

Original Article

Knee osteoarthritis pendulum therapy: *In vivo* evaluation and a randomised, single-blind feasibility clinical trialLixia Huang^a, Zhidao Xia^{b,1}, Derick Wade^c, Jicai Liu^a, Guoyong Zhou^a, Chuanhua Yu^d, Helen Dawes^{e,c}, Patrick Esser^c, Shijun Wei^{f,*}, Jiuhong Song^{g,**}^a Tianyuan Translational Medicine R&D Team, Medical School, Jiangnan University, Wuhan, Hubei Province, China^b Institute of Life Science, Swansea University Medical School, Singleton Park, Swansea, SA2 8PP, UK^c Centre for Movement, Occupation and Rehabilitation Sciences (MORES), Faculty of Health and Life Sciences, Oxford Brookes University, Gypsy Lane, Headington, Oxford, OX3 0BP, UK^d Department of Epidemiology and Biostatistics, School of Public Health, Wuhan University, Wuhan, Hubei Province, China^e NIHR Exeter BRC, College of Medicine, Department of Public Health & Sports Sciences, Faculty of Health and Life Sciences, University of Exeter, UK^f Department of Orthopaedics, General Hospital of Central Theatre Command of PLA, No. 627, Wuluo Road, Wuhan, Hubei Province, China^g Wuhan FL Medical Science & Technology Ltd., Machi Road, Dongxihu District, Wuhan, Hubei Province, China

ARTICLE INFO

Keywords:

Clinical trials

Intraarticular pressure

Knee osteoarthritis (KOA)

Knee osteoarthritis pendulum therapy (KOAPT)

ABSTRACT

Background: Exercise is recommended as the first-line management for knee osteoarthritis (KOA); however, it is difficult to determine which specific exercises are more effective. This study aimed to explore the potential mechanism and effectiveness of a leg-swinging exercise practiced in China, called 'KOA pendulum therapy' (KOAPT). Intraarticular hydrostatic and dynamic pressure (IHDP) are suggested to partially explain the signs and symptoms of KOA. As such this paper set out to explore this mechanism *in vivo* in minipigs and in human volunteers alongside a feasibility clinical trial. The objective of this study is 1) to analyze the effect of KOAPT on local mechanical and circulation environment of the knee in experimental animals and healthy volunteers; and 2) to test if it is feasible to run a large sample, randomized/single blind clinical trial.

Methods: IHDP of the knee was measured in ten minipigs and ten volunteers (five healthy and five KOA patients). The effect of leg swinging on synovial blood flow and synovial fluid content depletion in minipigs were also measured. Fifty KOA patients were randomly divided into two groups for a feasibility clinical trial. One group performed KOAPT (targeting 1000 swings/leg/day), and the other performed walking exercise (targeting 4000 steps/day) for 12 weeks with 12 weeks of follow-up.

Results: The results showed dynamic intra-articular pressure changes in the knee joint, increases in local blood flow, and depletion of synovial fluid contents during pendulum leg swinging in minipigs. The intra-articular pressure in healthy human knee joints was -11.32 ± 0.21 (cmH₂O), whereas in KOA patients, it was -3.52 ± 0.34 (cmH₂O). Measures were completed by 100% of participants in all groups with 95–98% adherence to training in both groups in the feasibility clinical trial. There were significant decreases in the Oxford knee score in both KOAPT and walking groups after intervention ($p < 0.01$), but no significant differences between the two groups.

Conclusion: We conclude that KOAPT exhibited potential as an intervention to improve symptoms of KOA possibly through a mechanism of normalising mechanical pressure in the knee; however, optimisation of the method, longer-term intervention and a large sample randomized-single blind clinical trial with a minimal 524 cases are needed to demonstrate whether there is any superior benefit over other exercises.

The translational potential of this article: The research aimed to investigate the effect of an ancient leg-swinging exercise on knee osteoarthritis. A minipig animal model was used to establish the potential mechanism underlying the exercise of knee osteoarthritis pendulum therapy, followed by a randomised, single-blind feasibility clinical trial in comparison with a commonly-practised walking exercise regimen. Based on the results of the

* Corresponding author.

** Corresponding author.

E-mail addresses: wsj1974@yeah.net (S. Wei), jiuhongsong@yeah.net (J. Song).¹ Equal contribution as the first author<https://doi.org/10.1016/j.jot.2024.02.008>

Received 4 June 2023; Received in revised form 29 December 2023; Accepted 26 February 2024

2214-031X/© 2024 The Author(s). Published by Elsevier B.V. on behalf of Chinese Speaking Orthopaedic Society. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

feasibility trial, a large sample clinical trial is proposed for future research, in order to develop an effective exercise therapy for KOA.

1. Introduction

Knee osteoarthritis (KOA) is one of the major skeletal disorders that causes activity limitation, joint pain, physical disability, excessive medical use, and poor quality of life but has no known cure [1–3]. Conventional knee joint replacement may only partially improve patient daily activity [4].

