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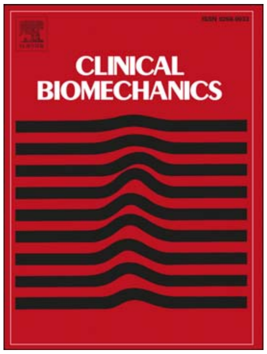

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Mechanisms underpinning longitudinal increases in the knee adduction moment following arthroscopic partial meniscectomy

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Abstract

Background

Knee osteoarthritis is common following arthroscopic partial meniscectomy and a higher external peak knee adduction moment is believed to be a contributor. The peak knee adduction moment has been shown to increase over 2 years (from 3-months post-arthroscopic partial meniscectomy surgery). The aim of this study was to evaluate mechanisms underpinning the increase in peak knee adduction moment over 2 years observed in people 3-months following arthroscopic partial meniscectomy.

Methods

Sixty-six participants with medial arthroscopic partial meniscectomy were assessed at baseline and again 2 years later. Parameters were evaluated at time of peak knee adduction moment as participants walked barefoot at their self-selected normal and fast pace for both time points.

Findings

For normal pace walking, an increase in frontal plane ground reaction force-to-knee lever arm accounted for 30% of the increase in peak knee adduction moment (B = 0.806 [CI 95% 0.501 to 1.110], $P < 0.001$). For fast pace walking, an increase in the frontal plane ground reaction force magnitude accounted for 21% of the increase in peak knee adduction moment (B = 2.343 [CI 95% 1.219 to 3.468], $P < 0.001$); with an increase in tibia varus angle accounting for a further 15% (B = 0.310 [CI 95% 0.145 to 0.474], $P < 0.001$).

Interpretation

Our data suggest that an increase in lever arm and increase in frontal plane ground reaction force magnitude are contributors to the increased knee adduction moment observed over time in people following arthroscopic partial meniscectomy.

Keywords: meniscectomy, knee joint load, mechanism, gait

1.1 Introduction

Knee osteoarthritis is considered a mechanical disease, whereby abnormal biomechanical loading is believed to cause a pathological response in susceptible joint tissues. The external knee adduction moment (KAM) is frequently used as an indicator of medial-to-lateral knee joint load distribution during gait [1, 2]. People following arthroscopic partial meniscectomy (APM), are at risk of developing tibiofemoral knee osteoarthritis [3], and experience a higher peak KAM during gait than healthy controls [4, 5]. Importantly, evidence suggests the KAM is a risk factor for structural disease in people with established knee osteoarthritis [6, 7]. Furthermore, we have found that in people 3-months post-APM, the peak KAM increased during gait by approximately 9% over the subsequent 2years [4]. Therefore, given the association between structural change following APM and high KAM, and its increase over time, the peak KAM is a logical target for interventions aiming to reduce knee joint load and ultimately delay or prevent the development or progression of knee osteoarthritis often observed in this population. It is currently unknown why the peak KAM increases over time in people following APM.

The KAM is predominantly considered a product of the magnitude of the frontal plane ground reaction force (GRF) and the perpendicular distance of the GRF vector from the knee joint center to the GRF (knee-GRF lever arm). Studies have found associations between static frontal plane knee alignment and peak KAM magnitude [8, 9], where increased varus malalignment is thought to increase the knee-GRF lever arm and consequently, the KAM during gait. Moreover, dynamic frontal plane alignment of the knee and the tibia has been shown to account for 46% and 61% of the variance in peak KAM, respectively [10, 11]. Although dynamic frontal plane alignment has not yet been studied in people following APM, we and others have observed that individuals following medial APM adopt a greater static varus position over time [4, 12]. Given that static frontal plane knee alignment measures are strongly correlated to dynamic frontal plane knee alignment [13], these patients may increase dynamic frontal plane knee varus malalignment during gait over 2-years, that could partially explain an increased peak KAM over time.

It is also plausible that the magnitude, origin (center of pressure position) and/or orientation of the frontal plane GRF vector at the time of peak KAM may change over time, and thus partially explain the increased peak KAM. Muscles (including the quadriceps and hamstrings) assist in controlling the position, velocity and acceleration of the body center mass during gait [14], which in turn influences the frontal plane GRF magnitude and orientation, and ultimately the KAM. Patients following APM exhibit changes in knee muscle activity patterns during functional tasks [15, 16], maximal knee muscle strength [4, 5], and proprioception [17, 18]; each of these, alone or in combination, may contribute to alterations in vertical, anterior-posterior and medio-lateral accelerations of the center of mass.

