;24(3):458–64, https://doi.org/10.1016/j.joca.2015.09.013.
9. Atukorala I, Kwoh CK, Guermazi A, Roemer FW, Boudreau RM, Hannon MJ, *et al*. Synovitis in knee osteoarthritis: a precursor of disease? Ann Rheum Dis 2016;75(2):390–5, https://doi.org/10.1136/annrheumdis-2014-205894.
10. Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis - results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis Cartilage 2005;13(5):361–7, https://doi.org/10.1016/j.joca.2005.01.005.
11. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, *et al*. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis July 2011;70(10):1804–9, http://ard.bmj.com/content/early/2011/07/25/ard.2011.150243.abstract.
12. Yusup A, Kaneko H, Liu L, Ning L, Sadatsuki R, Hada S, *et al*. Bone marrow lesions, subchondral bone cysts and subchondral bone attrition are associated with histological synovitis in patients with end-stage knee osteoarthritis: a cross-sectional study. Osteoarthritis Cartilage 2015;23(11):1858–64, https://doi.org/10.1016/j.joca.2015.05.017.
13. Wang X, Jin X, Han W, Cao Y, Halliday A, Blizzard L, *et al*. Cross-sectional and longitudinal associations between knee joint effusion synovitis and knee pain in older adults. J Rheumatol 2016;43(1):121–30, https://doi.org/10.3899/jrheum.150355.
14. Neogi T, Guermazi A, Roemer F, Nevitt MC, Scholz J, Arendt-Nielsen L, *et al*. Association of joint inflammation with pain sensitization in knee osteoarthritis: the multicenter osteoarthritis study. Arthritis Rheum 2016;68(3):654–61, https://doi.org/10.1002/art.39488.
15. O'Neill TW, Parkes MJ, Maricar N, Marjanovic EJ, Hodgson R, Gait AD, *et al*. Synovial tissue volume: a treatment target in knee osteoarthritis (OA). Ann Rheum Dis 2016, https://doi.org/10.1136/annrheumdis-2014-206927.
16. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. J Am Med Assoc 2001;286(2):188–95, https://doi.org/10.1001/jama.286.2.188.
17. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, *et al*. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann Rheum Dis 2010;69(11):1940–5, https://doi.org/10.1136/ard.2010.129742.
18. Tanamas S, Hanna FS, Cicuttini FM, Wluka AE, Berry P, Urquhart DM. Does knee malalignment increase the risk of development and progression of knee osteoarthritis? A systematic review. Arthritis Care Res 2009;61(4):459–67, https://doi.org/10.1002/art.24336.
19. Bennell KL, Bowles KA, Wang Y, Cicuttini F, Davies-Tuck M, Hinman RS. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann Rheum Dis 2011;70(10):1770–4, https://doi.org/10.1136/ard.2010.147082.
20. Chang AH, Moisio KC, Chmiel JS, Eckstein F, Guermazi A, Prasad PV, *et al*. External knee adduction and flexion moments during gait and medial tibiofemoral disease progression in knee osteoarthritis. Osteoarthritis Cartilage 2015;23(7):1099–106, https://doi.org/10.1016/j.joca.2015.02.005.
21. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5year cartilage changes in patients with medial knee osteoarthritis. Osteoarthritis Cartilage 2014;22(11):1833–9, https://doi.org/10.1016/j.joca.2014.08.009.
22. Birmingham TB, Marriott KA, Leitch KM, Moyer RF, Lorbergs AL, Walton DM, *et al*. Association between knee load and pain: within-patient, between-knees, case–control study

in patients with knee osteoarthritis. Arthritis Care Res 2019;71(5):647–50, https://doi.org/10.1002/acr.23704.
23. Marriott KA, Birmingham TB, Leitch KM, Pinto R, Giffin JR. Strong independent associations between gait biomechanics and pain in patients with knee osteoarthritis. J Biomech 2019;94:123–9, https://doi.org/10.1016/j.jbiomech.2019.07.015.
24. Birmingham TB, Moyer R, Leitch K, Chesworth B, Bryant D, Willits K, *et al*. Changes in biomechanical risk factors for knee osteoarthritis and their association with 5-year clinically important improvement after limb realignment surgery. Osteoarthritis Cartilage 2017;25(12):1999–2006, https://doi.org/10.1016/j.joca.2017.08.017.
25. Guilak F, Fermor B, Keefe FJ, Kraus VB, Olson SA, Pisetsky DS, *et al*. The role of biomechanics and inflammation in cartilage injury and repair. Clin Orthop Relat Res 2004;423(423):17–26, https://doi.org/10.1097/01.blo.0000131233.83640.91.
26. Moyer R, Birmingham T, Eckstein F, Wirth W, Maschek S, Chronik B, *et al*. Validation of a novel blinding method for measuring postoperative knee articular cartilage using magnetic resonance imaging. Magn Reson Mater Physics, Biol Med. 2019;32(6):693–702, https://doi.org/10.1007/s10334-019-00766-y.