There is strong evidence that exercise is beneficial in increasing mobility and decreasing pain of KOA [5–7]. Strengthening exercise is therefore recommended as the first-line management of KOA [2,8,9]. However, increasing the exercise people undertake is only sometimes successful [10–12], this may be partly due to limited access to appropriate training by health professionals, support of the exercise and facilities to ensure effective and safe exercises [13–15]. The complex interaction between a patient’s beliefs and preferences, pain, and exercise has been extensively studied and summarised in a Cochrane review in 2018 [15]. There is an urgent need to provide innovative exercises that are easily accessible, effective and convenient for practice, and safe to use.

In China, pendulum swinging of the legs has been recorded in the literature to reduce knee pain for thousands of years [16]. This method has been re-introduced recently and has been undertaken by people with osteoarthritis of the knee; it is thus an optional exercise intervention, but its mechanism and effectiveness have yet to be systematically studied. Pendulum swinging of the leg may reduce mechanical compression/loading of the knee, and improve joint circulation, but

experimental studies are lacking [16].

Consequently, we wished to investigate 1) whether there was experimental evidence to support the mechanism underlying this method; 2) whether there was sufficient evidence of benefit compared to the usual walking exercise to warrant a large trial. Experiments were performed *in vivo* using both a miniature pig model and human volunteers, and the clinical trial protocol of our study is available online. The experimental design is shown in Fig. 1, and the results are reported herein.

2. Methods

2.1. In vivo experiment

2.1.1. Experimental animals

Ten BAMA miniature pigs were purchased from Hubei Yizhicheng Biotech Ltd. and kept at Hubei Provincial Laboratory Animal Public Service Centre during the *in vivo* tests. This experiment was approved by Hubei Yizhicheng Biotech and Hubei Province Laboratory Animal Public Service Centre (IACUC Issue NO. WDRM-202111002) and all experimental procedures were carried out in accordance with provincial regulation of experimental animals.

BAMA minipigs were intubated with isoflurane gas anaesthesia, with ECG and blood oxygen saturation monitoring throughout the experiment using a high-frequency electrosurgical unit (Kangwei CV-2000D, Beijing Kangwei Electronic Technology Co., Ltd.). The pigs were then

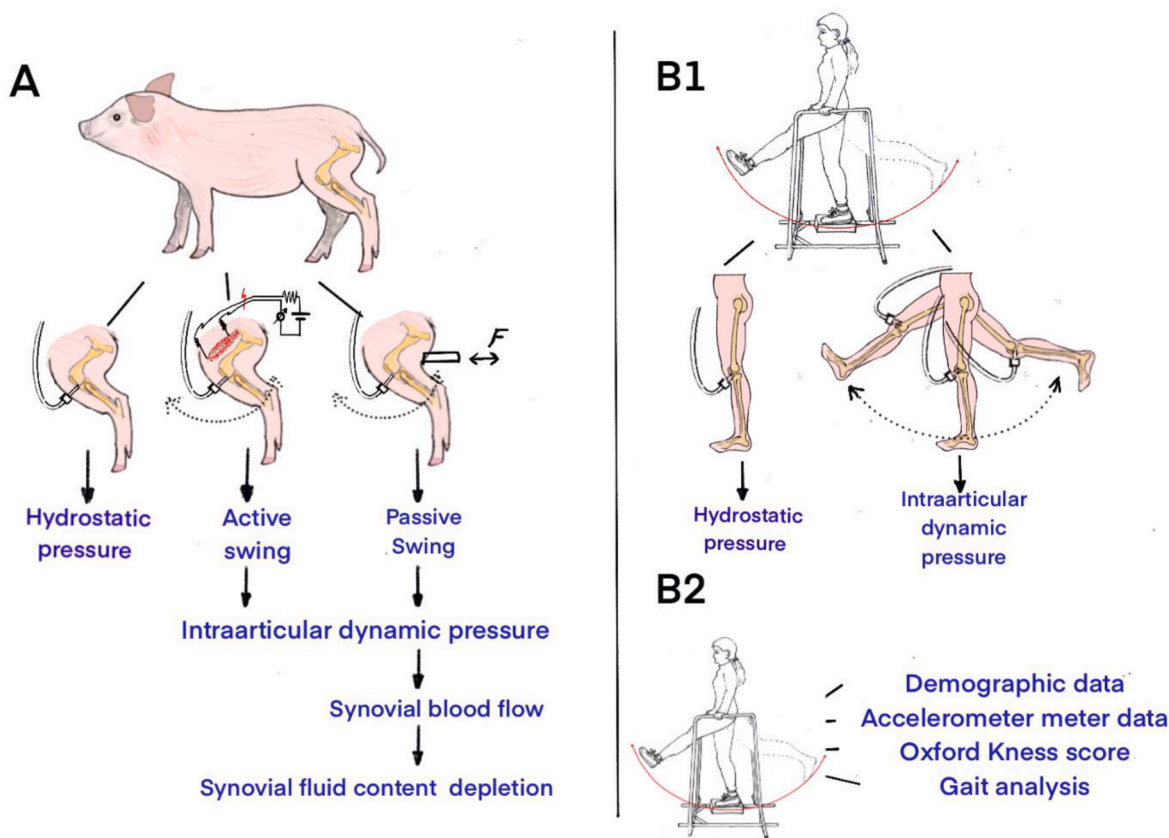


Fig. 1. The design of the study. A, *In vivo* study of the intraarticular hydrostatic pressure of the knee and the effect of leg swinging on the intraarticular dynamic pressure, synovial blood flow and depletion of synovial fluid contents. B1, intra-articular hydrostatic pressure of healthy volunteers and KOA patients, and intra-articular dynamic pressure of healthy volunteers. B2, a randomised, single-blind feasibility clinical trial.

