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Effect of Biomechanical Footwear on Knee Pain in People With Knee Osteoarthritis
The BIOTOK Randomized Clinical Trial

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IMPORTANCE Individually calibrated biomechanical footwear therapy may improve pain and physical function in people with symptomatic knee osteoarthritis, but the benefits of this therapy are unclear.

OBJECTIVE To assess the effect of a biomechanical footwear therapy vs control footwear over 24 weeks of follow-up.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted at a Swiss university hospital. Participants (N = 220) with symptomatic, radiologically confirmed knee osteoarthritis were recruited between April 20, 2015, and January 10, 2017. The last participant visit occurred on August 15, 2017.

INTERVENTIONS Participants were randomized to biomechanical footwear involving shoes with individually adjustable external convex pods attached to the outsole (n = 111) or to control footwear (n = 109) that had visible outsole pods that were not adjustable and did not create a convex walking surface.

MAIN OUTCOMES AND MEASURES The primary outcome was knee pain at 24 weeks of follow-up assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscore standardized to range from 0 (no symptoms) to 10 (extreme symptoms). The secondary outcomes included WOMAC physical function and stiffness subscores and the WOMAC global score, all ranging from 0 (no symptoms) to 10 (extreme symptoms) at 24 weeks of follow-up, and serious adverse events.

RESULTS Among the 220 randomized participants (mean age, 65.2 years [SD, 9.3 years]; 104 women [47.3%]), 219 received the allocated treatment and 213 (96.8%) completed follow-up. At 24 weeks of follow-up, the mean standardized WOMAC pain subscore improved from 4.3 to 1.3 in the biomechanical footwear group and from 4.0 to 2.6 in the control footwear group (between-group difference in scores at 24 weeks of follow-up, −1.3 [95% CI, −1.8 to −0.9]; $P < .001$). The results were consistent for WOMAC physical function subscore (between-group difference, −1.1 [95% CI, −1.5 to −0.7]), WOMAC stiffness subscore (between-group difference, −1.4 [95% CI, −1.9 to −0.9]), and WOMAC global score (between-group difference, −1.2 [95% CI, −1.6 to −0.8]) at 24 weeks of follow-up. Three serious adverse events occurred in the biomechanical footwear group compared with 9 in the control footwear group (2.7% vs 8.3%, respectively); none were related to treatment.

CONCLUSIONS AND RELEVANCE Among participants with knee pain from osteoarthritis, use of biomechanical footwear compared with control footwear resulted in an improvement in pain at 24 weeks of follow-up that was statistically significant but of uncertain clinical importance. Further research would be needed to assess long-term efficacy and safety, as well as replication, before reaching conclusions about the clinical value of this device.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02363712

Supplemental content

CME Quiz at jamacmelookup.com

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Knee osteoarthritis affects approximately 265 million people worldwide and was estimated in 2017 to account for 8.3 million years lived with disability.[1] The prevalence of knee osteoarthritis is rising due to population aging and the increasing prevalence of obesity. Acetaminophen, nonsteroidal anti-inflammatory drugs, and opioids are most commonly used to treat the pain associated with osteoarthritis,[2] but have limited effectiveness[3,4] and are associated with adverse effects.[3,5,6] In the US, the rates of knee replacement surgery, almost all related to osteoarthritis, have been increasing, in part because of ineffective nonsurgical treatments.

Biomechanical treatments for knee osteoarthritis have been developed to reduce pain, improve physical function, and potentially slow disease progression,[7] but evidence of their effectiveness has been inconclusive.[8,9] Two small prospective, nonrandomized clinical studies suggested that an individualized biomechanical footwear system may improve pain and physical function in people with symptomatic knee osteoarthritis.[10,11] In those studies, the footwear system consisted of shoes with 2 convex pods on the outsoles, individually calibrated based on findings from detailed gait studies. Adjustment of the location of the pods may alter limb biomechanics and reduce stress on osteoarthritic knee compartments.[12-14] Walking on the convex pods results in gait alterations, and these alterations are hypothesized to induce reconditioning of the neuromuscular system and improve pathological gait patterns.[15]

The objective of this study, the Biomechanical Therapy for Osteoarthritis of the Knee (BIOTOK) randomized clinical trial, was to determine whether the use of biomechanical footwear was more effective than the use of control footwear for improving knee pain in participants with knee osteoarthritis.

Key Points

Question Is an individualized biomechanical footwear therapy effective for reducing knee pain in people with knee osteoarthritis?

Findings In this randomized clinical trial that included 220 participants with knee pain due to knee osteoarthritis, treatment with an individualized biomechanical footwear therapy compared with control footwear resulted in a lower Western Ontario and McMaster Universities Osteoarthritis Index pain subscore (range, 0-10) after 24 weeks of follow-up (1.3 vs 2.6, respectively), a difference that was statistically significant.

Meaning Although use of biomechanical footwear compared with control footwear resulted in an improvement in knee pain at 24 weeks of follow-up that was statistically significant, the difference was of uncertain clinical importance, and further research is needed to assess long-term efficacy and safety.

Methods

Study Design and Participants

The trial protocol and statistical analysis plan appear in Supplement 1 and Supplement 2, respectively. This was an investigator-initiated single-center randomized clinical trial conducted among participants with symptomatic knee osteoarthritis, which compared a biomechanical footwear therapy using shoes with 2 individually calibrated convex pods on the outsoles (AposTherapy, Apos Medical Assets; eFigures 1 and 2 in Supplement 3) with a similarly appearing control footwear.

