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Exercise and footwear in medial knee osteoarthritis: a randomized controlled trial comparing flat flexible footwear to stable supportive shoes

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Abstract

Objective: This randomized controlled trial (RCT) investigated whether adding daily use of flat flexible footwear (FFF) to a strengthening and aerobic exercise program improved short- and longer-term outcomes compared with adding stable supportive shoes (SSS) in people with medial tibiofemoral OA.

Methods: Participants ($n = 97$) with medial tibiofemoral OA were randomly assigned (1:1) to the FFF ($n = 50$) or SSS ($n = 47$) group. Participants in both groups received a 9-month intervention (3 months supervised followed by 6 months unsupervised exercise). The primary outcome was the change in knee pain on walking at 3 months measured using an 11-point numeric rating scale (NRS). Secondary outcomes included the change from baseline to 3 and 9 months in the severity of knee pain overall (NRS), physical function (WOMAC subscale), habitual physical activity level (Physical Activity Scale for the Elderly), quality of life (QoL) (European Quality of Life 5-Dimensions 5-Levels questionnaire) and markers of inflammation (effusion and Hoffa synovitis) and structural disease progression (bone marrow lesions).

Results: There were no significant differences between the groups in the change in pain on walking [between-group difference −0.67 (95% CI −1.62, 0.29)] at 3 months. Knee pain on walking and overall knee pain significantly decreased in both groups at 3 and 9 months. Physical function and QoL improved in both groups at 3 and 9 months. We found no between-group differences in any secondary outcome at any time.

Conclusions: FFF added to exercise therapy did not provide additional better symptom nor structure-modification benefit compared with conventional SSS and exercise in people with medial tibiofemoral OA.

Trial registration: ClinicalTrials.gov (http://clinicaltrials.gov), NCT03796832.

Lay Summary

What does this mean for patients?

This study aimed to see if wearing flexible flat footwear (FFF) alongside a 9-month exercise program could provide more pain relief and functional improvement for people with knee osteoarthritis (OA) than wearing stable supportive shoes (SSS) with the same exercise program. We randomly assigned 97 participants with (medial tibiofemoral) knee OA into two groups: one wore FFF and the other wore SSS, with both groups doing exercises (strength and endurance) for 3 months supervised by physiotherapists followed by exercising 6 months at home. After 3 months, the main outcome was knee pain during walking, rated on a scale of 0 to 10. Both groups showed similar improvements in pain and overall knee function, and these improvements continued after 9 months. There was no significant difference between the FFF and SSS groups for knee pain, physical functioning, quality of life and physical activity. In summary, exercise benefits knee pain during walking in people with knee OA. Adding FFF to this program did not provide extra benefits over wearing SSS.

Keywords: osteoarthritis, knee, footwear, shoes, clinical trial, RCT, magnetic resonance imaging, MRI, knee pain, inflammation, synovitis, effusion.

Key messages

- Clinical guidelines suggest using 'appropriate' footwear for knee osteoarthritis self-management, but evidence is limited.
- Flat flexible footwear does not provide superior therapeutic benefits compared with stable supportive shoes during exercise.
- Patients should adhere to existing clinical guidelines.
- Future studies must identify optimal footwear for knee osteoarthritis patients that effectively reduces medial knee loading with consequent therapeutic benefits.

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Introduction

Clinical guidelines recommend the use of 'appropriate' footwear for self-management of knee OA [1, 2]. However, these recommendations are largely based on expert opinion alone. Biomechanical data show that walking in heeled or conventional everyday shoes can cause an increase in medial knee loading of up to 12% compared with walking barefoot [3, 4]. Consequently, there is growing interest in flat flexible or 'minimalistic' footwear (FFF), which tries to mimic barefoot walking and may be an appealing alternative to common footwear. The addition of FFF to exercise therapy may be a feasible option to enhance the therapeutic effects by offloading the medial tibiofemoral compartment. FFF demonstrated unloading capacities [5, 6], in contrast to the mostly recommended stable supportive shoes (SSS) [7]. Nevertheless, recent evidence suggests SSS are effective, compared with FFF, in reducing walking knee pain and medial tibiofemoral contact force (MTCF) in individuals with medial tibiofemoral OA [8]. However, another study proved FFF to be effective in reducing pain and improving function in patients with medial tibiofemoral OA [9]. Since no consensus exists, it remains unclear whether the addition of FFF to exercise therapy may be a feasible option to enhance the therapeutic effects of exercises by offloading the medial tibiofemoral compartment.

The aim of this study was to evaluate the efficacy of integrating daily use of FFF into a concurrent strengthening and aerobic exercise program in order to improve short- and longer-term treatment outcomes for patients with medial tibiofemoral OA compared with conventional SSS. We hypothesized that after 3 months the FFF group would demonstrate greater improvement in average knee pain during walking compared with the SSS group. Our secondary hypotheses were that the FFF group would also show greater improvement in knee pain during walking at 9 months, greater reductions in inflammation and structural disease progression at 3 and 9 months and better outcomes in physical functioning, average knee pain severity, patient-perceived global change in symptoms, physical activity and health-related quality of life (QoL) at 3 and 9 months compared with the SSS group.