fixed on a custom-made animal leg swing bracket in the prone position. The hair of the hind limbs was clipped and the skin was sterilised using an iodophor. A portable intelligent Doppler ultrasound detector (MyLab™ Gamma, Esaote, Genoa, Italy) was used to locate the joint cavity penetrating point at the anterolateral side of the knee joint.

2.1.2. Intraarticular knee joint static and dynamic pressure

To measure the intraarticular knee joint hydrostatic and dynamic pressure, a sterile pressure transducer (YPJ01H, Chengdu Instrument, Chengdu, China) was connected to a 5-gauge syringe needle to zero the level at the marked site of the knee, then the needle was inserted about 30 mm vertically from the marked site into the joint cavity. The pressure of the static knee joint cavity was recorded, followed by slowly flexing the hip joint forward and backward, and the dynamic pressure in the joint cavity was also recorded.

2.1.3. Synovial blood flow

A surgical incision was made to expose the synovium of both knees and sensors of a laser Doppler blood flowmeter (PeriFlux 5000, Perimed, Järfälla, Sweden) were stitched to accessory fascia of the synovium, then the skin wound was sutured. Miniature pigs were placed prone and fixed on a custom-made leg swing aluminium frame to support the pig's forelimbs without affecting the movements of the hind limbs. The initial blood flow value of the synovium was recorded.

To mimic active leg swinging, two acupuncture needles (0.30 mm in diameter, 75 mm in length) were inserted into the biceps femoris muscle of the right leg to a depth of 40 mm and connected to a low-frequency electronic pulse therapy Instrument (G6805-1A, Shanghai Huayi Medical Instrument Co., Ltd.). Electrical stimulation of 1 HZ, 4 mA was applied to produce leg pendulum swinging at a frequency of 50 times/min for 6 min (Fig. 1A). The left leg without stimulation was used as control.

To mimic passive leg swinging, a custom-made automatic leg swing control device with a metal rod fixed at the skin posterior midsection of the right femur was used to push the leg forward and back by a motor, at a frequency of 50 times/min for 6 min (Fig. 1A). The left leg without stimulation was used as control.

Synovium blood flow was recorded from both knee joints, starting at 30 s after the completion of the 6-min leg swing, and every 30 s thereafter for 10 min. The pendulum swing and local synovial blood flow were repeated three times with a 10 min interval between each time.

2.1.4. Synovial gadopentetate meglumine depletion

Three miniature pigs were subjected to passive leg pendulum swinging as described above (Fig. 1A). Instead of surgical implantation of a blood flow sensor, 2 mL (0.94 g) of gadopentetate meglumine (Shanghai Xudong Haipu Pharmaceutical Co. Ltd., Shanghai, China) was injected into the knee joint cavity. To observe the gadopentetate meglumine depletion from synovial fluid, one pig was given a left knee injection and then underwent left leg swinging (L–L), one was given a right knee injection then underwent left leg swinging (R–L), and another was given a left knee injection without leg swinging of either leg (control). The leg swing time was 6 min for each animal. Blood samples were collected before and 3 min after leg swing, and every 3 min thereafter for 60 min. The blood samples were centrifugated to separate serum. The concentration of gadopentetate meglumine was quantified using an inductively coupled plasma mass spectrometer (Nexion350x, Perkin Elmer, Waltham, MA, USA).

2.2. Intraarticular knee joint static and dynamic pressure of human volunteers

2.2.1. Subjects and methods

Clinical studies were performed at the Department of Orthopaedics, Central Theatre General Hospital of the Chinese People's Liberation Army. All research protocols were approved by the Medical Ethics

Committee of the hospital [(2021)052-01].

2.2.2. Intraarticular knee joint static and dynamic pressure

A total of ten subjects were enrolled between September 2021 and May 2022, including five healthy volunteers and five KOA patients with informed consent. However, only 6 samples were successfully completed the measurement. The demographic information of these participants is shown in Table 1.

A portable intelligent Doppler ultrasound detector (MyLab™ Gamma, Esaote) was used to locate the joint cavity penetrating point at the anterolateral side of the knee joint.

After local anaesthesia using 0.1 g (5 mL) of 1% lidocaine (Tianjin Jinyao Pharmaceuticals Co. Ltd., Tianjin, China), needles were connected to the pressure transducer to record the synovial static pressure for both healthy volunteers and KOA patients.