We enrolled men and nonpregnant women aged 40 years or older who had symptomatic, radiologically confirmed knee osteoarthritis according to criteria from the American College of Rheumatology.[16] At the screening visit, participants had knee pain lasting 6 months or longer and a score of 3 or greater on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale[17] (standardized to range from 0-10). The full eligibility criteria and description for the selection of the index knee appear in Supplement 3.

Individuals were excluded if they had a history of inflammatory rheumatic disease, had undergone knee surgery during the prior 6 months, had a planned hip or knee surgery within 24 weeks of the baseline assessment, had received glucocorticoid knee injections within the prior 3 months, or had a high risk for falls.

The trial was approved by the independent research ethics committee of Canton Bern (KEK-BE 041/215). All participants provided written informed consent.

Randomization and Blinding

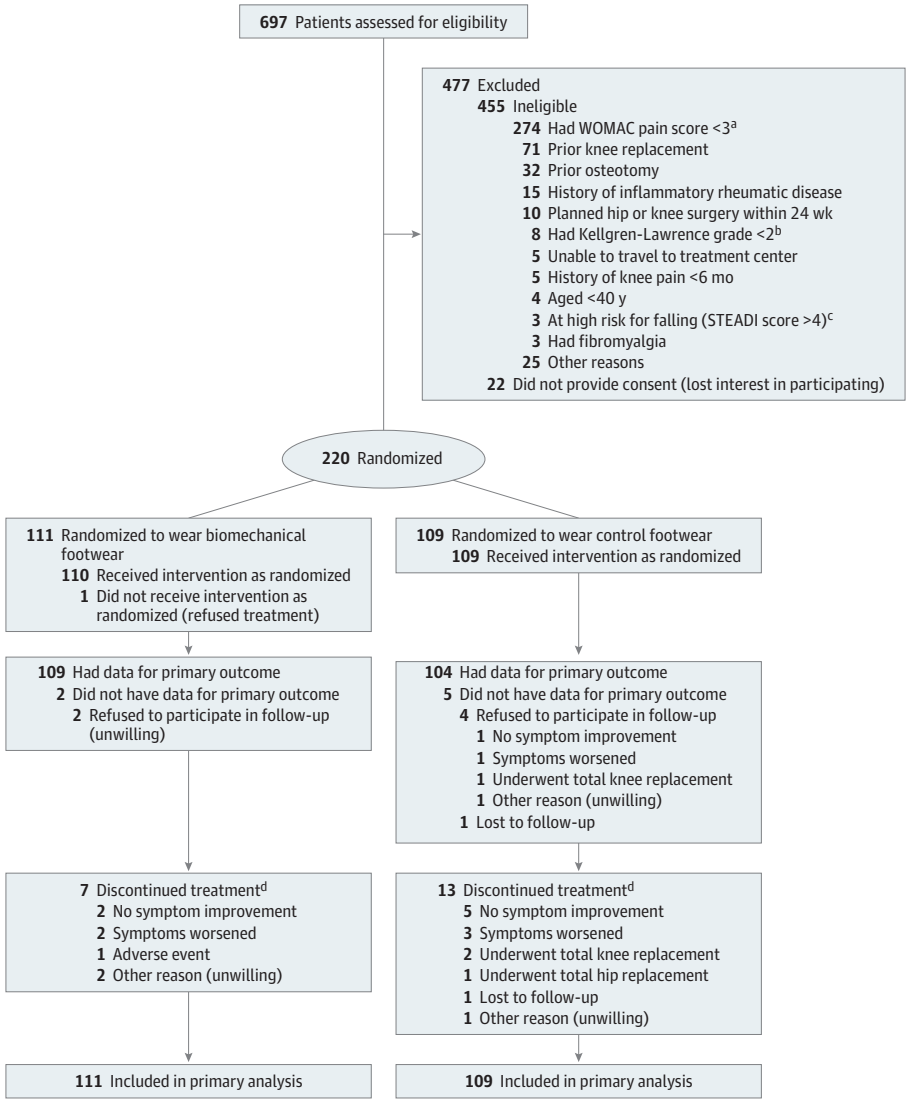
Participants were randomized 1:1 to the biomechanical footwear group or to the control footwear group using a concealed and secure web-based system (**Figure 1**). Randomization was computer-generated using varied block sizes of 2 and 4 and stratified by unilateral vs bilateral knee disease and predominantly affected compartment (medial vs lateral) in the index knee.

The biomechanical footwear device consisted of 2 shoes with 2 convex adjustable rubber pods screwed to the outsole at the heel and forefoot (eFigures 1 and 2 in Supplement 3). The control footwear was specifically designed by the manufacturer for this trial to have a similar appearance to the biomechanical footwear, but with pods embedded in the transparent outsole so that they were visible yet did not create a convex walking surface (eFigure 3 in Supplement 3).

To try to maintain blinding of the participants, they were kept unaware of the study design and the use of the control footwear. Participants were informed in a neutral manner that 2 different types of footwear were being compared (Supplement 3). Both the biomechanical and control footwear were presented on the manufacturer's website, and the control footwear was described as a device with a novel design of the sole (eFigure 3 in Supplement 3).

The technicians and study nurses who coordinated the clinical visits could not be blinded to treatment group but were asked not to disclose the treatment or the nature of the control footwear study component to participants. The technicians were from Israel and did not speak German, therefore, direct interaction between the technicians and participants was limited. Verbal communication was carried out through the

Figure 1. Participant Recruitment, Randomization, and Follow-up



[a] The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a self-administered questionnaire with a score range from 0 to 10 (0, no symptoms; 10, extreme symptoms).

[b] The Kellgren-Lawrence grade ranges from 0 to 4; a grade of 2 or greater indicates definite osteoarthritis on anteroposterior weight-bearing radiograph.