Understanding the mechanisms that underpin the increase in peak KAM over time will assist with developing and refining therapeutic interventions aimed at reducing the peak KAM in people following APM. Therefore, the purpose of this study in people assessed 3 months following medial APM (baseline) and 2-years later (follow-up) was to evaluate how potentially modifiable frontal plane postures and movements are associated with an increase in peak KAM over time..

2. Methods

2.1 Participants

This is a further analysis of a 2-year longitudinal cohort study [4]. Individuals between 30-50 years old with an isolated medial APM performed 3 months previously were recruited. These participants have been previously described [4]. Exclusion criteria were any of the following: lateral meniscal resection; greater than one third of medial meniscus resected; >2 tibiofemoral cartilage lesions; a single tibiofemoral cartilage lesion > approx 10mm in diameter or exceeding half of cartilage thickness; previous knee or lower limb surgery (other than current APM); history of knee pain (other than that leading to APM); clinical or structural signs of OA; post-operative complications; cardiac, circulatory or neuromuscular conditions; diabetes; stroke; multiple sclerosis; contraindication to MRI. The University of Melbourne Human Research Ethics Committee approved the study and written informed consent was provided by each participant.

2.2 Gait analysis

Kinematic data (120Hz) were acquired using a Vicon motion capture system (Vicon, Oxford, UK) with eight M2/MX CMOS cameras (1280 x 1024) while kinetic data (1080Hz) were captured in synchrony using two 0R6-6-2000 force plates and one BP-600-900 force plate (Advanced Mechanical Technology, Watertown Massachusetts, USA). A custom seven-segment lower limb direct kinematics and inverse dynamics model written in BodyBuilder (Vicon, Oxford, UK) was used to estimate lower limb joint kinematics and kinetics [19]. Following the application of reflective markers, participants performed three functional hip and knee movement trials, that were used to define hip joint centers and knee joint flexion/extension axes in Matlab (Mathworks, Massachusetts) [19]. Participants then performed five barefoot walking trials at a self-selected normal and fast pace described as a 'natural and comfortable pace' and a pace 'you would walk in a hurry' respectively. The peak KAM in the first half of stance, was expressed as an external moment and applied to the distal segment. The peak KAM was measured from each trial, averaged, and normalised to body size (Nm/(BWxHT)%). The test-retest reliability for the external frontal plane moment curve during walking has previously been reported as 0.75 (curve coefficient of multiple determination, r^2) [19]. Walking speed was measured by two photoelectric beams as participants walked along the 10-m walkway.

The variables of interest for this study are defined in Table 1. The knee-GRF lever arm, frontal plane GRF angle, knee varus-valgus angle, frontal plane tibia angle, frontal plane femur angle, center of pressure offset, lateral trunk lean, frontal plane knee-pelvis distance, and foot progression angle were determined using a custom-written Body Builder program (Vicon, Oxford, UK). For each walking pace, the variables that occurred at time of peak KAM were averaged over five trials. The changes in variables were determined by subtracting the baseline (3 months post-APM) from the follow-up scores (2 years post-APM), such that a negative score represented a reduction at follow-up.

2.3 Statistical analysis

Statistical analyses were performed using SPSS (SPSS Inc. Chicago, Illinois, USA) and an alpha level of 0.05. Analyses were performed separately for normal and fast pace walking. Using a similar approach to our previous work evaluating mechanisms underpinning change in peak KAM with lateral wedge orthotics [23], we first evaluated change in variables (Table 1) using paired t-tests. For those variables that changed significantly, we examined their relationship with change in the peak KAM using Pearson correlations. Change variables that were significantly associated with change in peak KAM were then entered as independent variables into a stepwise regression model (probability of entry = 0.05 and probability of removal = 0.10), with change in peak KAM as the dependent variable.

Finally, in the event where change in knee-GRF lever arm was a significant predictor of change in peak KAM, further analysis was performed to explore the mechanisms underpinning the change in knee-GRF lever arm. Pearson correlations were used to determine the relationship between change in knee-GRF lever arm and change in hip adduction angle, change in knee flexion angle, change in tibia angle, change in femur angle, change in varus-valgus angle, change in center of pressure offset, change in frontal plane GRF angle and change in foot progression angle. These variables were selected as the knee-GRF lever arm can be altered by position of the knee joint center and/or orientation and position of the frontal plane GRF vector. Variables that demonstrated a significant relationship were entered into a stepwise regression model with change in knee-GRF lever arm as dependent variable (probability of entry = 0.05 and probability of removal = 0.10).