A disposable indwelling needle (18G × 29 mm/Y-G, Weihai Jierui Medical Products Co. Ltd., Weihai, China) was then inserted into the knee joint cavity to replace the metal needle for local anaesthesia, and the indwelling needle was connected to the pressure transducer and securely fixed on the skin. The subjects stood with their support leg on a 15 cm wooden platform, while their swing leg connected to the pressure transducer was suspended in a neutral position and the pressure was zeroed at this position. The subjects then performed a pendulum leg swing exercise (Fig. 1). The hip joint was flexed forward between 45 and 60° and extended backwards at 15–20°, forming a cycle of one swing. The dynamic pressures in the forward, vertical, and backward position were recorded only in the healthy volunteer group.

2.3. Randomised, single-blind controlled clinical feasibility trial

2.3.1. Trial design

This was a pilot randomised, controlled trial. It was registered with the Chinese Clinical Trial Registry (number: ChiCTR2100051275), received ethical approval from the Medical Ethics Committee of the General Hospital of the Central Theatre of the PLA on October 21, 2021 (Registration number: [2021]052-01), and the protocol is submitted for publication (under review). Wuhan FL Medical Science & Technology Ltd. funded the research. There were no secondary sponsors.

Patient recruitment started on November 3rd, 2021, and the last follow-up data collection was in July 2022. This paper adheres to the CONSORT guidance [17].

The study was undertaken as outlined in the protocol and in the trial registration, and only the main points are outlined here.

Patients were recruited from among inpatients and outpatients attending the Orthopaedic department of the Central Theatre General Hospital of the PLA, Wuhan. Some patients were recruited through publicity in the community. All patients were given information about the trial at first contact and, if interested, saw a clinician who provided more information, answered questions and obtained consent if the patient was eligible.

2.3.2. Inclusion criteria

To be included the patient had to be aged 18 years or older with a clinical diagnosis of KOA in one or both knees. If both knees were

Table 1
Demographic information of the health volunteers and KOA patients (mean ± SE).

	Health volunteers		KOA patients	
	Male	Female	Male	Female
Gender	1	2	2	1
Age	45 ± 2.51		56 ± 1.73 ^a	
VAS scale	0		3.67 ± 1.20 ^a	

p < 0.05

^a t-test

affected, data from the more affected side was collected.

2.3.3. Exclusion criteria

Patients were **excluded** if they.

- had additional knee pathology such as joint dystrophy, infected joint, rheumatoid arthritis, osteonecrosis, cruciate ligament injury or post-traumatic arthritis.
- had had hip or knee replacement surgery or tibial osteotomy.
- had used steroid medication orally over the previous month or injected within the last three months.
- had a neurological or mental disorder affecting cognitive ability sufficiently to reduce participation in the exercises and/or the research.
- were pregnant, anticipating becoming pregnant, or breastfeeding.
- had a body mass index of 36 kg/m² or above.

2.3.4. Randomisation

Before the trial started, a series of consecutively-numbered opaque envelopes were filled with a group allocation using a random number generator in a 1:1 ratio, and then sealed. Every patient recruited and giving consent was registered by a researcher in the research office, who then opened the next numbered envelope and informed the treating researcher of the patient’s group allocation.

2.3.5. Intervention

All patients were allowed to continue with their pharmacological treatments. The allocated treatment was used for 12 weeks; patients were free to do as they wished after that point.

One group were taught pendulum therapy. In short, they were asked to stand on the better leg on a 15 mm raised platform, using support as they wished, while swinging the other leg forward between 45 and 60° and backward about 15–20° from vertical in each direction (Fig. 1 and supplement 3, KOAPT video). They were asked to swing it at a rate between 30 and 50 swings/minute as a guideline.

The target for swing exercise was 1000 swings/day for each leg according to literature and previous report [16]. However, for many patients who did not have a training period, it was very difficult to meet the target at the beginning. We had a small-scale pre-trial to find out that it was relatively easy to start from 300 swings/leg/day with gradual increases at 100 more swings each week until they meet the target, and they were given a gradually increasing schedule as shown in Table 2.

The other group were asked to undertake additional, therapeutic walking also using a gradually increasing schedule as shown in Table 2.

All patients, both in KOAPT and walk group were fitted with two accelerometers (BWT61CL, WIT-motion, Shenzheng, China) at each foot to record either the walking steps, or swing cycles of the legs. Patients were instructed to switch on the pedometers before exercise and switch off at the end. The data were saved in a SD card of each pedometer and collected and downloaded by researchers every week. Each patient was allocated a dedicated researcher who would provide training for the KOAPT/walk, the fitting and use of pedometers. The researcher visited the patients once a week for inspection, troubleshooting, and SD card downloading.

All patients were told that they could undertake additional therapy (walking or pendulum therapy as allocated) if they wished and were reassured that therapy could be split into two or more sessions in the day. The walking group were asked not to undertake pendulum therapy while in the trial.

Table 2

Minimum daily exercise/intervention and daily target with gradual increases.

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Walking group (steps/day)	1200	1600	2000	2400	2800	3200	3600	4000
KOAPT group (swings/leg/day)	300	400	500	600	700	800	900	1000

2.3.6. Pendulum swing exercise record

To monitor the exercise of each patient, all patients were also taught how to fit an accelerometer during their exercise, and were asked to record in a diary how much exercise they undertook each day and any other comments including adverse effects noticed.