[c] STEADI indicates Stopping Elderly Accidents, Deaths, and Injuries; a score greater than 4 at the screening visit was considered to indicate a high risk of falls. The score range is 0 to 14.

[d] Of the 7 participants in the biomedical footwear group and 13 participants in the control footwear group who discontinued treatment, 2 and 5, respectively, did not have data for the primary outcome and were counted as part of those who discontinued treatment. Multiple imputation was used for missing outcome data.

translating study nurses, who were independent of the manufacturer and were encouraged to facilitate unbiased participant interaction. The remaining study personnel (performing data entry, management, and data cleaning) and the statistician were blinded to the intervention until all primary and secondary analyses were completed.

The consent form did not state that the control footwear was intended to be ineffective; rather, it implied that both types of shoes may be effective. Furthermore, the manufacturer's website was altered to imply potentially therapeutic benefits of both the intervention and the control footwear. Therefore, the trial could be considered potentially deceptive according to international guidelines.[18]

Both the biomechanical and control footwear included some therapeutic elements. Both were high-top shoes, which provided more stability and proprioceptive input than loose shoes or sandals. Furthermore, proposed mechanisms of the biomechanical footwear were hypothetical at the initiation of this trial, and the trial was considered to entail no more than minimal risk and burden to participants according to Article 2 of the Swiss clinical trials ordinance.[19]

Therefore, the responsible research ethics committee did not classify the trial as involving incomplete participant information (ie, did not consider the study procedures to be deceptive) according to Article 18 of the Swiss human research act.[20] Nonetheless, because the trial may have been considered deceptive by some individuals, participants were debriefed after the trial was completed.

Participants were advised of the rationale of the placebo-controlled design, informed of differences between the biomechanical footwear and the control footwear, and informed about their group allocation, and were given the opportunity to withdraw consent to participate. The criteria specified in the international guidelines[18] for trials that withhold information or use deception with respect to this trial appear in Supplement 3.

Procedures

Participants in both groups underwent an initial fitting of their assigned footwear by technicians at baseline and during recalibration at 4, 8, 12, and 16 weeks of follow-up. The positioning of the external pods was individually adjusted on the biomechanical footwear, in accordance with gait patterns and reported pain intensity during walking, with the aim of decreasing clinically observed malalignment and reported pain intensity, and increasing gait symmetry[13,14,21,22] as determined by 2-dimensional computerized spatiotemporal gait analysis software (Zeno walkway version Z-216T and PKMAS version 5.07C3, both manufactured by ProtoKinetics; Supplement 3). Participants in the control footwear group received a simulated calibration that mimicked calibration of the biomechanical footwear. The technicians provided by the manufacturer performed all device-related procedures (gait analyses, fitting, and calibrations of the biomechanical and control footwear).

Participants were instructed to use the footwear during indoor activities for a half hour each day during the first week of the intervention, with subsequent increases of 10 minutes per week on average but were not given explicit instructions to perform specific home-based exercises. After 6 weeks of follow-up, the participants were advised to use the footwear to walk outdoors. The participants were asked to discontinue their regular pain medication and advised that other interventions, such as physical therapy, should be avoided during the trial. They were permitted daily therapy as needed with acetaminophen at a maximum dose of 2 g and the amounts taken were recorded at each visit.

Outcomes

The prespecified primary outcome was pain at the end of treatment (24-week follow-up) in the index knee assessed with the WOMAC pain subscore (visual analog version) (standardized range, 0-10; 0 = no symptoms and 10 = extreme symptoms).[17]

The secondary outcomes prespecified in the protocol were WOMAC global score and WOMAC physical function and stiffness subscores (all 3 with standardized range, 0-10; 0 = no symptoms) at 12 and 24 weeks of follow-up; WOMAC pain subscore at 4, 8, 12, and 16 weeks of follow-up; the physical and mental component summary scores of the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) (standardized to have a mean of 50 [SD, 10] for the general population; theoretical range, 0-100; 100 = best)[23] at 12 and 24 weeks of follow-up; gait velocity, step length, and single limb support measured by 2-dimensional computerized gait analysis when walking barefoot at 4, 8, 12, 16, and 24 weeks of follow-up; self-reported time spent wearing the footwear per day; self-reported health care use; and self-reported analgesic use (because between-group differences in analgesic use could result in performance bias).[24] The minimal clinically important differences were not considered when planning the trial.

Other prespecified outcomes were treatment response defined as decreases of 30% and 50% in WOMAC pain subscore from baseline.[25] A treatment response defined as a 50% decrease in WOMAC pain subscore from baseline was not prespecified in the protocol (Supplement 1), but was included in the statistical analysis plan (Supplement 2).

The adverse events prespecified in the protocol were falls, any adverse events, serious adverse events, dropped out for any reason, and dropped out due to adverse events (Supplement 1). The WOMAC scores,[17] analgesic intake, and gait analysis parameters were recorded at baseline and at 4, 8, 12, 16, and 24 weeks of follow-up; and the SF-36 scores and health care use were recorded at baseline and at 12 and 24 weeks of follow-up. The adverse events and the time spent wearing the footwear were recorded at each follow-up visit. Two investigators (S.R. and P.J.) blinded to the assigned treatment adjudicated all potential adverse events based on notes by participants and nurses, and, in cases of potential serious adverse events, based on relevant medical records.

Statistical Analysis

A sample size of 100 participants per group yielded 80% power to detect a between-group difference of 1.05 on a standardized WOMAC pain scale ranging from 0 to 10 at a 2-sided α level of .05. This between-group difference corresponds to a moderate effect size of 0.4-SD units, assuming a typical SD of 2.65.[4] The protocol prespecified the use of analyses of covariance for all continuous outcomes, adjusted for the outcome's baseline values. For this approach, a sample size of 100 participants per group would yield approximately 90% power, assuming a correlation of 0.5 between baseline and 24 weeks of follow-up. Anticipating an attrition rate of 10%, the target sample size was 220 participants.