3. Results

Sixty-six of the 82 (80%) participants returned at follow-up with 65 participants included in normal pace walking analyses and 64 included in fast pace analyses. The average time to follow-up was 2.06 years (SD 0.15, range 1.8-2.4). The study sample was middle-aged (mean 41.3 yrs SD 5.4yrs), largely male (n=56; 86%), and overweight (mean 27.28 kg/m^2 SD 4.23) according to the World Health Organization standards. As previously reported [4], a significant increase in peak KAM was observed over a 2 year period for normal and fast pace walking (Table 2) while no differences in walking speed were observed (Table 2).

Generally there were changes towards larger lateral (varus) frontal plane deviations over time (Table 2). For normal pace walking, the knee-GRF lever arm and frontal plane GRF magnitude significantly increased over time. There was also a reduction in toe-out angle for normal pace walking. For fast pace walking, a more varus-aligned tibia, an increased knee-GRF lever arm, a more valgus-aligned femur, reduced lateral trunk lean, and an increased frontal plane GRF were observed at 2 years relative to baseline.

For normal pace walking, change in knee-GRF lever arm and change in frontal plane GRF magnitude were positively correlated to change in peak KAM (Table 3) and were significant predictors in a stepwise linear regression, together explaining 39% of the increase in peak KAM in the final model (Table 4). The direction of these relationships were such that an increase in knee-GRF lever arm and increase in frontal plane GRF magnitude were associated with an increase in peak KAM.

A number of variables were correlated to the change in knee-GRF lever arm during normal pace walking (Table 5). However, stepwise regression analysis demonstrated that only the change in frontal plane tibia angle significantly predicted change in knee-GRF lever arm length ($B = 0.299$ [CI 95% 0.218 to 0.381], $p < 0.001$), accounting for 46 % of the variance.

For fast pace walking, change in knee-GRF lever arm, change in frontal plane GRF magnitude and change in frontal plane tibia alignment were positively correlated to change in peak KAM (Table 3). In stepwise regression, change in frontal plane GRF and change in tibia frontal plane alignment were significant predictors of the change in peak KAM; together they explained 37% of the variance in the final model (Table 4). The direction of these relationships was such that an increase in frontal plane GRF magnitude and more varus malalignment of the tibia were associated with an increase in peak KAM.

4. Discussion

The key finding of this study is that greater frontal plane tibia varus alignment at the time of peak KAM emerged as an important variable underpinning increases in peak KAM at both walking paces. This is despite the primary mechanism of action explaining the increase in peak KAM differing for normal and fast pace walking. Improving our understanding of which potentially modifiable gait parameters are associated with increases in KAM will aid consideration and design of therapeutic interventions targeted towards reducing the peak KAM, in an effort to delay or prevent the development and/or progression of knee osteoarthritis in these middle-aged adults.

Of the variables evaluated in the present study, the increase in knee-GRF lever arm was the primary predictor associated with the increase in peak KAM during normal pace walking. Moreover, our results suggest that an increased dynamic varus in the frontal plane tibial alignment is the major factor contributing to the change in knee-GRF lever arm. Thus it seems that the increased knee-GRF lever arm results primarily from changes in the position of the knee joint center (greater varus), rather than changes in frontal plane orientation and location of the GRF vector. Interestingly no significant change in knee joint varus angle or frontal plane GRF location and orientation was observed over time.

Increased dynamic frontal plane tibia varus malalignment was a significant predictor of the increase in peak KAM in fast walking (only). The final regression model for fast pace walking suggests that for every 1° increase in dynamic varus angle of the tibia the peak KAM increases by 0.31 Nm/(BWxHT)%. As patients following APM develop a more pronounced varus position dynamically (Table 2) and statically [4, 12] over time, these findings suggest dynamic tibia malalignment may be a logical target to minimize the increase in peak KAM over time following

APM. The results suggest that interventions could prevent the increase in peak KAM (Table 2) by reducing dynamic tibia varus orientation by even 1°. However, it is important to acknowledge that the amount of peak KAM change required to prevent/delay disease onset and/or progression after APM remains unknown. As such, the amount of change in dynamic tibia orientation required to reduce the peak KAM by a clinically meaningful magnitude also remains unknown. No other study has evaluated longitudinal changes in frontal plane mechanics; however our results add to recent evidence highlighting the potent influence of lower limb alignment on the distribution of medial knee joint load during gait [20, 21].

Although it is unclear why dynamic tibia varus malalignment becomes more pronounced as time elapses from APM surgery, it may be related to the partial removal of the medial meniscus. Overall our data collectively suggest that minimising the increase in knee-GRF lever arm by targeting the increasing tibia varus malalignment is likely to reduce the increase in peak KAM. Possible strategies to reduce the knee-GRF lever arm [22] include interventions related to footwear [23-25], gait re-training strategies such as medial thrust [26-28] and lateral trunk lean [29], valgus knee bracing [30] and neuromuscular exercise [31]. However, none of the aforementioned interventions have yet been reported in an APM population.