2.3.7. Clinical measurement

Data of Oxford knee score (OKS), knee pain, muscle strength, 30 s sit-to-stand test, 6-min walking and 10 m walk gait analysis were collected at baseline and at 12 weeks, while additional OKS and knee pain data were collected at 24 weeks as follow-up by researchers who did not know the patient allocation. All baseline and 12-week data were collected at the hospital. Fig. 7 the SPIRIT figure, shows the data collected at each time point [18]. It is notable that the 24-week data was only the OKS which was collected by telephone. Data about compliance was also collected weekly, using a score system from 0 to 10, where 0 is no exercise and 10 is full exercise according to the protocol. This was undertaken by researchers who visited patients at home to download data from the accelerometers; they could offer support, advice, or information if requested.

The following demographic and clinical information was extracted from the clinical record.

- gender, age, weight in kilograms, height in centimetres, estimated age of onset
- Kellgren–Lawrence X-ray grading of the most affected knee [19].

The following clinical data were collected when the patient visited the hospital by researchers unaware of the patient’s group.

- Pain, measured from 0 to 10 on a numerical rating scale from 0, “no pain”, to 10, “worst pain”. [20].
- Oxford Knee score [21,22].
- Six-minute walking distance, measured in a gym or corridor [23].
- 30-s sit-to-stand test [24].
- strength of the quadriceps muscle, using a hand-held dynamometer [25].
- gait kinematics using a triaxial accelerometer [26].

In addition, data were collected on the feasibility and experience of (a) the allocated treatment and (b) the research processes. The data included.

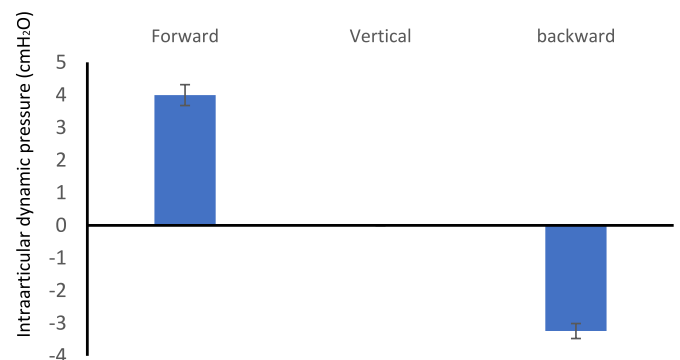


Fig. 2. Dynamic pressure changes of knee joint pressure during leg pendulum swinging (mean ± SE, unit: cmH₂O).

- recruitment rate to the study and reasons for non-participation
- adverse events
- recording missing data from each measure at each point for both intervention arms
- recording how many patients dropped out, when and if a reason was given, why
- reviewing comments within treatment diaries
- recording degree of reported adherence to the exercise intervention
- reviewing the data collected during treatment sessions from the accelerometers or pedometers

Most data were initially recorded on paper, delivered to the research office, and transferred to a computer database (SAS).

There are no data available to allow an estimate of the relative effect size of the comparator intervention (pendulum swinging of the leg). Sample sizes between 24 and 50 are recommended for feasibility studies to estimate standard deviations in measures for use in a future sample size calculation for fully powered testing [27,28]. A total sample size of 50 allowed us to estimate a drop-out rate of 80% to within a 95% confidence interval of $\pm 11\%$ [7,12]. A sample of 50 will also allow for process and feasibility issues to be explored, emphasising the context and mechanism of using the system (data collection and feedback). This sample size is supported by other empirical work [29].

2.4. Statistical analysis

All data are presented as mean \pm SD. Microsoft Excel (Microsoft Inc., Seattle, WA, USA) was used to perform t-tests for intraarticular pressure analysis. SAS software (SAS Institute, Cary, NC, USA) was used for analysis of variance (ANOVA) of dynamic pressure and blood flow analysis, and a linear mixed model (LMM) was used for clinical feasibility trial results including OKS and gait data (supplement 1). A value of $p < 0.05$ was set as statistically significant.

Power analysis was performed based on the results of a feasibility trial to predict sample numbers for a large sample clinical trial. Detailed calculation is shown in supplement 2.

3. Results

3.1. 1. In vivo experiment

3.1.1. Intraarticular knee joint static and dynamic pressure

The intraarticular knee joint static pressure of minipigs was -11.90

± 2.66 cmH₂O, which shows a negative pressure.

Pendulum swinging of the legs by flexing the hip joint forward and extending it backward moved the knee joint forward and backward. This movement caused dynamic changes of the dynamic pressure of the knee joints, on average between 3.40 ± 0.32 and -3.24 ± 0.23 cmH₂O. (Fig. 2)

Due to technical difficulty, it was not possible to provide sufficient data of joint pressure post-swing exercise for analysis.