Continuous outcomes were analyzed using analysis of covariance adjusted for the outcome's baseline values and variables used for stratified randomization, considering only the assessments of the index knee for each participant. Binary outcomes were analyzed using Cochran-Mantel-Haenszel tests stratified by stratification variables.[26] Participants were included in the analyses according to their randomized allocation,[27] using multiple imputation for missing outcome data, using all baseline characteristics (age, sex, body mass index, blood pressure, medical history, WOMAC scores, SF-36 scores, and parameters of gait analysis), outcomes at all time points, the treatment indicator, and stratification variables to generate 20 imputed data sets (Supplement 2 and Supplement 3).

Prespecified subgroup analyses of the primary outcome were performed according to the predominantly affected compartment and the presence or absence of symptomatic contralateral knee osteoarthritis and were accompanied by tests for interaction. A post hoc subgroup analysis was performed according to WOMAC pain intensity at baseline.[28] Prespecified sensitivity analyses of the primary outcome included a per-protocol analysis, a complete case analysis, adjustments for potential procedural confounders, and a linear mixed-effects model to analyze all knees (ie, index or both index and contralateral knee) with a baseline WOMAC pain subscale score of 3 or greater. Post hoc sensitivity analyses of WOMAC scores, SF-36 scores, and parameters of gait analyses were performed using all

Table 1. Participant Characteristics at Baseline

Characteristic	Biomechanical Footwear (n = 111)	Control Footwear (n = 109)
Sex, No. (%)		
Female	51 (45.9)	53 (48.6)
Male	60 (54.1)	56 (51.4)
Age, mean (SD), y	65.3 (9.2)	65.0 (9.3)
Weight, mean (SD), kg	80.6 (15.7)	82.7 (14.2)
Height, mean (SD), cm	170.4 (8.6)	170.9 (8.2)
Body mass index, mean (SD)[a]	27.7 (4.8)	28.3 (4.3)
Knee-related characteristics[b]		
History of meniscal resection	55 (49.5)	50 (45.9)
Knee joint effusion	18 (16.2)	17 (15.6)
Kellgren-Lawrence grade[c]		
2	33 (29.7)	36 (33.0)
3	50 (45.0)	46 (42.2)
4	28 (25.2)	27 (24.8)
Medial knee osteoarthritis	101 (91.0)	99 (90.8)
WOMAC score, mean (SD)[d]		
Pain	4.3 (1.8)	4.0 (2.0)
Physical function	3.5 (1.8)	3.4 (1.8)
Stiffness	5.0 (2.4)	4.4 (2.4)
Global	3.8 (1.7)	3.6 (1.7)
SF-36 score, mean (SD)[e]		
Physical component	40.4 (7.1)	40.3 (6.2)
Mental component	57.0 (7.4)	56.4 (8.8)
Analgesic use during past week, No. (%)	44 (39.6)	35 (32.1)

Abbreviations: SF-36, 36-item Short Form Health Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] These characteristics are in regard to the index knee and are expressed as No. (%) unless otherwise indicated. The percentages may not total 100 because of rounding. Additional baseline characteristics appear in eTable 1 in Supplement 3.

[c] Ranges from 0 to 4. A grade of 2 or greater indicates definite osteoarthritis on anteroposterior weight-bearing radiograph. A grade of 2 indicates definite osteophytes and possible joint space narrowing; grade 3, multiple osteophytes, definite joint space narrowing, sclerosis, and possible bony deformity; and grade 4, large osteophytes, marked definite joint space narrowing, severe sclerosis, and definite bony deformity.

[d] A self-administered questionnaire including 5 questions on pain, 17 questions on physical function, and 2 questions on stiffness. All 4 composite scores were standardized to range from 0 to 10 (0, no symptoms; 10, extreme symptoms). For the WOMAC pain subscore, a score of 4 or less indicates mild pain; a score of 5 to 7, moderate pain; and a score greater than 7, severe pain.[28]

[e] Each component score has a mean of 50 (SD, 10) for the general population. Higher summary scores indicate better health.

time points in a linear mixed-effects regression model (Supplement 2 and Supplement 3).

The *P* values and 95% CIs were 2-sided and *P* values ≤.05 were considered statistically significant. Because of the potential for type I error due to multiple comparisons, the findings for the analyses of the secondary outcomes should be interpreted as exploratory. All analyses were performed using R version 3.3.2 (R Foundation for Statistical Computing)[29] by an independent statistician located within an academic clinical trials unit (in Bern, Switzerland) who was unaware of group assignment. The statistical analysis plan was finalized after completion of follow-up, but before examination of the data. Data were interpreted and conclusions formulated prior to the unblinding of the investigators.

Results

Between April 20, 2015, and January 10, 2017, 220 participants were randomized. There were 111 participants randomized to the biomechanical footwear group and 109 participants randomized to the control footwear group (Figure 1). One participant in the biomechanical footwear group refused treatment and did not receive the intervention. Seven participants in the biomechanical footwear group and 13 participants in the control footwear group discontinued treatment during follow-up. The last participant visit occurred on August 15, 2017. There were complete data for the primary outcome at 24 weeks of follow-up for 109 participants (98.2%) in the biomechanical footwear group and 104 participants (95.4%) in the control footwear group.