Methods

Study design and participants

We conducted a two-arm, parallel-group, single-centre comparative efficacy randomized controlled trial (RCT). The study was approved by the Ethics and Research Committee of Ghent University (project number EC2018/0084, approved on 5 March 2018) and prospectively registered at ClinicalTrials.gov (NCT03796832). The trial was reported according to the recommendations of the Consolidated Standards of Reporting Trials statement [10, 11]. All participants provided written informed consent. This study consisted of a 9-month intervention with three data collection points: baseline, 3 months (primary time point) and 9 months. Between February 2019 and February 2022, we recruited patients with medial tibiofemoral OA from the Flanders (Belgium) community via social media ($n = 856$), mailings ($n = 119$), general and specialist medical practitioners ($n = 65$) and fliers and posters in hospitals ($n = 28$), pharmacies and residential care homes ($n = 18$). First, eligibility was confirmed through an online and telephone survey, followed by radiographic screening, scored by a rheumatologist with >10 years of experience in grading radiographic knee OA (R.W.). Participants meeting all the inclusion and exclusion criteria (Supplementary Table S1, available at *Rheumatology Advances in Practice* online) were enrolled. The most painful knee was considered the study knee. In cases of bilaterally eligible knees, the right knee was studied.

Randomization and blinding

All procedures were performed at the Department of Rehabilitation Sciences, Ghent University. Participants were randomly assigned to either the FFF or SSS groups in a 1:1 ratio. The randomization schedule, with block sizes of 2, 4, 6 and 8 and stratification by sex and radiographic severity [Kellgren–Lawrence (KL) grade 2, 3 or 4], was prepared by an independent biostatistician. Allocation concealment was ensured using sealed opaque envelopes stored securely and opened sequentially within each stratum by a non-involved researcher. Baseline data collection occurred before randomization. Follow-up testing involved two researchers, one blinded to group allocation while the other (the physiotherapist overseeing the intervention) was not. Data processing and analysis were conducted by a researcher blinded to group allocation. Patients were blinded to research hypotheses but not the intervention, due to the impracticality of concealing shoe characteristics. The therapist monitoring exercise therapy minimized contact between subjects in different arms. Assessment was interrupted for 3 months during the COVID-19 pandemic, resulting in missing MRI data (Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

Intervention

Our intervention combined exercise therapy and two types of shoes.

Shoes

Participants were assigned appropriately sized shoes based on their random assignment and instructed to wear them daily for 9 months as much as possible, aiming for a minimum of 4 h/day, including during exercise, and to minimize use of other shoes. Off-the-shelf commercially available shoes were provided, complying with previously published criteria [5]. The intervention group received FFF, also known as 'minimalistic shoes' (Vivobarefoot, Primus Lite III), while the comparator group received SSS (Merrell, Jungle Moc) (Supplementary Fig. S1, available at *Rheumatology Advances in Practice* online) [5]. Shoe manufacturers had no involvement in this trial.

Exercise therapy

Participants underwent a physiotherapist-supervised program for the first 3 months [12], involving a weekly 30-min group session comprising a 10-min warm-up followed by circuit training of strengthening and neuromuscular exercises targeting the trunk, hips and knees. Home-based exercises complemented the sessions to achieve a minimum of four weekly sessions. Elastic bands or body weight served as resistance, with exercise dosage tailored to reach three sets of 10 repetitions at 80% of 1 repetition maximum. Progression of resistance or coordination difficulty was tailored based on the individual (technique evaluated by the physiotherapist) and according to a prespecified progression protocol (Supplementary Data S1, available at *Rheumatology Advances in Practice* online) [12].

Participants were also encouraged to engage in daily aerobic physical activity, aiming for at least 70 min/week at moderate intensity [grade 5–6 (out of 10, maximum exertion) on a rate of perceived exertion (RPE) scale]. In the subsequent 6 months, an unsupervised program comprised six prescribed exercises to maintain leg muscle strength and increase aerobic physical activity to 150 min/week, aligning with general physical activity guidelines for older adults (moderate intensity of RPE grade 5–6) [13, 14]. A manual facilitated home-based exercise (Supplementary Data S1, available at *Rheumatology Advances in Practice* online). Monthly supervised booster sessions ensured technique evaluation, progression adjustment and adherence enhancement. Remote guidance was provided for some patients between March and May 2020 due to COVID-19 restrictions.

Outcome measures

The primary outcome measure was the change from baseline to 3 months in average knee pain on walking in the past week measured using a 11-point numeric rating scale (NRS) with terminal descriptors of 0 (no pain) to 10 (worst pain imaginable) and a minimum clinically important difference (MCID) of 1.8 NRS units was defined [15].