3.1.2. Synovial blood flow

Knee synovial blood flows post pendulum swinging of the legs are shown in Fig. 3. Both active swinging and passive swinging increased the relative synovial blood flow 7- and 5-fold respectively immediately after the pendulum swing movement, which was significantly higher than control legs ($p < 0.05$). In 3–4 min the blood flow reduced to around 1 fold compared before leg swing. There were no significant differences between active and passive leg swing on the effect of stimulating synovial blood flow.

3.1.3. Synovial gadopentetate meglumine depletion

The effect of leg pendulum swinging on depletion of the synovial contents in the knee joint cavity is shown in Fig. 4.

For the L(Ga)-L(Swing) group that started left leg swinging immediately after gadopentetate injection into the left knee joint cavity, the gadopentetate was rapidly depleted and released into the bloodstream at the end of the first swing and reached a peak at the end of the second swing movement. Both control (no swing in either leg) and L(Ga)-R (swing) that started left leg swing immediately after gadopentetate injection into the right knee joint cavity, animals showed slow release of gadopentetate into the blood at 6 min. At the second swing the gadopentetate in L(Ga)-R(swing) group slowly increase and peaked at 42 min post-injection; whereas the control group remained slow depletion of gadopentetate till 60 min post-injection.

3.2. Intraarticular knee joint static and dynamic pressure of human volunteers

The intraarticular static synovial pressure in healthy volunteers and KOA patients is shown in Fig. 5. Healthy volunteers (-11.32 ± 0.21 cmH₂O) demonstrated lower intraarticular pressure compared to KOA patients (-3.52 ± 0.34 cmH₂O, $p < 0.05$).

The dynamic intraarticular pressure of the knee in healthy volunteers

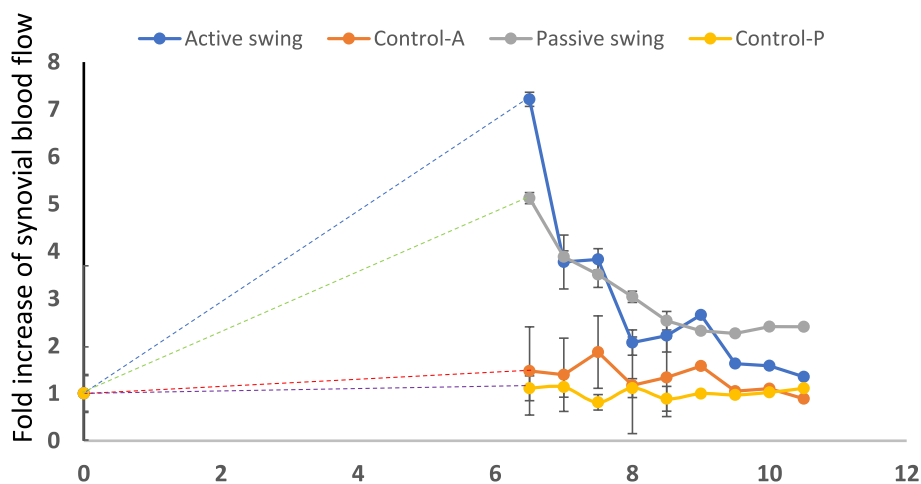


Fig. 3. The effect of leg pendulum movement on knee synovial blood flow immediately after a 6-min exercise by electrical stimulation (Active swing) group, the no leg exercise in the same animal (Control-A); or 6 min exercise by mechanical pushing (Passive swing) and the no exercise leg in the same animal (Control-P). There were 7- and 5-fold increases of knee synovial blood flow 30 s after exercises in both the active and passive swing groups in comparison with their respective control groups ($p < 0.05$). The increases of synovial blood flow recovered to less than a 2-fold increase in 3.5 min.