Change in frontal plane GRF magnitude also accounted for change in peak KAM during normal and fast pace walking, 7% and 22% respectively. Walking speed is known to affect GRF magnitude [32]. Although walking speed did not differ between baseline and follow-up assessments for either walking pace, we conducted post-hoc analyses to explore the effects of change in walking speed on change in frontal plane GRF. For normal pace walking we found that change in walking speed correlated with change in frontal plane GRF magnitude ($r=0.649$, $p<0.001$), accounting for 42% of the variance in the change in frontal plane GRF over time.

Therefore, a considerable proportion of the change in frontal plane GRF during normal pace walking can be explained by change in walking speed. However, for fast pace walking we found no relationship between change in walking speed and change in frontal plane GRF magnitude ($r=0.211$, $p=0.094$), suggesting that other factors contributed to the increase in frontal plane GRF observed. Neuromuscular changes reported following APM could possibly alter the control of the vertical and medial/lateral center of mass accelerations during fast pace walking. These alterations would potentially in turn affect the magnitude and orientation of the vertical and medial-lateral GRF components that result in the frontal plane GRF. While not directly related to the frontal plane GRF, we have recently found no evidence to support an association between maximal knee muscle strength 3 months after APM and change in KAM over the subsequent 2 years [33].It remains unclear which particular measurable aspects of muscle function control acceleration of the center of mass in this context, and this could be explored in future research.

This is the first study, to our knowledge, to explore mechanisms underpinning increases in peak KAM over time, in any population. While our findings provide insight into the mechanisms explaining increases in peak KAM, our regression models only explained 37-39% of the increase in peak KAM. Possible explanations for the unexplained variance relate to how the KAM is quantified. The KAM magnitude can be influenced by numerous adjustments as reflected by the list of possible variables quantified in the current study (Table 1). Therefore it is likely that different individuals adjust their gait patterns over time in various ways, such that more consistent / homogenous changes in biomechanical variables assessed in this study were not evident. This is also supported by the fact that changes in the frontal plane biomechanics, although significant, were notably small. Furthermore, it is important to acknowledge that although the KAM is predominantly a product of the knee-GRF lever arm and frontal plane GRF magnitude, it was calculated using inverse dynamics. Therefore, as segment accelerations and inertial properties of the lower leg contribute to the calculation of the external knee moment [34], changes in these parameters may also partially explain the remaining unexplained variance in the change of peak KAM over time.

In conclusion, this is the first study to evaluate mechanisms underpinning change in peak KAM over time, in a relatively large homogenous cohort who are at increased risk to develop/progress early signs of knee osteoarthritis. The large cohort enabled us to evaluate a number of frontal plane biomechanical variables using stepwise regression. Our findings suggest that the increases in peak KAM over time following APM could possibly be addressed by targeting the increased varus malalignment of the tibia. Interventions such as footwear, knee bracing, exercise and gait retraining may be appropriate in these patients to reduce varus tibial malalignment and should be evaluated. Furthermore research is needed to better understand which aspects of muscle function contribute to alterations in frontal plane GRF so that interventions may reduce the increases observed.

Conflict of interest

None.