After trial completion, 217 of the 220 randomized participants were reached and advised of the potential for deception in the study design. Of the 3 participants who were not reached (all in the biomechanical footwear group), 1 had died and 2 were lost to follow-up. None of the remaining 217 participants withdrew consent after learning that the trial involved randomization to either the biomechanical footwear group or the control footwear group that was expected to be ineffective.

Baseline characteristics were similar between the participants randomized to each group (**Table 1** and eTable 1 in Supplement 3). The study population had a mean age of 65.2 years (SD, 9.3 years), 104 were women (47.3%), and the population had a mean body mass index (calculated as weight in kilograms divided by height in meters squared) of 28.0 (SD, 4.6). Medial knee osteoarthritis was present in 90.9% of participants and unilateral disease in 67.7%. The number of participants with missing data was between 0 and 3 (1.4%) for baseline characteristics (eTable 2 in Supplement 3) and between 2 (0.9%) and 29 (13.2%) for outcomes (eTable 3 in Supplement 3).

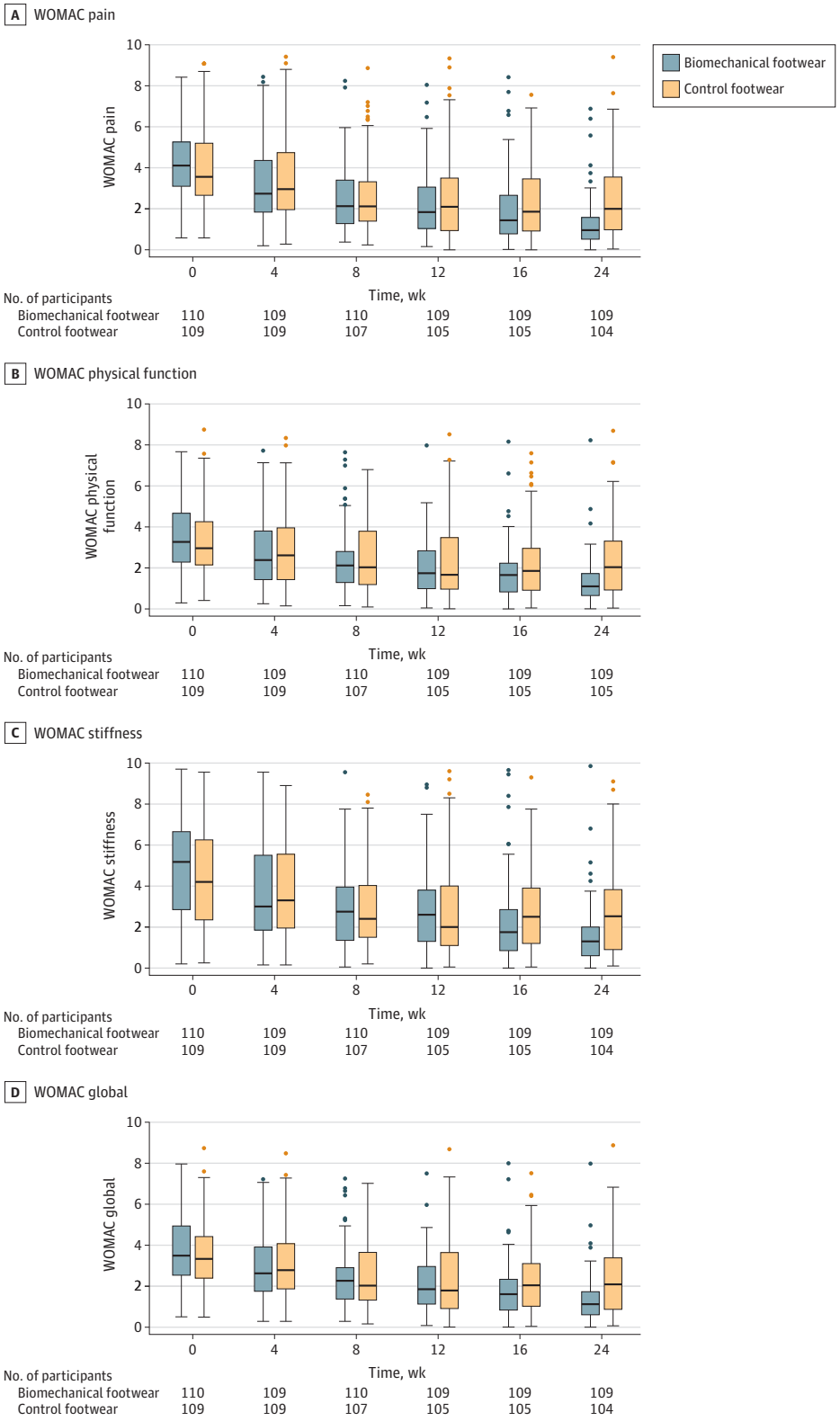
Primary Outcome

The biomechanical footwear group had a larger decrease in standardized WOMAC pain subscore at 24 weeks of follow-up than the control footwear group (mean score, 1.3 vs 2.6, respectively; between-group difference, −1.3 [95% CI, −1.8 to −0.9]; *P* < .001) (**Figure 2** and **Table 2**).

Secondary Outcomes

The biomechanical footwear group had larger declines in the secondary outcomes of WOMAC physical function and stiffness subscores and WOMAC global score at 24 weeks of follow-up (Figure 2 and Table 2). Between-group differences in velocity, step length, and single limb support emerged in favor of the biomechanical footwear group between 12 and 24 weeks of follow-up (Table 2). The mean self-reported time

Figure 2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Scores During 24 Weeks of Follow-up



The box represents the median and interquartile range, the whiskers represent the most extreme values within 1.5 times of the interquartile range beyond the 25th and 75th percentile, and the circles represent the more extreme values. The WOMAC is a self-administered questionnaire including 5 questions on pain, 17 questions on physical function, and 2 questions on stiffness. All 4 composite scores were standardized to range from 0 to 10 (0, no symptoms; 10, extreme symptoms).