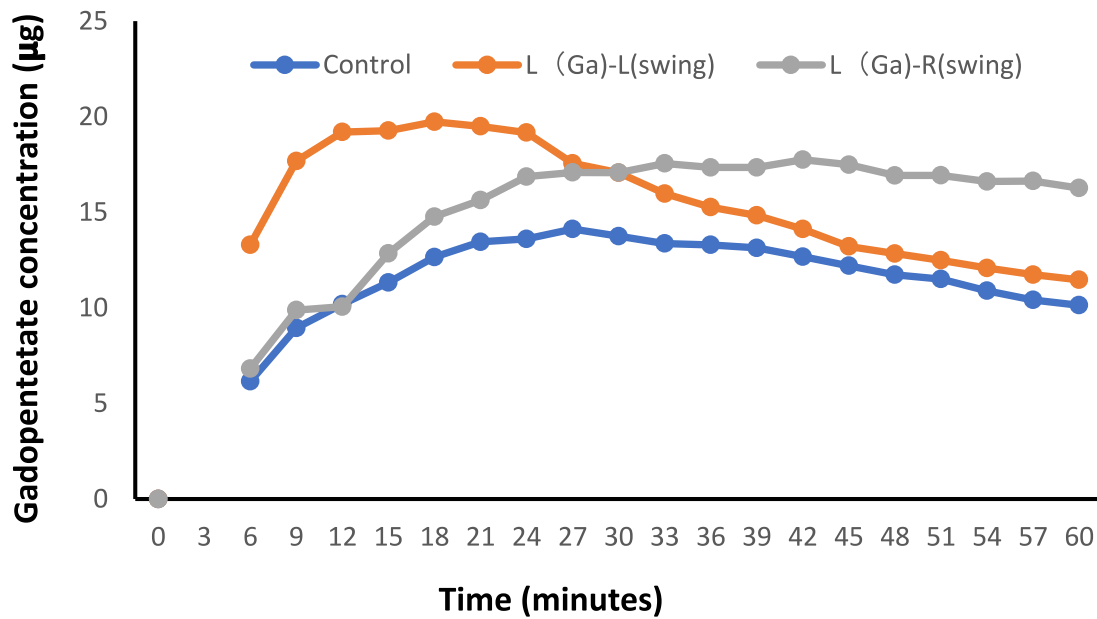


Fig. 4. The effect of leg pendulum movement on potential synovial content depletion. Control, control group with gadopentetate meglumine injection without exercise. L(Ga)-L(Swing), gadopentetate was injected into the left knee joint cavity followed by 2 × 6 min left leg pendulum movement. L(Ga)-R(swing), gadopentetate was injected into the left knee joint cavity followed by 2 × 6 min right leg pendulum movement. Gadopentetate injected into the knee joint cavity was rapidly depleted and released into the blood at the end of the first swing and reached a peak at the end of the second swing movement. Both control and L(Ga)-R (swing) animals showed slow release of gadopentetate into the blood at 6 min. At the second swing the gadopentetate in the L(Ga)-R(swing) group slowly increased and peaked at 42 min, whereas the control group maintained a slow release.

is shown in Fig. 6. During leg swinging, the dynamic pressure oscillated between positive and negative.

3.3. Randomised clinical trials

3.3.1. Demographic data

A total of 174 participants were recruited. Following pre-screening, 50 patients were accepted, provided informed consent, and randomised for this trial. The flow of patients is shown in Fig. 7.

Demographic data are shown in Table 3.

3.3.2. Pendulum swing exercise record

The target for swing exercise was 1000 swings/day for each leg. Two accelerometers were used to record how many swings a patient performed daily. The patients were suggested to start from 300 times per leg per day to get used to the exercise, and gradually increase to meet the target of 1000 swings/leg/day (Table 2).

A total of 4698 recordings of swing activity in the KOAPT group were recorded in 26 participants (Fig. 8)

On average participants performed 749.2 swing cycles per day

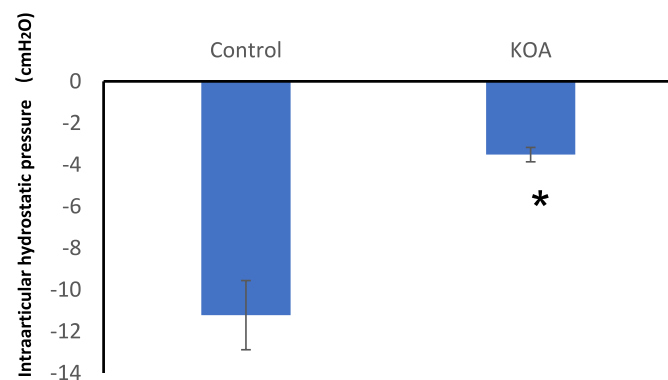


Fig. 5. Healthy and KOA joint pressure (mean ± SE, unit: cmH₂O).

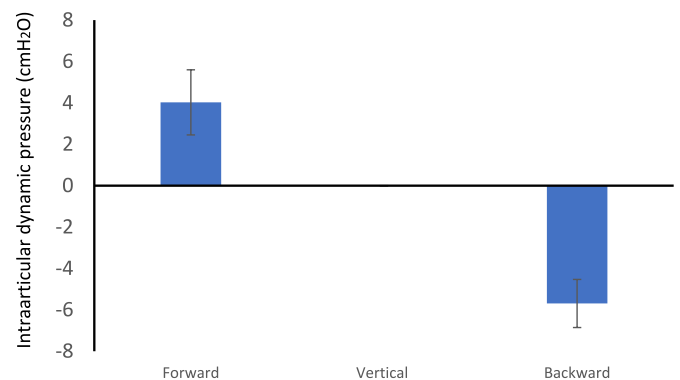


Fig. 6. Dynamic pressure changes of knee joint pressure during leg pendulum swinging of healthy human volunteers (mean ± SE, unit: cmH₂O).

(range: 372.7–1078.2 cycles), for 17.8min (range: 8.5–23.9 min) per leg.

On 16% of intervention days, participants decided to split their daily targets up into more than one session (range 2–6 sessions/day).

Group averages showed an increase of 7.1 swings per day ($R^2 = 0.80$), whereby the target of 1000 swings per day was achieved by day 58. (Fig. 8)

Table 4 shows the mean and standard deviations of all major variables between control and KOAPT groups.

The OKS evaluates knee function and provides a composite score based on pain, function, and daily activity. Both the KOAPT group and the control group showed significant improvements in pain, function, and daily activity over the 12 week-intervention and the 24-week follow-up ($p < 0.001$); however, there was no significant difference between the two groups.