Secondary outcomes included pain, function, physical activity and QoL:

- knee pain severity overall on an 11-point NRS (0–10);
- physical dysfunction using the WOMAC function subscale (Likert version, 0–68, higher score indicates greater dysfunction, MCID of 6 units) [16];
- habitual physical activity level, measured using the Physical Activity Scale for the Elderly (PASE) (range 0–≥400, higher scores indicate greater physical activity) [17];
- average daily step count, measured using a hip worn pedometer (Walking Style Pro 2.0; Omron Healthcare, Lake Forest, IL, USA) for 7 consecutive days at baseline and 3 and 9 months.
- health-related QoL, assessed using the European Quality of Life 5-Dimensions 5-Levels questionnaire, containing five questions rated on a 5-point scale from 1 (no problems) to 5 (unable to perform), converted into a weighted index score ranging from 0 to 1, with a higher score indicating better health-related QoL [18–20];

and markers of inflammation and structural lesions. The following measurements were obtained using the MRI Osteoarthritis Knee Score (MOAKS) [21] at baseline, 3 months and 9 months: Hoffa synovitis (range 0–3), effusion synovitis (range 0–3) and bone marrow lesions (BMLs) (range 0–3).

MRI procedures were performed as previously described [22] (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). Briefly, MRIs were scored independently by one expert musculoskeletal radiologist and a doctoral student.

BMLs were scored in 14 subregions [23]. We focused solely on the size component of BML assessment, combining ill-defined and cystic parts for clinical relevance, as subchondral cysts have marginal symptom association [23]. The change in the overall number of subregions affected by any BML (size >0) was calculated by the difference between 3 months and baseline [23]. The same was done to compare the change between baseline and 9 months. Following established methods [24, 25], subregion scores for BMLs were consolidated into a continuous total score (total bone marrow lesions). The same approach was used for Hoffa synovitis and effusion synovitis (total score effusion synovitis) [25].

Adherence to shoe wearing time and patients' expectations

Self-reported (logbooks) wearing time of allocated shoes was measured for 7 consecutive days each week during the first 3 months and for 7 consecutive days each month during the last 6 months. Participants averaging ≥4 h/day [26] during the first 3 months (primary time point) were defined as 'compliers'. Overall compliance with shoe and exercise therapy instructions was rated on a 11-point NRS [from 0 (never worn) to 10 (always worn) and from 0 (not at all compliant) to 10 (extremely compliant)]. Additionally, a shoe-mounted pedometer (Omron Walking Style Pro 2.0) tracked shoe usage. Patient expectations on exercise therapy and the allocated shoes' effects on pain and QoL were assessed using an 11-point NRS [from 0 (strongly disagree) to 10 (completely agree)]. Expectations on the effects of allocated shoes on the knee joint, walking support and pain reduction were also rated on the 11-point NRS. Because wearing time was not available, we included step count data for days with at least 1000 steps, approximating 10 min of walking [27]. Mean daily step averages were calculated when participants had at least 3 days with data, providing a reliable estimate of physical activity [28, 29].

Perceived change

Participant-perceived global change in pain, physical function and global change overall was scored on a 7-point ordinal scale [from 1 (much worse) to 7 (much better)]. Participants reporting 'moderately better' and above were classified as 'improved' [33].

Descriptive measurements were measured at baseline and included age, sex, symptom duration, BMI, radiographic OA severity (KL grade) [30] and foot posture using the Foot Posture Index [31].

Sample size

The trial was powered to detect a significant difference between treatment arms in the change in average knee pain on walking, measured at 3 months as compared with baseline (primary outcome). The MCID to be detected in OA was 1.8 units [15]. We assumed a between-participant standard deviation of 2.5 units for pain (adjusted for a baseline–3 months correlation of 0.3). Using analysis of covariance adjusted for baseline score, we needed at least 42 participants in each arm to achieve 90% power and $\alpha = 0.05$ in detecting an MCID, or a total sample of $n = 106$, including a 20% drop-out rate.

Statistical analysis

Baseline data are presented as mean and SD. Categorical or dichotomous data were summarized with frequencies. Demographic characteristics and baseline data were examined for those who dropped out and those who remained (Supplementary Table S5, available at *Rheumatology Advances in Practice* online). As the main analysis, a generalized linear mixed model (GLMM) was used with random intercept and restricted maximum likelihood estimation to assess treatment group effects. The GLMM included group

and time as fixed effects and subject as a random effect, with stratification variables (sex and KL grade) as covariates and baseline as the reference. The interaction effects group*time was the primary analysis. The results are presented as marginal means with 95% CIs. No imputation was performed for missing data. All models were performed on two a priori decided cohorts, intention-to-treat (ITT) including all randomized patients (main results) and per-protocol (PP), which included participants who wore study shoes for ≥4 h/day (compliers) and provided 3 months follow-up for the primary outcome. Adverse events (all combined) were compared between groups using the chi-squared test; Fisher's exact test was used for comparing the frequencies of the individual adverse events. All tests were two-tailed with statistical significance set at the conventional level of 0.05. All analyses were performed using SPSS version 28 (IBM, Armonk, NY, USA).