Table 2. Primary and Secondary Outcomes[a]

Outcome	Biomechanical Footwear (n = 111)	Control Footwear (n = 109)	Effect (95% CI)	*P* Value
Primary outcome				
WOMAC pain subscore at 24 wk, mean (SD)[b,c]	1.3 (1.3)	2.6 (2.0)	Mean difference, −1.3 (−1.8 to −0.9)	<.001
Secondary outcomes[d]				
WOMAC pain subscore, mean (SD)[c]				
4 wk	3.2 (1.9)	3.4 (2.0)	Mean difference, −0.4 (−0.9 to 0)	.04
8 wk	2.5 (1.6)	2.6 (1.8)	Mean difference, −0.3 (−0.7 to 0.1)	.19
12 wk	2.3 (1.7)	2.6 (2.1)	Mean difference, −0.5 (−0.9 to −0.1)	.03
16 wk	2.0 (1.7)	2.4 (1.9)	Mean difference, −0.5 (−1.0 to −0.1)	.02
WOMAC physical function subscore, mean (SD)[c]				
12 wk	2.1 (1.4)	2.5 (2.0)	Mean difference, −0.5 (−0.9 to −0.1)	.01
24 wk	1.4 (1.2)	2.4 (1.8)	Mean difference, −1.1 (−1.5 to −0.7)	<.001
WOMAC stiffness subscore, mean (SD)[c]				
12 wk	2.9 (2.0)	2.8 (2.3)	Mean difference, −0.3 (−0.8 to 0.2)	.25
24 wk	1.6 (1.5)	2.8 (2.2)	Mean difference, −1.4 (−1.9 to −0.9)	<.001
WOMAC global score, mean (SD)[c]				
12 wk	2.2 (1.4)	2.5 (2.0)	Mean difference, −0.5 (−0.9 to −0.1)	.25
24 wk	1.4 (1.2)	2.5 (1.8)	Mean difference, −1.2 (−1.6 to −0.8)	<.001
SF-36 physical component, mean (SD)[e]				
12 wk	43.1 (7.6)	43.8 (7.3)	Mean difference, −0.7 (−2.4 to 0.9)	.39
24 wk	45.9 (7.4)	44.5 (8.0)	Mean difference, 1.4 (−0.5 to 3.2)	.14
SF-36 mental component, mean (SD)[e]				
12 wk	57.1 (7.0)	56.2 (8.9)	Mean difference, 0.6 (−1.2 to 2.4)	.51
24 wk	56.8 (6.7)	56.0 (9.0)	Mean difference, 0.5 (−1.4 to 2.4)	.59
Self-reported health care use up to 24 wk, No. (%)[f]	41 (36.9)	29 (26.6)	Risk difference percentage, 10.3 (−2.5 to 22.7)[g]	.10
Self-reported analgesic use at 24 wk, No. (%)	45 (40.5)	49 (45.0)	Risk difference percentage, −4.4 (−17.5 to 8.8)[g]	.51
Self-reported acetaminophen equivalence dose at 24 wk, median (IQR), mg/d[h]	(n = 45) 875 (250 to 2569)	(n = 49) 875 (250 to 2500)	Median difference, 0 (−1038 to 1038)	>.99
Gait analysis in bare feet, mean (SD)				
Gait velocity, cm/s				
4 wk	107.7 (16.1)	109.9 (17.7)	Mean difference, 1.1 (−1.8 to 4.0)	.44
8 wk	111.9 (16.8)	112.2 (19.5)	Mean difference, 2.9 (−0.7 to 6.4)	.12
12 wk	114.0 (17.3)	112.8 (19.3)	Mean difference, 4.3 (0.7 to 7.9)	.02
16 wk	114.3 (18.0)	113.2 (19.1)	Mean difference, 4.0 (−0.1 to 8.2)	.06
24 wk	115.7 (17.1)	114.8 (19.2)	Mean difference, 3.6 (−0.4 to 7.6)	.08

(continued)

Table 2. Primary and Secondary Outcomes[a] (continued)

Outcome	Biomechanical Footwear (n = 111)	Control Footwear (n = 109)	Effect (95% CI)	*P* Value
Step length in index knee, cm				
4 wk	60.4 (6.5)	60.4 (7.6)	Mean difference, 0.7 (−0.3 to 1.6)	.16
8 wk	61.3 (6.9)	61.1 (8.3)	Mean difference, 0.9 (−0.3 to 2.1)	.15
12 wk	61.8 (7.0)	60.9 (8.3)	Mean difference, 1.5 (0.3 to 2.8)	.02
16 wk	62.3 (7.1)	61.2 (8.0)	Mean difference, 1.6 (0.2 to 3.1)	.03
24 wk	62.5 (6.9)	61.6 (8.2)	Mean difference, 1.4 (−0.1 to 3.0)	.07
Single limb support in index knee, % of gait cycle				
4 wk	37.0 (1.7)	37.0 (1.9)	Mean difference, 0.1 (−0.2 to 0.4)	.39
8 wk	37.3 (1.7)	37.3 (1.9)	Mean difference, 0.1 (−0.2 to 0.4)	.59
12 wk	37.4 (1.7)	37.3 (1.9)	Mean difference, 0.3 (0 to 0.6)	.09
16 wk	37.4 (1.6)	37.4 (1.8)	Mean difference, 0.1 (−0.2 to 0.5)	.43
24 wk	37.5 (1.5)	37.3 (2.0)	Mean difference, 0.3 (0 to 0.7)	.07
Self-reported time spent wearing footwear, min/d during past week				
4 wk	70.3 (48.6)	58.1 (34.2)	Mean difference, 12.6 (1.4 to 23.8)	.03
8 wk	129.3 (60.8)	98.9 (45.2)	Mean difference, 30.4 (15.9 to 44.9)	<.001
12 wk	176.7 (82.3)	133.3 (66.1)	Mean difference, 43.4 (23.0 to 63.8)	<.001
16 wk	207.8 (90.0)	146.7 (99.2)	Mean difference, 61.2 (35.1 to 87.3)	<.001
24 wk	209.2 (102.9)	173.5 (122.9)	Mean difference, 35.4 (4.2 to 66.6)	.03