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REFERENCES

1. Zhao, D., Banks, S.A., Mitchell, K.H., D'Lima, D.D., Colwell, C.W., Jr., Fregly, B.J., 2007. Correlation between the knee adduction torque and medial contact force for a variety of gait patterns. J. Orthop. Res. 25, 789-97.
2. Birmingham, T.B., Hunt, M.A., Jones, I.C., Jenkyn, T.R., Giffin, J.R., 2007. Test-retest reliability of the peak knee adduction moment during walking in patients with medial compartment knee osteoarthritis. Arthritis Rheum. 57, 1012-7.
3. Lohmander, L.S., Englund, P.M., Dahl, L.L., Roos, E.M., 2007. The long-term consequence of anterior cruciate ligament and meniscus injuries:osteoarthritis. Am. J. Sports Med. 35, 1756-69.
4. Hall M, Wrigley, T.V., Metcalf, B.R., Hinman, R.S., Dempsey, A.R., Mills, P.M., Cicuttini, F.M., Lloyd, D.G., Bennell K.L., 2013. A longitudinal study of strength and gait after arthroscopic partial meniscectomy. Med. Sci. Sports Exerc. 45, 2036-43.
5. Sturnieks, D.L., Besier, T.F., Mills, P.M., Ackland, T.R., Maguire, K.F., Stachowiak, G.W., Podsiadlo, P. Lloyd, D.G., 2008. Knee joint biomechanics following arthroscopic partial meniscectomy. J. Orthop. Res. 26, 1075-80.
6. Bennell, K.L., Bowles, K.A., Wang, Y., Cicuttini, F., Davies-Tuck, M., Hinman, R.S., 2011. Higher dynamic medial knee load predicts greater cartilage loss over 12 months in medial knee osteoarthritis. Ann. Rheum. Dis. 70, 1770-4.
7. Miyazaki, T., Wada, M., Kawahara, H., Sato, M., Baba, H., Shimada, S., 2002. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann. Rheum. Dis. 61, 617-22.
8. Barrios, J.A., Higginson, J.S., Royer, T.D., Davis, I.S., 2009. Static and dynamic correlates of the knee adduction moment in healthy knees ranging from normal to varus-aligned. Clin. Biomech. 24, 850-4.
9. Andrews, M., Noyes, F.R., Hewett, T.E., Andriacchi, T.P., 1996. Lower limb alignment and foot angle are related to stance phase knee adduction in normal subjects: a critical analysis of the reliability of gait analysis data. J. Orthop. Res. 14, 289-95.
10. Barrios, J.A., Royer, T.D., Davis, I.S., 2012. Dynamic versus radiographic alignment in relation to medial knee loading in symptomatic osteoarthritis. J. Appl. Biomech. 28, 551-9.
11. Foroughi, N., Smith, R.M., Lange, A.K., Baker, M.K., Fiatarone Singh, M.A., Vanwanseele, B., 2010. Dynamic alignment and its association with knee adduction moment in medial knee osteoarthritis. Knee. 17, 210-6.
12. Yoon, K.H., Lee, S.H., Bae, D.K., Park, S.Y., Oh, H., 2013. Does varus alignment increase after medial meniscectomy? Knee Surg. Sports Traumatol. Arthrosc. 21, 2131-6.
13. Hunt, M.A., Birmingham, T.B., Jenkyn, T.R., Giffin, J.R., Jones, I.C., 2008. Measures of frontal plane lower limb alignment obtained from static radiographs and dynamic gait analysis. Gait Posture. 27, 635-40.
14. Pandy, M.G., Lin, Y.C., Kim, H.J., 2010. Muscle coordination of mediolateral balance in normal walking. J. Biomech. 43, 2055-64.
15. Sturnieks, D.L., Besier, T.F., Lloyd, D.G., 2011. Muscle activations to stabilize the knee following arthroscopic partial meniscectomy. Clin. Biomech. 26, 292-7.
16. Thorlund, J.B., Damgaard, J., Roos, E.M., Aagaard, P., 2012. Neuromuscular function during a forward lunge in meniscectomized patients. Med. Sci. Sports Exerc. 44, 1358-65.