Results

A total of 97 patients were enrolled, with 47 allocated to SSS and 50 allocated to FFF (Fig. 1). Seventy-one (73%) completed the 9-month treatment period. Twelve participants (12%) withdrew in the initial 3 months and 26 (27%) withdrew over the 9-month period, with similar reasons for discontinuation across groups. Baseline characteristics were comparable between groups (Table 1). The study population [mean age 64 years (S.D. 7), mean BMI 28 kg/m^2 (S.D. 4)] included 52 (54%) women. Forty-two (43%), 45 (46%) and 10 (10%) had KL grade 2, 3 and 4, respectively. The mean reported daily shoe wearing time was 6.8 h (S.D. 2.5) for FFF and 6.6 h (S.D. 2.2) for SSS (Supplementary Table S6, available at *Rheumatology Advances in Practice* online). High and comparable compliance with both shoe wearing and exercise therapy were observed in both groups throughout the study (Supplementary Table S6, available at *Rheumatology Advances in Practice* online). Co-interventions, including medication and other treatments, were similar between groups, except for slightly higher reported use of weight-loss treatments and paracetamol in the SSS group (Supplementary Table S5, available at *Rheumatology Advances in Practice* online). Intra- and interrater reliability in MRI scoring ranged from good to very good agreement (weighted linear $\kappa = 0.7$–0.9) (Supplementary Table S4, available at *Rheumatology Advances in Practice* online).

ITT analysis

At 3 months there was no significant between-group differences in changes in knee pain on walking in the past week [between-group difference −0.67 (95% CI −1.62, 0.29)]. Both groups had a clinically relevant improvement (>1.8 NRS units) of average knee pain severity on walking at 3 months [−2.59 units (95% CI −3.42, −1.76) and −1.92 units (95% CI −2.74, −1.10) respectively] (Table 2 and Fig. 2).

We found no between-group differences in the change in any continuous secondary outcome at any time (Table 2). Average knee pain severity on walking improved at 9 months in both groups [−2.45 units (95% CI −3.35, −1.58) and −2.56 units (95% CI −3.42, −1.69), respectively] (Table 2 and Fig. 2). Overall knee pain significantly decreased in both groups at 3 and 9 months. Physical function and QoL improved in both groups at 3 and 9 months. No statistically significant differences were found between the two groups in the overall number of subregions affected by any BML at 3 and 9 months, as well as the change in effusion synovitis total score at these time points (Table 3). Descriptive data on the number of BMLs in the knee and each subregion, as well as Hoffa synovitis and effusion synovitis, are provided in Supplementary Tables S7 and S8, available at *Rheumatology Advances in Practice* online.

The participant-perceived improvement in pain, physical function and overall global change were similar between groups (Table 4). Participants' expectations were similar between groups (Supplementary Table S9, available at *Rheumatology Advances in Practice* online).

PP analysis

Participants defined as compliers (participants who self-reported wearing the study shoes for ≥4 h/day) and received treatment for 3 months were included in the PP analysis (38 patients in the SSS group and 41 patients in the FFF group). The PP analysis showed that at 3 months there was no significant between-group differences in changes in knee pain on walking in the past week and in any of the secondary outcomes (Supplementary Tables S10 and S11, available at *Rheumatology Advances in Practice* online).

Adverse events

Adverse events were more prevalent in the SSS group as compared with the FFF group (23 *vs* 15; $P = 0.073$; Supplementary Table S12, available at *Rheumatology Advances in Practice* online). Low back pain was more prevalent in the SSS group as compared with the FFF (9 *vs* 2; $P = 0.025$) with 2 (4%) classified as unrelated to the study and the remaining 7 (15%) possibly study related. In contrast, knee pain was reported more often in the FFF group (8 *vs* 2; $P = 0.093$), yet the proportion of persons discontinuing treatment for knee pain did not differ between groups [$n = 2$ (4%), $n = 2$ (4%)]. Adverse event classifications were conducted by a rheumatologist (R.W.), who was blinded to treatment allocation.

Discussion

Adding daily FFF use to concurrent strengthening and aerobic exercise did not result in greater improvement in knee pain during walking at 3 months for patients with medial tibiofemoral OA compared with conventional SSS. Similarly, no greater reduction in knee pain on walking at 9 months or in inflammation and structural disease progression at 3 and 9 months was observed in the FFF group. Additionally, FFF did not result in better physical functioning, average knee pain severity, patient-perceived global change, physical activity or health-related QoL at 3 and 9 months compared with SSS. Our findings suggest that people with medial tibiofemoral OA can improve their symptoms, function and QoL following a strengthening and aerobic exercise program with no significant difference observed between daily FFF or conventional SSS use.