Abbreviations: IQR, interquartile range; SF-36, 36-item Short Form Health Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Analyzed at each time point using a linear regression model adjusted for the outcome's baseline values and stratification variables, and considering only the assessments of the index knee for each participant.

[b] A score of 4 or less indicates mild pain; a score of 5 to 7, moderate pain; and a score greater than 7, severe pain.[28]

[c] A self-administered questionnaire including 5 questions on pain, 17 questions on physical function, and 2 questions on stiffness. All 4 composite scores were standardized to range from 0 to 10 (0, no symptoms; 10, extreme symptoms).

[d] Additional secondary outcomes appear in eTables 4 and 5 in Supplement 3.

[e] Each component score has a mean of 50 (SD, 10) for the general population. Higher summary scores indicate better health.

[f] Includes any self-reported visits to a primary care physician, rheumatologist, orthopedic surgeon, physiotherapist, occupational therapist, complementary or alternative health care practitioner, and community nurse.

[g] Mantel-Haenszel risk differences were adjusted for the 2 stratification factors (medial or lateral osteoarthritis status and unilateral or bilateral knee disease at randomization).

[h] Among those who reported any analgesic use.

Table 3. Adverse Events[a]

	No. (%)	
	Biomechanical Footwear (n = 111)	Control Footwear (n = 109)
Any adverse events	26 (23.4)	38 (34.9)
Minor adverse events	23 (20.7)	30 (27.5)
Musculoskeletal	15 (13.5)	21 (19.3)
Knee pain or swelling[b]	2 (1.8)	3 (2.8)
Low back pain	5 (4.5)	5 (4.5)
Hip pain	5 (4.5)	3 (2.8)
Foot pain	2 (1.8)	3 (2.8)
Other	3 (2.7)	8 (7.3)
Injury	6 (5.4)	9 (8.3)
Ankle sprain	2 (1.8)	1 (0.9)
Fall[c]	2 (1.8)	4 (3.7)
Other	2 (1.8)	4 (3.7)
Genitourinary	2 (1.8)	2 (1.8)
Circulatory	1 (0.9)	1 (0.9)
Nervous system	0	2 (1.8)
Eye	0	1 (0.9)
Respiratory system	1 (0.9)	0
Digestive system	1 (0.9)	0
Serious adverse events[d]	3 (2.7)	9 (8.3)
Musculoskeletal	0	4 (3.7)
Total hip or knee replacement surgery	0	3 (2.8)
Low back pain[e]	0	1 (0.9)
Circulatory	1 (0.9)	3 (2.8)
Coronary heart disease[f]	1 (0.9)	2 (1.8)
Other	0	1 (0.9)
Genitourinary	1 (0.9)	0
Eye	0	1 (0.9)
Digestive system	1 (0.9)	1 (0.9)

[a] Adverse event categories correspond to chapters in the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision,* and are summarized as clinical subcategories if at least 3 participants experienced a specific type of event.

[b] Corresponds to local adverse events as prespecified in the protocol.

[c] Prespecified in the statistical analysis plan. One participant in the control footwear group experienced a fall while wearing the study footwear.

[d] Defined as events resulting in hospitalization, prolongation of hospitalization, persistent or significant disability, congenital abnormality or birth defects of offspring, life-threatening events, or death.

[e] One participant in the control footwear group underwent lumbar disc herniation surgery.

[f] One participant in the biomechanical footwear group had an acute myocardial infarction.

spent wearing the footwear at 24 weeks of follow-up was 209 minutes/day in the biomechanical footwear group vs 174 minutes/day in the control footwear group (between-group difference, 35 minutes/day [95% CI, 4-67 minutes/day]).

For the SF-36 physical component summary score, there was no statistically significant between-group difference for the biomechanical footwear group vs the control footwear group (mean score, 45.9 vs 44.5, respectively; between-group difference 1.4 [95% CI, −0.5 to 3.2]). There were no significant between-group differences in the SF-36 mental component summary score, for analgesic use, or for health care use. Additional prespecified secondary outcomes, including types of analgesics, types of clinicians visited, use of corticosteroid injections, and performed or planned knee replacement surgeries appear in eTable 4 in Supplement 3.

The other prespecified outcomes appear in eTable 5 in Supplement 3, including participants with a treatment response achieving a 30% or 50% reduction for the WOMAC pain subscore from baseline to 24 weeks of follow-up. Among participants in the biomechanical footwear group, 92% achieved a 30% reduction for the WOMAC pain subscore vs 58% in the control footwear group (risk difference, 34% [95% CI, 23%-45%]), and 83% vs 42%, respectively, achieved a 50% reduction for the WOMAC pain subscore (risk difference, 41% [95% CI, 28%-52%]); the corresponding numbers needed to treat were 3 (95% CI, 2-5) and 3 (95% CI, 1-4).