17. Al-Dadah, O., Shepstone, L., Donell, S.T., 2011. Proprioception following partial meniscectomy in stable knees. Knee Surg. Sports Traumatol. Arthrosc. 19, 207-13.
18. Malliou, P., Gioftsidou, A., Pafis, G., Rokka, S., Kofotolis, N., Mavromoustakos, S., Godolias, G., 2012. Proprioception and functional deficits of partial meniscectomized knees. Eur. J. Phys. Rehabil. Med.48, 231-6.
19. Besier, T.F., Sturnieks, D.L., Alderson, J.A., Lloyd, D.G., 2003. Repeatability of gait data using a functional hip joint centre and a mean helical knee axis. J. Biomech. 36, 1159-68.
20. Leitch, K.M., Birmingham, T.B., Dunning, C.E., Giffin, J.R., 2013. Changes in valgus and varus alignment neutralize aberrant frontal plane knee moments in patients with unicompartmental knee osteoarthritis. J. Biomech. 46, 1408-12.
21. Halder, A., Kutzner, I., Graichen, F., Heinlein, B., Beier, A., Bergmann, G., 2012. Influence of limb alignment on mediolateral loading in total knee replacement: in vivo measurements in five patients. J. Bone Joint Surg. Am. 94, 1023-9.
22. Simic, M., Hinman, R.S., Wrigley, T.V., Bennell, K.L., Hunt, M.A., 2011. Gait modification strategies for altering medial knee joint load: a systematic review. Arthritis Care Res. 63, 405-26.
23. Hinman, R.S., Bowles, K.A., Metcalf, B.B., Wrigley, T.V., Bennell, K.L, 2012. Lateral wedge insoles for medial knee osteoarthritis: effects on lower limb frontal plane biomechanics. Clin. Biomech.27,27-33.
24. Kerrigan, D.C., Lelas, J.L., Goggins, J., Merriman, G.J., Kaplan, R.J., Felson, D.T., 2002. Effectiveness of a lateral-wedge insole on knee varus torque in patients with knee osteoarthritis. Arch. Phys. Med. Rehabil. 83, 889-93.
25. Fisher, D.S., Dyrby, C.O., Mundermann, A., Morag, E., Andriacchi, T.P., 2007. In healthy subjects without knee osteoarthritis, the peak knee adduction moment influences the acute effect of shoe interventions designed to reduce medial compartment knee load. J. Orthop. Res. 25, 540-6.
26. Fregly, B.J., 2009. Design of optimal treatments for neuromusculoskeletal disorders using patient-specific multibody dynamic models. Int. J. Comput. Vis. Biomech. 2, 145-55.
27. Fregly, B.J., D'Lima, D.D., Colwell, C.W., Jr., 2009. Effective gait patterns for offloading the medial compartment of the knee. J. Orthop. Res. 27, 1016-21.
28. Fregly, B.J., Reinbolt, J.A., Rooney, K.L., Mitchell, K.H., Chmielewski, T.L., 2007. Design of patient-specific gait modifications for knee osteoarthritis rehabilitation. IEEE Trans. Biomed. Eng. 54, 1687-95.
29. Mundermann, A., Asay, J.L., Mundermann, L., Andriacchi, T.P., 2008. Implications of increased medio-lateral trunk sway for ambulatory mechanics. J. Biomech. 41, 165-70.
30. Pollo, F.E., Otis, J.C., Backus, S.I., Warren, R.F., Wickiewicz, T.L., 2002. Reduction of medial compartment loads with valgus bracing of the osteoarthritic knee. Am. J. Sports Med. 30, 414-21.
31. Bennell, K.L., Egerton, T., Wrigley, T.V., Hodges, P.W., Hunt, M., Roos, E.M., Kyriakides, M., Metcalf, B., Forbes, A., Ageberg, E., Hinman, R.S. 2011. et al. Comparison of neuromuscular and quadriceps strengthening exercise in the treatment of varus malaligned knees with medial knee osteoarthritis: a randomised controlled trial protocol. BMC Musculoskelet. Disord. 12, 276-88.
32. Mundermann, A., Dyrby, C.O., Hurwitz, D.E., Sharma, L., Andriacchi, T.P., 2004. Potential strategies to reduce medial compartment loading in patients with knee osteoarthritis of varying severity: reduced walking speed. Arthritis Rheum. 50, 1172-8.

33. Hall M, Wrigley, T.V., Metcalf, B.R., Hinman, R.S., Dempsey, A.R., Mills, P.M., Cicuttini, F.M., Lloyd, D.G., Bennell K.L., 2014 Knee muscle strength after recent partial meniscecomty does not relate to 2-year change in knee adduction moment. Clin. Orthop. Relat. Res. *In press.*
34. Winter, D.A., Wells, R.P., 1981. Kinetic assessments of human gait. J. Bone Joint Surg. Am. 63, 1350.

Table 1 Biomechanical variables of interest

Variable	Definition
Peak knee adduction moment ((Nm/(BWxHT)%)	Peak external knee adduction moment during first half of stance
Knee-GRF lever arm ((mm/HT)%)	Perpendicular distance between the GRF vector and knee joint center in the laboratory frontal plane
GRF magnitude (BW)	Resultant magnitude of GRF in laboratory frontal plane
Hip external rotation angle (º)	Hip angle in transverse plane
Knee flexion angle (º)	Knee angle in sagittal plane
Knee-pelvis-distance ((mm/HT)%)	Relative frontal plane distance between pelvis center and the knee joint center [34]
Hip-knee-ankle angle (º)	Angle determined from hip-knee-ankle centers in laboratory frontal plane, positive values indicated varus
Tibia angle (º)	Angle of knee-ankle center vector in laboratory frontal plane, positive values indicate varus
Femur angle (º)	Angle of hip-knee center vector in laboratory frontal plane, positive values indicate varus
Knee varus-valgus angle (º)	Varus-valgus angle calculated as first Euler-Cardan angular rotation of the shank with respect to thigh (equivalent to shank varus-valgus angle projected on thigh coordinate system), positive values indicate varus
Lateral trunk lean (º)	Angle of the trunk in laboratory frontal plane, positive values indicate lateral trunk lean
Center of pressure offset (mm)	Distance of the center of pressure from the long axis of the foot (ankle joint center to the 2nd metatarsal), negative values indicate

	lateral offset
Frontal plane GRF angle (º)	Angle of the GRF vector in laboratory frontal plane, positive values indicate varus leaning GRF
Foot progression angle (º)	Angle between long foot axis (ankle joint centre to 2nd metatarsal) with respect to the pelvis, negative values indicate toe out