Despite evidence showing that walking in everyday shoes significantly increases knee loading compared with barefoot walking [3, 4] and that FFF reduces medial knee load compared with SSS [5, 32], we were unable to demonstrate that combining FFF with exercise resulted in greater symptoms compared with SSS. The unloading properties of FFF may not sufficiently enhance symptom and function

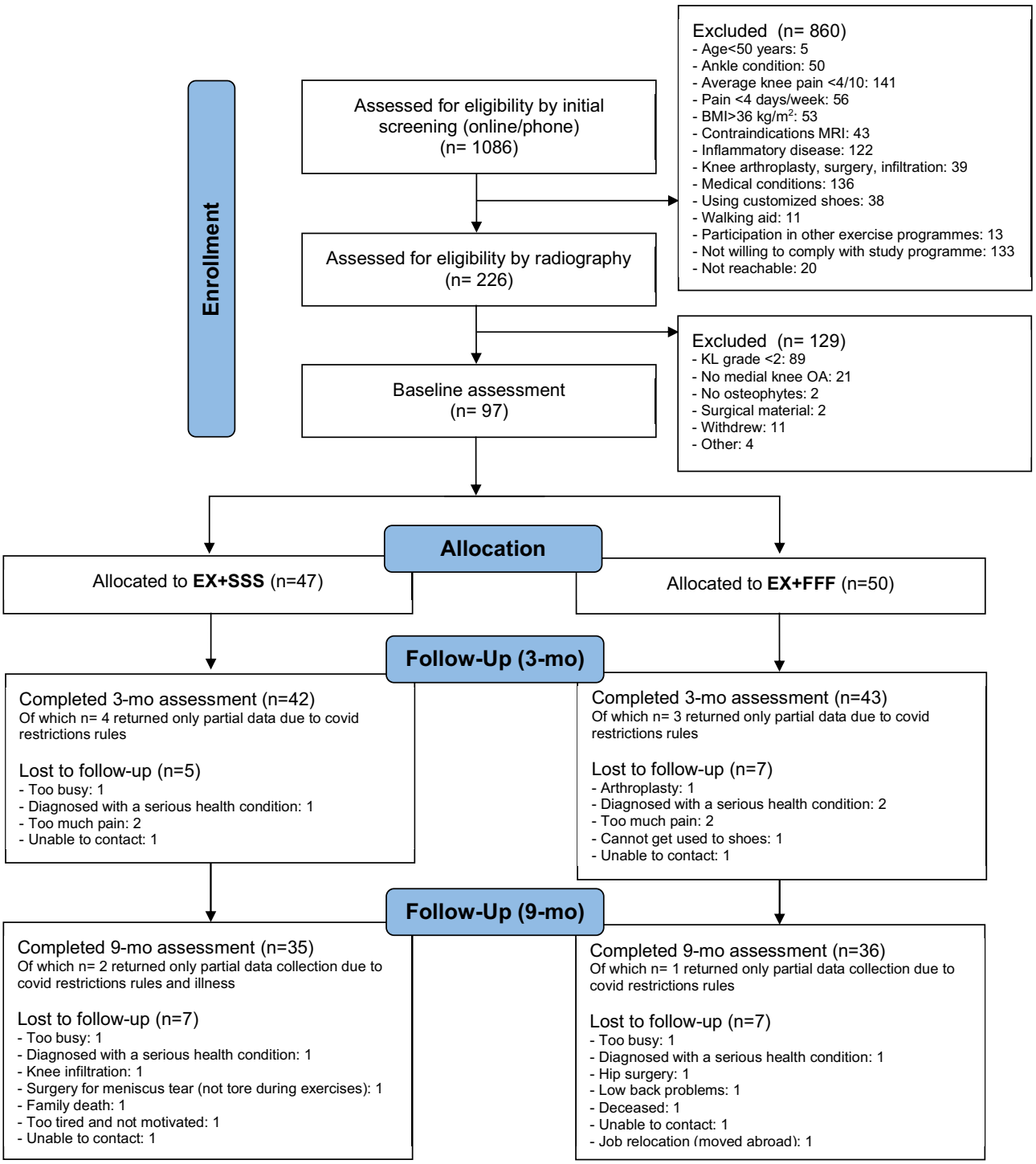

Figure 1. Study flow diagram

improvements when combined with exercise, possibly overshadowed by exercise effects. Additionally, more participants in the SSS group reported baseline paracetamol use, which may have influenced their pain perception and consequently the outcomes when comparing the two groups. FFF participants reported more knee pain adverse events, but the exact reasons are unclear. It is possible that participants need more time to adapt to the new shoes compared with the more commonly worn SSS by patients with knee OA. Another potential factor influencing our findings is that FFF may not provide unloading features for everyone, as shown by a recent randomized crossover study revealing higher MTCF during loading with FFF compared with SSS for people with medial knee OA and varus malalignment [8]. Thus individual characteristics, such as knee alignment, could impact the unloading effects of both FFF and SSS.

