Long-Term Effectiveness of Walking Training in Patients with Knee Osteoarthritis

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1.1 Participants and enrollment

Individuals with medial compartment knee osteoarthritis were recruited for this parallel, participant-blinded randomized controlled trial. All participants provided informed consent in accordance with Stanford University Institutional Review Board protocols. Participants were recruited via clinician referrals, approved searches of medical record databases, and advertisements in print media and online. Eligible individuals were adults (18+) who met the following criteria: 1) medial compartment knee osteoarthritis grade between one and three on the Kellgren-Lawrence (KL) scale as determined from radiographs by a radiologist with more than 20 years of experience, 2) medial knee pain of three or greater on an 11-point numeric rating scale (NRS), 3) able to walk safely on a treadmill without an ambulatory aid for 25 minutes, and 4) BMI less than 35 kg/m^2.

An *a priori* power analysis was conducted prior to the start of the study. For the primary hypothesis that there would be a greater reduction in pain for the *altered* compared to the *consistent FPA* group, an effect size of 0.57 was assumed (Brosseau et al., 2012; Shull, personal communication). To achieve 80% power with an alpha of 0.05, 39 participants per group were needed, so our recruitment goal was 40 subjects per group.

Interested individuals were initially screened with a telephone or web-based questionnaire. Eligible individuals then underwent an in-person screen to confirm the presence, location, and severity of knee pain. Anterior-posterior weightbearing radiographs were obtained and given a KL grade. Participants who met the radiographic inclusion criteria were invited to the motion laboratory for a gait assessment (see *Section 1.2*). Those who were able to reduce their KAM peak by at least 5% with an FPA modification were randomized. Prior to study initiation, we generated a block randomization spreadsheet (block size=8, 1:1) and stored it on

the study coordinator's computer. Once a participant met all inclusion criteria, their group allocation was revealed by unhiding a row in the randomization spreadsheet. Study staff were not blinded to group allocation during gait retraining sessions but were blinded for data processing and analysis. We enrolled 68 of the desired 80 participants, and the trial was concluded four months prior to the final subject's final visit due to an institutional shutdown caused by the COVID-19 pandemic.

1.2 Gait Analysis and Retraining

Participants completed 13 visits to the motion laboratory for gait evaluation and retraining over the one-year study duration. During all visits, they walked on a force-instrumented treadmill (Bertec Corporation, Columbus, OH, USA) in an 11-camera optical motion capture volume (Motion Analysis Corp., Santa Rosa, CA, USA). Forces and marker positions were collected at 2000Hz and 100Hz, respectively, and data were low-pass filtered at 15 Hz (4^{th} order, zero-lag Butterworth). MATLAB R2015b (MathWorks, Inc., Natick, MA, USA) was used to compute the KAM and FPA as well as to deliver real-time vibrotactile feedback through two C2 vibrotactile motors (Engineering Acoustics, Inc., Casselberry, FL, USA) affixed to the proximal tibia as described in Uhlrich et al. (Uhlrich et al., 2020, 2018).

Prior to randomization, participants visited the motion laboratory two times to evaluate if an FPA modification could reduce their peak KAM. During the initial familiarization visit, we identified participants' self-selected walking speed and they practiced walking with the following conditions until they felt comfortable: natural walking without feedback, 10° toe-in (relative to natural FPA) with feedback, and 10° toe-out with feedback. One week later, participants completed the FPA personalization (i.e., week 0) visit. After warming up on the treadmill for five minutes, participants completed a two-minute natural walking trial. They then

practiced walking with 5° and 10° toe-in and toe-out for at least one minute. Finally, the participants walked for two minutes at each of the four FPA modifications in a random order. Each participant's larger KAM peak was identified from the natural walking trial, and the FPA modification that maximally reduced this peak was identified. For individuals whose early and late-stance KAM peaks were within 5% of one another, the FPA that maximally reduced one peak without increasing the other was selected. Only individuals who were able to reduce their KAM peak by at least 5% (Erhart-Hledik et al., 2012) were included and randomized as described in *Section 1.1*.