The prespecified subgroup analyses of the primary outcome according to the predominantly affected compartment and symptomatic contralateral disease did not show significant treatment × subgroup interactions (eTable 6 in Supplement 3). The sensitivity analyses of the primary outcome, including a per-protocol analysis, a complete case analysis, adjustments for potential procedural confounders, and a linear mixed-effects model to analyze all knees with a baseline WOMAC pain subscore of 3 or greater were consistent with the primary outcome analysis (eTables 7-11 in Supplement 3).

Adverse Events

Twenty-six participants (23.4%) in the biomechanical footwear group and 38 participants (34.9%) in the control footwear group experienced an adverse event and 3 (2.7%) and 9 (8.3%), respectively, experienced serious adverse events (**Table 3**). None were considered to be related to treatment. Of the serious adverse events, there were 0 in the biomechanical footwear group vs 4 in the control footwear group that were musculoskeletal, 1 vs 3, respectively, that were circulatory, and 2 vs 2 that were in other categories (eTable 12 in Supplement 3). One or more falls occurred in 2 participants (1.8%) in the biomechanical footwear group and in 4 participants (3.7%) in the control footwear group. One participant in the control group fell while wearing the control footwear.

Post Hoc Analyses

A post hoc subgroup analysis of the primary outcome by WOMAC pain intensity at baseline did not show significant treatment × subgroup interactions (eTable 6 in Supplement 3). The post hoc use of a mixed-effects model simultaneously including all time points showed results similar to those of the main analyses. In the mixed-effects models, there were significant between-group differences in the WOMAC pain and physical function subscores and in the WOMAC global score at 12, 16, and 24 weeks of follow-up, and in the WOMAC stiffness subscore at 16 and 24 weeks of follow-up. Significant between-group differences in parameters of gait analysis were observed for velocity and step length at 12, 16, and 24 weeks of follow-up and for single limb support at 24 weeks of follow-up (eTable 13 in Supplement 3).

eFigure 4 in Supplement 3 contrasts WOMAC pain subscore with the time spent wearing the footwear over the duration of the trial. The maximal between-group difference in time spent wearing the footwear occurred at 16 weeks of follow-up, whereas the maximum between-group difference in the WOMAC pain subscore was observed 8 weeks later at 24 weeks of follow-up.

Discussion

In this randomized clinical trial, the biomechanical footwear system with individually calibrated outsole convex pods was significantly more effective than the control footwear at reducing pain at 24 weeks of follow-up in participants with knee pain from symptomatic knee osteoarthritis. The results were consistent for the secondary outcomes of WOMAC physical function and stiffness subscores and the WOMAC global score at 24 weeks of follow-up. There were no significant between-group differences in the physical and mental components of the SF-36.

There are 2 differences between the biomechanical footwear system tested in this trial and other biomechanical devices such as shoes[9] or wedges.[8] First, in this trial, the individualized calibration of proximal and distal pods of the biomechanical device in the coronal and sagittal planes shifts the trajectory of the foot's center of pressure, thereby specifically changing the direction of the ground reaction force vector as appropriate for each individual.[12,13,30] Second, the convexity of the pods in the biomechanical footwear results in repetitive gait perturbation, with mild destabilization of the knee during walking, which in turn may elicit neuromuscular responses.

To our knowledge, no other published randomized clinical trials have investigated the effectiveness of this biomechanical footwear system in people with symptomatic knee osteoarthritis. Of 6 published clinical studies,[10,11,15,31-33] 4 were uncontrolled studies conducted by the manufacturer,[15,31-33] the remaining 2 were prospective and controlled, but not randomized.[10,11] The most rigorous investigation was a prospective nonrandomized controlled study among 57 participants with symptomatic knee osteoarthritis,[10] which found improved pain and physical function with the biomechanical footwear system compared with the control footwear. However, the between-group difference in the WOMAC pain subscore at 8 weeks of follow-up was not consistent with the negative 8-week result in the current study. The reason for this between-group difference is unclear but may be due to lack of randomization in the prior trial.[10]

Limitations

This study has several limitations. First, there were differences in the appearance of the biomechanical footwear and the control footwear. To overcome this limitation and minimize the likelihood that participants would correctly guess that they were not receiving the active intervention, participants were kept unaware that the control footwear was not expected to have therapeutic benefits. Participants were informed in a neutral fashion that 2 different types of footwear were being compared. The manufacturer's website described the control footwear as a device with a novel design of the sole, and the participants randomized to the control group received a simulated calibration that mimicked the actual calibration.

Second, the use of a blinding index[34] to determine the success of blinding was not performed because such an index assumes indistinguishable interventions. Third, the self-reported time per day wearing the footwear was longer in the biomechanical footwear group than in the control footwear group. It is possible that the greater benefit in the biomechanical footwear group was due to longer wear time.

Fourth, analgesic treatment for pain was allowed during the trial; however, the rates of analgesic use did not differ between groups. Fifth, it was not possible to explore changes in knee adduction moments using 3-dimensional gait analyses.

Sixth, the trial was conducted at a single center, potentially limiting generalizability. Seventh, the between-group differences occurred only late during follow-up and were smaller than the observed within-group change from baseline in the control group. Therefore, the clinical importance of these findings remains uncertain. Eighth, the findings from this trial are not generalizable to people at high risk for falls because these individuals were not eligible to participate. Ninth, the findings are not generalizable to people with severe knee pain because these individuals were underrepresented in the trial.

Conclusions

Among participants with knee pain from osteoarthritis, use of biomechanical footwear compared with control footwear resulted in an improvement in pain at 24 weeks of follow-up that was statistically significant but of uncertain clinical importance. Further research would be needed to assess long-term efficacy and safety, as well as replication, before reaching conclusions about the clinical value of this device.

ARTICLE INFORMATION

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