Our study uniquely combines FFF with exercise therapy, making direct comparison with previous literature challenging. A recent robust RCT demonstrated that in individuals with moderate to severe medial knee OA, those wearing SSS

Table 1. Baseline characteristics of knee OA patients.

Characteristics	Total ($n = 97$)	SSS ($n = 47$)	FFF ($n = 50$)
Age, years, mean (S.D.)	64 (7)	63 (8)	65 (6)
Female, *n* (%)	52 (54)	27 (57)	25 (50)
Symptom duration (years), *n* (%)			
<1	6 (6)	2 (4)	4 (8)
1–2	19 (20)	11 (23)	8 (16)
3–5	26 (27)	14 (30)	12 (24)
6–10	20 (21)	7 (15)	13 (26)
>10	26 (27)	13 (28)	13 (26)
Height, cm, mean (S.D.)	169.1 (8.7)	168.8 (8.6)	169.1 (9.0)
Weight, kg, mean (S.D.)	81.6 (14.4)	81.7 (12.9)	80.9 (14.7)
BMI, kg/m^2, mean (S.D.)	28.4 (3.7)	28.6 (3.4)	28.2 (4.0)
KL, *n* (%)			
2 (mild)	42 (43)	19 (40)	23 (46)
3 (moderate)	45 (46)	23 (49)	22 (44)
4 (severe)	10 (10)	5 (11)	5 (10)
Foot posture index classification, *n* (%)			
Normal	67 (69)	32 (68)	35 (70)
Supinated	16 (17)	9 (19)	7 (14)
Highly supinated	1 (1)	0 (0)	1 (1)
Pronated	12 (12)	6 (13)	6 (12)
Highly pronated	1 (1)	0 (0)	1 (2)
Current pain medication use[a], n (%)			
Anti-inflammatory			
NSAIDs	18 (19)	9 (19)	9 (18)
Cyclooxygenase-2 inhibitors	7 (7)	5 (11)	2 (4)
Analgesics			
Paracetamol	13 (13)	10 (21)	3 (6)
Paracetamol combined with codeine	2 (2)	1 (2)	1 (2)
Opioids			
Tramadol	1 (1)	0 (0%)	1 (2.0)
Oral opioids	1 (1)	0 (0%)	1 (2.0)
Topical			
Anti-inflammatory gel	12 (12)	6 (13)	6 (12)
Balm gel	5 (5)	1 (2)	4 (8)
Oral corticosteroids	2 (2)	1 (2)	1 (2)
Glucosamine	21 (22)	10 (21)	11 (22)

[a] Defined as at least once per week over the prior month.

Table 2. Changes in pain, physical function and QoL in the SSS and FFF groups across visits[a].

Group	Estimated marginal means (95% CI)		Between-group difference compared with baseline (95% CI)
	SSS	FFF	
NRS pain on walking (0–10)			
Baseline	5.55 (4.97, 6.13)	4.96 (4.40, 5.52)	Reference
3 months	2.97 (2.36, 3.58)	3.04 (2.44, 3.64)	−0.67 (−1.62, 0.29)
9 months	3.09 (2.43, 3.75)	2.41 (1.76, 3.05)	0.09 (−0.92, 1.10)
NRS pain average (0–10)			
Baseline	4.81 (4.31, 5.31)	4.52 (4.04, 5.00)	Reference
3 months	2.33 (1.80, 2.85)	2.38 (1.87, 2.90)	−0.34 (−1.18, 0.49)
9 months	2.32 (1.75, 2.88)	1.79 (1.23, 2.35)	0.24 (−0.64, 1.12)
WOMAC physical function (0–68)			
Baseline	25.57 (22.55, 28.60)	26.36 (23.43, 29.29)	Reference
3 months	13.67 (10.54, 16.81)	15.62 (12.55, 18.70)	−1.17 (−5.18, 2.85)
9 months	12.43 (9.09, 15.77)	11.13 (7.89, 14.38)	2.09 (−2.22, 6.39)
PASE (0–>400)			
Baseline	150.91 (131.75, 170.04)	144.22 (125.65, 162.78)	Reference
3 months	155.08 (135.13, 175.02)	141.17 (121.56, 160.78)	7.22 (−20.12, 34.56)
9 months	165.91 (144.50, 187.33)	155.73 (134.91, 176.56)	3.50 (−25.80, 32.80)
EQ-5D-5L QoL (−0.532–1)			
Baseline	0.781 (0.751, 0.810)	0.801 (0.772, 0.830)	Reference
3 months	0.834 (0.803, 0.866)	0.863 (0.832, 0.894)	−0.009 (−0.058, 0.041)
9 months	0.846 (0.812, 0.880)	0.883 (0.850, 0.916)	−0.017 (−0.070, 0.036)

[a] Analysis was performed using linear mixed models.