GRF = ground reaction force magnitude; BW = body weight; HT = height

Table 2 Change in measured biomechanical variables over time

	Baseline Mean (SD)	Follow-up Mean (SD)	Mean difference[b]	(95% CI)	Change[c]	*P* Value
Normal Pace Walking						
Peak KAM (Nm/(BWxHT)%)	2.33 (0.89)	2.54 (0.97)	0.21	0.03 to 0.38	9.4%	**0.022**
Frontal knee-GRF lever arm ((mm/HT)%)[a]	2.54 (0.77)	2.66 (0.79)	0.13	0.01 to 0.25	5.0%	**0.036**
Frontal GRF magnitude (BW)[a]	1.11 (0.12)	1.13 (0.11)	0.03	0.00 to 0.05	2.7%	**0.045**
Hip external rotation angle (º)[a]	-14.93 (6.9)	-15.07 (6.6)	-0.13	-1.41 to 1.14	0.9%	0.835
Knee flexion angle (º)[a]	21.90 (4.8)	21.89 (5.2)	-0.01	-1.06 to 1.04	0.0%	0.986
Knee-pelvis distance ((mm/HT)%)[a]	4.31 (0.8)	4.35 (0.94)	0.05	-0.08 to 0.17	0.9%	0.451
Hip-knee-ankle angle (º)[a]	2.05 (3.86)	2.14 (4.65)	0.09	-0.80 to 0.97	4.4%	0.845
Frontal plane tibia angle (º)[a]	4.76 (1.91)	4.89 (2.11)	0.13	-0.17 to 0.42	2.7%	0.390
Frontal plane femur angle (º)[a]	-2.71 (2.57)	-3.15 (2.82)	-0.44	-0.92 to 0.04	-16.2%	0.070
Knee varus-valgus angle (º)[a]	-1.78 (3.39)	-1.50 (4.37)	0.28	-0.65 to 1.22	15.7%	0.548
Lateral trunk lean (º)[a]	1.63 (1.58)	1.53 (1.35)	-0.10	-0.44 to 0.23	-6.1%	0.550
Centre of pressure offset (mm)	-9.73 (4.79)	-9.49 (4.34)	0.25	-0.59 to 1.08	2.6%	0.558
GRF frontal angle (º)[a]	-2.88 (0.72)	-2.94 (0.88)	-0.07	-0.23 to 0.10	2.4%	0.431
Foot progression angle (º)[a]	-15.13 (5.6)	-13.92 (6.3)	-1.21	-2.39 to -0.02	-8.0%	**0.046**
Walking speed (m/s)	1.36 (0.15)	1.37 (0.16)	0.01	-0.03 to 0.04	0.01%	0.665
Fast Pace Walking						
Peak KAM (Nm/(BWxHT)%)	2.91 (1.19)	3.12 (1.23)	0.28	0.05 to 0.51	9.6%	**0.019**
Frontal knee-GRF lever arm ((mm/HT)%)[a]	2.63 (0.87)	2.85 (0.71)	0.22	0.07 to 0.36	8.4%	**0.004**
Frontal GRF magnitude (BW)[a]	1.28 (0.23)	1.33 (0.19)	0.05	0.00 to 0.09	3.9%	0.050
Hip external rotation angle (º)[a]	-16.87 (6.5)	-16.82 (6.4)	0.05	-1.29 to 1.39	0.3%	0.941
Knee flexion angle (º)[a]	27.03 (6.4)	27.06 (5.6)	0.03	-1.34 to 1.40	0.0%	0.964
Knee-pelvis distance ((mm/HT)%)[a]	4.59 (1.0)	4.54 (0.9)	-0.05	-0.18 to 0.09	-1.1%	0.500
Hip-knee-ankle angle (º)[a]	2.31	2.11	-0.20	-0.87 to	8.7%	0.559

	(4.42)	(4.12)		0.47		
Frontal plane tibia angle (º)[a]	4.68 (1.90)	5.07 (1.89)	0.39	0.10 to 0.68	8.3%	**0.008**
Frontal plane femur angle (º)[a]	-2.37 (3.17)	-2.96 (2.92)	-0.59	-1.10 to -0.08	24.9%	**0.025**
Knee varus-valgus angle (º)[a]	-2.60 (4.27)	-2.57 (4.38)	0.03	-0.99 to 1.06	1.2%	0.951
Centre of pressure offset (mm)	-10.28 (4.32)	-10.58 (4.05)	0.01	-0.88 to 0.89	0.1%	0.990
Lateral trunk lean (º)[a]	1.92 (1.81)	1.44 (1.57)	-0.48	-0.80 to -0.16	25%	**0.004**
GRF frontal angle (º)[a]	-2.99 (1.10)	-2.99 (0.92)	0.01	-0.25 to 0.27	0.3%	0.951
Foot progression angle (º)[a]	-14.66 (6.1)	-15.37 (5.5)	-0.71	-1.92 to 0.49	4.8%	0.241
Walking speed (m/s)	1.86 (0.28)	1.88 (0.20)	0.01	-0.06 to 0.09	0.5%	0.704