27. Hulley S, Cummings S, Browner W, Grady D, Newman T. Designing Clinical Research: An Epidemiological Approach. 4th edn. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 201379. Appendix 6C.
28. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29(8):1039–49, https://doi.org/10.1002/art.1780290816.
29. Specogna A, Birmingham T, DaSilva J, Milner J, Kerr J, Hunt M, *et al*. Reliability of lower limb frontal plane alignment measurements using plain radiographs and digitized images. J Knee Surg 2010;17:203–10, https://doi.org/10.1055/s-0030-1248222. 04.
30. Fowler PJ, Tan JL, Brown GA. Medial opening wedge high tibial osteotomy: how I do it. Operat Tech Sports Med 2012;20(1):87–92, https://doi.org/10.1053/j.otsm.2012.03.010.
31. Birmingham TB, Hunt MA, Jones IC, Jenkyn TR, Giffin JR. Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. Arthritis Care Res 2007;57(6):1012–7, https://doi.org/10.1002/art.22899.
32. Leitch KM, Birmingham TB, Dunning CE, Robert Giffin J. Changes in valgus and varus alignment neutralize aberrant frontal plane knee moments in patients with unicompartmental knee osteoarthritis. J Biomech 2013;46(7):1408–12, https://doi.org/10.1016/j.jbiomech.2013.01.024.
33. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, *et al*. 3D slicer as an image computing platform for the quantitative imaging network. Magn Reson Imaging 2012;30(9):1323–41, https://doi.org/10.1016/j.mri.2012.05.001.
34. Crema MD, Roemer FW, Li L, Alexander RC, Chessell IP, Dudley AD, *et al*. Comparison between semiquantitative and quantitative methods for the assessment of knee synovitis in osteoarthritis using non-enhanced and gadolinium-enhanced MRI. Osteoarthritis Cartilage 2017;25(2):267–71, https://doi.org/10.1016/j.joca.2016.09.016.
35. Wang X, Cicuttini F, Jin X, Wluka AE, Han W, Zhu Z, *et al*. Knee effusion-synovitis volume measurement and effects of vitamin D supplementation in patients with knee osteoarthritis. Osteoarthritis Cartilage 2017;25(8):1304–12, https://doi.org/10.1016/j.joca.2017.02.804.
36. Jafarzadeh SR, Clancy M, Li JS, Apovian CM, Guermazi A, Eckstein F, *et al*. Changes in the structural features of osteoarthritis in a year of weight loss. Osteoarthritis Cartilage 2018;26(6):775–82, https://doi.org/10.1016/j.joca.2018.03.003.
37. Landsmeer MLA, de Vos BC, van der Plas P, van Middelkoop M, Vroegindeweij D, Bindels PJE, *et al*. Effect of weight change on progression of knee OA structural features assessed by MRI in overweight and obese women. Osteoarthritis Cartilage 2018;26(12):1666–74, https://doi.org/10.1016/j.joca.2018.08.006.
38. Daugaard CL, Henriksen M, Riis RGC, Bandak E, Nybing JD, Hangaard S, *et al*. The impact of a significant weight loss on inflammation assessed on DCE-MRI and static MRI in knee osteoarthritis: a prospective cohort study. Osteoarthritis Cartilage March 2020, https://doi.org/10.1016/j.joca.2020.02.837.
39. Watt FE, Hamid B, Garriga C, Judge A, Hrusecka R, Custers RJH, *et al*. The molecular profile of synovial fluid changes upon joint distraction and is associated with clinical response in knee osteoarthritis. Osteoarthritis Cartilage 2020;28(3):324–33, https://doi.org/10.1016/j.joca.2019.12.005.
40. Fernandez-Madrid F, Karvonen RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected by MR imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. Magn Reson Imaging 1995;13(2):177–83, https://doi.org/10.1016/0730-725X(94)00119-N.
41. Roemer FW, Felson DT, Yang T, Niu J, Crema MD, Englund M, *et al*. The association between meniscal damage of the posterior horns and localized posterior synovitis detected on T1-weighted contrast-enhanced MRI-The MOST study. Semin Arthritis Rheum 2013;42(6):573–81, https://doi.org/10.1016/j.semarthrit.2012.10.005.
42. Wang X, Blizzard L, Halliday A, Han W, Jin X, Cicuttini F, *et al*. Association between MRI-detected knee joint regional effusion-synovitis and structural changes in older adults: a cohort study. Ann Rheum Dis 2016;75(3):519–25, https://doi.org/10.1136/annrheumdis-2014-206676.
43. Perry TA, Gait A, O'Neill TW, Parkes MJ, Hodgson R, Callaghan MJ, *et al*. Measurement of synovial tissue volume in knee osteoarthritis using a semiautomated MRI-based quantitative approach. Magn Reson Med 2019;81(5):3056–64, https://doi.org/10.1002/mrm.27633.