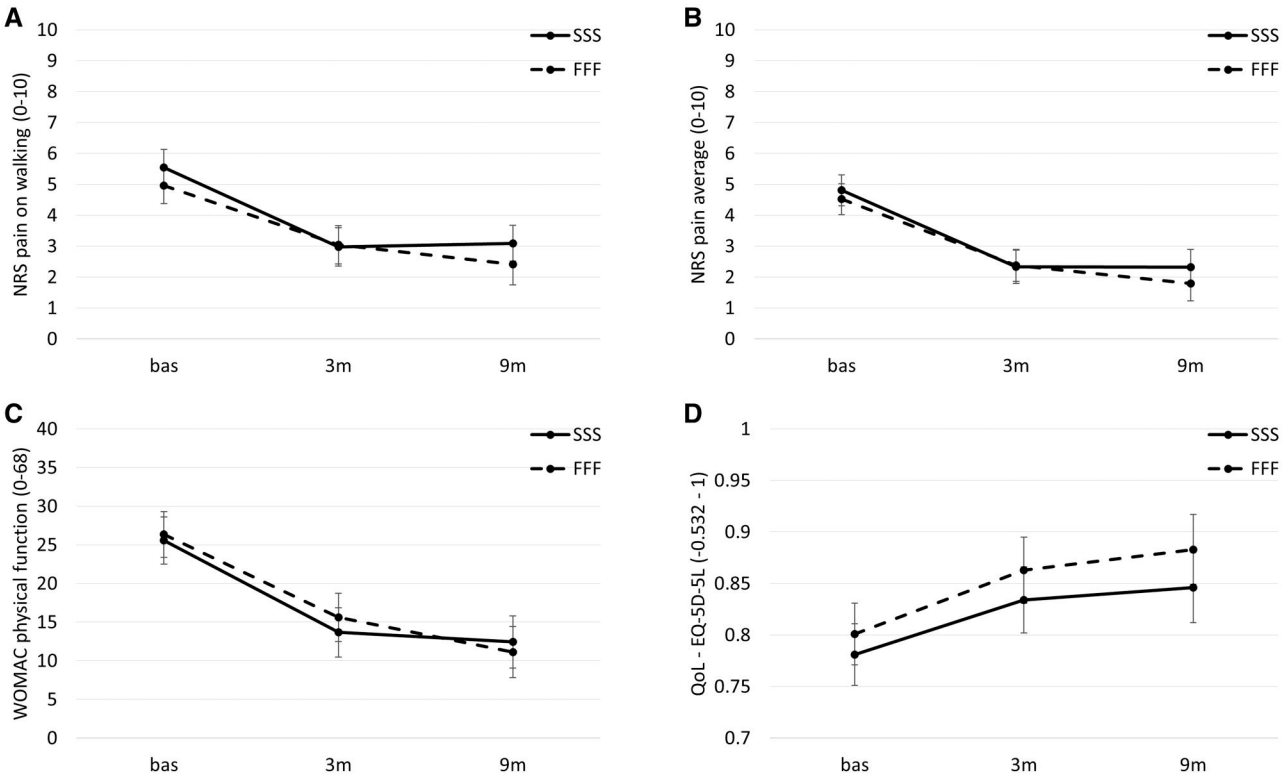

Figure 2. Changes in knee pain, QoL and physical function from baseline to 9 months in both groups. Marginal means (95% CIs) as a result of mixed model analyses of the scores in (**A**) NRS pain on walking, (**B**) NRS pain average, (**C**) WOMAC physical function and (**D**) EQ-5D-5L in the SSS (solid line) and FFF (dash dot line) groups. Higher scores represent worse pain (A, B), worse physical function (C) and improved QoL (D). Bas: baseline; 3 m: 3 months; 9 m: 9 months

Table 3. Changes in overall number of BMLs in the whole knee and effusion synovitis in the SSS and FFF groups across visits[a].

Group	Estimated marginal means (95% CI)		Between-group difference compared with baseline (95% CI)
	SSS	FFF	
Total bone marrow lesions (0–42)			
Baseline	3.92 (3.05, 4.78)	4.42 (3.59, 5.26)	Reference
3 months	4.17 (3.24, 5.12)	4.39 (3.47, 5.31)	0.28 (−0.85, 1.42)
9 months	4.02 (3.07, 4.97)	4.75 (3.81, 5.69)	−0.23 (−1.39, 0.94)
Total score effusion synovitis (0–6)			
Baseline	1.89 (1.44, 2.35)	2.32 (1.88, 2.76)	Reference
3 months	2.48 (1.97, 2.99)	2.48 (1.98, 2.98)	0.42 (−0.25, 1.09)
9 months	2.24 (1.73, 2.76)	2.36 (1.85, 2.87)	0.31 (−0.38, 0.99)

[a] Analysis was performed using linear mixed models.