Included participants visited the motion laboratory for six once-per-week gait retraining visits (weeks 1-6). In both the consent form and during the first week of gait retraining, participants were told that everyone would receive biofeedback teaching them to walk consistently with a personalized target FPA that was selected from the week 0 visit. They were told that the only difference between groups was the target FPA. The target FPA for the *altered FPA* group was the FPA that maximally reduced their peak KAM from week 0, and the target for the *consistent FPA* group was the average natural FPA from week 0. During gait retraining visits, participants performed a two-minute pre-training evaluation trial without feedback, four blocks of biofeedback (12-24 minutes total) following a faded feedback scheme (Barrios et al., 2010), and a one-minute post-training evaluation trial without feedback. Participants were instructed to practice their FPA outside the lab for at least 20 minutes daily and, once comfortable, to walk with this FPA at all times. Participants completed daily logs of walking time and the percentage of time walking with their target FPA. During each visit, study staff reviewed the log and encouraged participants to meet the walking goals.

Following training, participants visited the lab for five evaluation and refresher training visits at week 10, month 3, month 6, month 9, and year 1 after the week 0 visit. Evaluation and retraining trials were similar to the week 1-6 retraining visits, and participants received 18 minutes of biofeedback.

1.3 Self-reported and activity outcomes

Pain, function, and activity outcomes were assessed for the week preceding the week 1, week 6, and year 1 visits. NRS pain was evaluated by study staff prior to the visit as the typical pain over the past week in the medial compartment. The WOMAC survey was completed on a computer. Participants carried an Omron HJ-323U pedometer (Omron Corporation, Kyoto, Japan) for one week and daily steps were averaged, excluding the first and last day of registered steps. Participants also estimated the percentage time walking at their target FPA (i.e., compliance) for the week preceding the year 1 visit.

1.4 MRI

Femoral cartilage microstructure was evaluated at week 0 and at year 1 using quantitative MRI ($T_{1\rho}$ and T_2). All scans were performed at 3T (DISCOVERY MR750, General Electric Company, Boston, MA, USA) using a 16-channel phased-array flexible coil. T_2 relaxation times were calculated using a 3D quantitative Double Echo in Steady State (qDESS) sequence (Chaudhari et al., 2018, 2017) (TR=24.96 ms, TE_1/ TE_2=7.54/42.38 ms, FA=30°, FOV=160x160x120 mm^3, voxel size=0.3125x0.3125x1.5 mm^3, scan time=5 min 32 s). $T_{1\rho}$ relaxation times were estimated using a magnetization-prepared pseudo-steady-state 3D Fast Spin Echo sequence (Spin Lock Frequency=500 Hz, TR/TE=1292/16 ms, flip angle=90°, FOV=160x160x120 mm^3, voxel size=0.5x0.625x3 mm^3, Spin Lock Time = 1, 10, 30, 60 ms,

total scan time=5 min 12 s). T_2 was calculated using signal models from the two DESS echoes (Sveinsson et al., 2017) and $T_{1\rho}$ values were calculated pixelwise using a mono-exponential decay model. All follow-up scans were non-rigidly registered to the qDESS baseline scan. Subsequently the medial and lateral weight-bearing portions of femoral cartilage were manually segmented and applied to all scans. The voxelwise difference between follow-up and baseline scans was calculated and mean difference $T_{1\rho}$ and T_2 ($\Delta T_{1\rho}$ and ΔT_2) values were extracted. A denoising filter was applied to the difference maps to eliminate noise and spurious peaks, while preserving larger clusters of longitudinal changes. Image processing was performed using QMRITools (Froeling, 2019), and registrations were implemented using Elastix (Klein et al., 2010).

1.5 Statistical analysis

All primary and secondary analyses were performed using intent-to-treat approaches. The percent of missing data ranged from 1-32% and the data were normally distributed. Missing data were imputed using the Markov chain Monte Carlo method (Schafer, 1997) for Continuous Variables because the pattern of missing data was arbitrary and all outcome variables were continuous.

To test group differences in the primary outcomes of change in NRS medial pain and change in KAM from week 0 to year 1, linear regression models were used, adjusting for baseline scores. Linear regression models were also used to test group differences in the secondary outcomes of $\Delta T_{1\rho}$ and ΔT_2 in the medial and lateral compartments. The threshold for significance was set at alpha = 0.05.

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