[a] At time of first peak knee adduction moment; KAM = knee adduction moment; GRF = ground reaction force magnitude; BW = body weight; HT = height [b] Calculated at follow-up minus baseline [c] Calculated at mean difference divided by mean value at baseline, multiplied by 100.

Table 3: Simple linear correlations between change in peak knee adduction moment during normal and fast pace walking and change in other measured biomechanical variables.

		Δ Peak KAM (Nm/(BWxHT)%)
Normal Pace Walking		
Δ Frontal knee-GRF lever arm ((mm/HT)%) [a]	*r*	0.569
	p	<0.001
Δ Frontal GRF magnitude (BW)[a]	*r*	0.362
	p	0.003
Δ Foot progression angle (º)[a]	*r*	-0.233
	p	0.062
Fast Pace Walking		
Δ Frontal knee-GRF lever arm ((mm/HT)%)[a]	*r*	0.357
	p	0.004
Δ Frontal GRF magnitude (BW)[a]	*r*	0.468
	p	<0.001
Δ Frontal plane tibia angle (º)[a]	*r*	0.403
	p	<0.001
Δ Frontal plane femur angle (º)[a]	*r*	0.225
	p	0.074
Δ Lateral trunk lean (º)[a]	*r*	0.123
	p	0.334

[a] At time of first peak knee adduction moment; KAM = knee adduction moment; GRF = ground reaction force magnitude; BW = body weight; HT = height

Table 4 Summary of regression outputs for the change in peak knee adduction moment for normal and fast pace walking

	Variables Entered	Coefficients	Model Summary				
		B (95% CI)	R	R^2	Adj R^2	R^2 Δ	p-value
Model	**Normal Pace Walking**						
1	Δ Knee-GRF lever arm ((mm/HT)%) [a]	0.824 (0.524 to 1.124)	0.569	0.324	0.313	-	< 0.001
2	Δ Knee-GRF lever arm ((mm/HT)%) [a] Δ Frontal GRF magnitude (BW) [a]	0.755 (0.463 to 1.046) 1.876 (0.475 to 3.278)	0.627	0.394	0.374	0.070	< 0.001
	Fast Pace Walking						
1	Δ Frontal GRF magnitude (BW) [a]	2.343 (1.219 to 3.468)	0.468	0.219	0.206	-	< 0.001
2	Δ Frontal GRF magnitude (BW) [a] Δ Frontal plane tibia angle (º) [a]	2.263 (1.241 to 3.285) 0.310 (0.145 to 0.474)	0.605	0.366	0.345	0.148	< 0.001

[a] At time of first peak knee adduction moment; KAM = knee adduction moment; GRF = ground reaction force magnitude; BW = body weight; HT = height

Table 5 Simple linear correlations between change in knee-GRF lever arm during normal pace walking and change in other measured biomechanical variables

		Δ knee-GRF lever arm (Nm/(BWxHT)%)
Normal Pace Walking		
Δ Hip adduction angle (º)[a]	*r*	0.067
	p	0.598
Δ Knee flexion angle (º)[a]	*r*	0.123
	p	0.333
Δ Frontal plane tibia angle (º) [a]	*r*	0.680
	p	<0.001
Δ Frontal plane femur angle (º) [a]	*r*	0.451
	p	<0.001
Δ Knee varus-valgus angle (º)	*r*	0.267
	p	0.032
Δ Centre of pressure offset (mm)[a]	*r*	0.227
	p	0.071
Δ GRF frontal angle (º)[a]	*r*	-0.223
	p	0.077
Δ Foot progression angle (º)[a]	*r*	-0.180
	p	0.152

[a] At time of first peak knee adduction moment; GRF = ground reaction force magnitude; BW = body weight; HT = height

Highlights for Review:

- First longitudinal study to evaluate 2-yr increase in the peak external knee adduction moment in a cohort at risk to develop knee osteoarthritis
- Findings suggest, and support previous studies that frontal plane tibia alignment is a potent contributor to explain increases in the peak external knee adduction moment