Table 4. Participants classified as 'improved'

Classification	3 months – baseline, *n* (%)		9 months – baseline, *n* (%)	
	SSS (*n* = 42)	FFF (*n* = 43)	SSS (*n* = 35)	FFF (*n* = 36)
Improved pain[a]	16 (38)	23 (54)	20 (57)	24 (67)
Improved function[a]	19 (45)	22 (51)	19 (54)	21 (58)
Improved overall[a]	19 (45)	24 (56)	21 (60)	24 (67)
Improvement >1.8 NRS units[b]	29 (69)	24 (56)	25 (71)	26 (72)

Number (percentage) of participants classified as 'improved' based on self-perceived global change (3-months minus baseline and 9-months minus baseline) in pain, function and global change overall or achieving a clinically relevant improvement of 1.8 NRS units on pain during walking, by groups.
[a] Rated using a 7-point ordinal scale with terminal descriptors of 1 (much worse) to 7 (much better), with participants reporting 'moderately better' or 'much better' classified as 'improved'.
[b] Improvement of >1.8 NRS units is the MCID.

for 6 months (≥6 h/day) experienced a greater reduction in knee pain during walking compared with those wearing FFF [mean difference 1.1 units (95% CI 0.5, 1.8)] [33].

In contrast, another 6-month RCT focused on FFF effects in medial knee OA patients without concurrent exercise. The study revealed that women with medial knee OA wearing flat flexible 'Moleca' shoes for 6 months had greater improvements in pain (effect size 1.41, $P < 0.001$) and physical function compared with those in neutral tennis shoes [9]. Although both groups in our study showed comparable improvements, our results did not favour one type of shoe over the other. Notably, our sample included mild to moderate knee OA patients, differing from Paterson et al. [33], which involved moderate to severe cases, and Trombini-Souza et al. [9], which included only females with mild to moderate knee OA. Another significant difference that could account for variations in the results across trials is that our study instructed participants to wear shoes for >4 h/day, whereas in the other trials, they were asked to wear shoes for >6 h/day [9, 33].

No significant changes were observed in structural disease progression and inflammation measures, including BMLs and inflammatory markers like Hoffa synovitis and effusion synovitis, throughout the study period. Several factors, such as genetics, age, sex, joint malalignment, obesity, previous joint injury and joint geometry, may also contribute to the subchondral bone integrity in addition to alteration in loading [34], providing a possible explanation for the observed lack of significant findings. Consistent with a meta-analysis that demonstrated low-quality evidence of no treatment effect on the odds of a change in synovitis [35], our study found no significant difference in the change in inflammatory markers measured on non-contrast MRI between the two groups over time. Similarly, a recent RCT revealed that despite a reduction in pain, synovitis measured on both contrast- and non-contrast-enhanced MRI remained unchanged in patients with knee OA who underwent 3 months of exercise therapy compared with a no-attention control group [36].

To the best of our knowledge, this is the first RCT to investigate the effects of daily use of FFF or SSS combined with a strengthening and aerobic exercise program on improving short- and long-term outcomes in people with medial tibiofemoral OA. We acknowledge a series of strengths and limitations. Drop-out rate in the first 3 months was lower (12%) than anticipated (20%). Due to the impact of COVID-19 during our trial and the consequent time constraints, we did not manage to recruit 106 participants as per our sample size calculation. Nevertheless, 42 participants in each arm completed 3 months of follow-up, providing 90% power to detect significant differences in average knee pain during walking (primary outcome). The GLMM, a very robust methodology against missing data, along with the PP analysis (whose results align with the ITT analysis), suggests that the lack of a statistical difference in pain reduction between the two groups from baseline to 3 months is unlikely to be due to compliance issues. Due to a higher drop-out rate in the 9-month period, we did no achieve 90% statistical power for the secondary outcomes analysis.

Participants were not blinded to shoe allocation and supervision of the exercise session was performed by an investigator participating in data collection and therefore not blinded to shoe allocation. However, the investigator analysing the data remained blinded to group allocation. We did not include biomechanical data demonstrating that FFF reduce medial knee loading more effectively than SSS, leaving the unloading effects in our study uncertain. Furthermore, the unloading properties of the FFF used in this trial may have different biomechanical properties compared with the ones used in previous studies [9, 26, 33]. Tibiofemoral alignment was not assessed, and a third group with exercise alone was absent, preventing a direct comparison with the combined intervention group. Additionally, our step count data did not include measures of sedentary time, upright time and walking time, which may provide a more comprehensive understanding of activity patterns.

In conclusion, the results of this study showed that adding daily use of either FFF or SSS into a concurrent strengthening and aerobic exercise program resulted in significant improvements in symptoms, function and QoL for individuals with medial tibiofemoral OA, but FFF did not result in greater improvement over conventional SSS. This RCT is, to the best of our knowledge, the first study to investigate the potential benefits of adding daily use of FFF to a concurrent strengthening and aerobic exercise program for patients with medial tibiofemoral OA compared with conventional SSS.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

All data relevant to the study are included in the article or its supplementary material. Full datasets are available from the corresponding author upon reasonable request.

Authors' contributions

All authors made substantial contributions to the conception or design of the work and the acquisition and interpretation of data. All authors contributed to the critical review and revision of the manuscript and approved the final version. All the authors agreed to be accountable for all aspects of the work.

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