A visual analogue scale (VAS) score is a visual pain scale from 0 to 10. Both the KOAPT group and the control group showed significant improvement over the 12 week-intervention ($p < 0.001$), yet there was no difference between the two groups.

Gait analysis over a 10-m walk was used to evaluate the walking

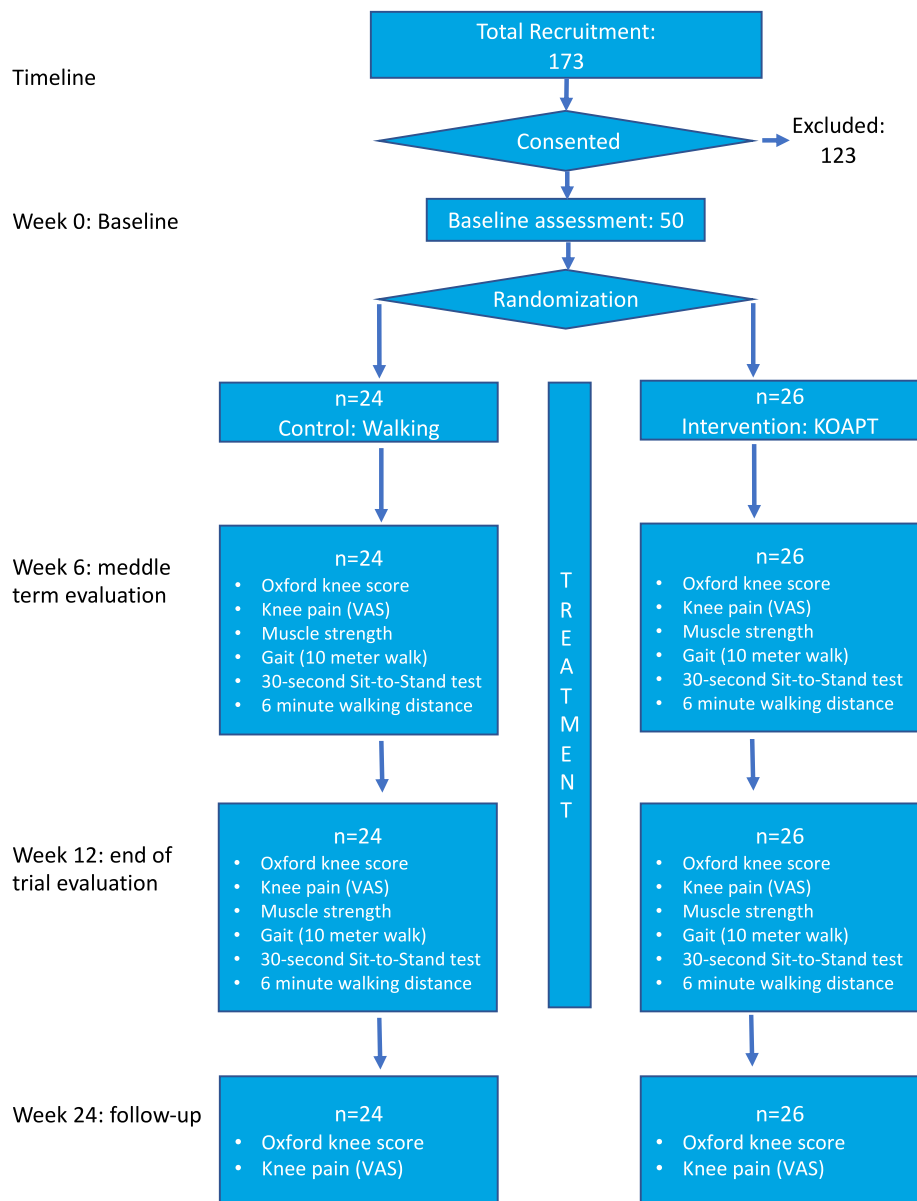


Fig. 7. The flow of patients in the trial.

speed, cadence, and stride length while walking ten metres. There were significant differences between control and KOAPT groups in walking speed and step time ($p < 0.05$) and between the two groups over time in step length ($p < 0.01$). However, these differences were variable and not consistent across the gait parameters.

The 6-min walking tests demonstrated identical and consistent results of 10 m walking. Only 10 m walking analysis is provided.

Muscle strength and other parameters showed similar trends to the OKS and there were no significant differences between the KOAPT and control groups.

Data on compliance with pendulum swinging exercise was available for all 50 patients at 6 weeks and 12 weeks. All patients complied with the protocol, and there were no differences between the two groups.

All additional pharmacological and other treatments during the course of the clinical trial were recorded and shown as Table 5. It is interesting to see the reduced use of additional interventions over 12 weeks.

All adverse events, causes and treatments are shown in Table 6. The most common symptoms were lower back pain in six patients. Pain and soreness of the buttock, thigh and knee were also common. Some

patients also experienced other pain or soreness in the hip, instep, calf or ankle. All adverse events either recovered or improved after rest or treatment.

This clinical trial demonstrated good adherence as all participants completed their interventions and follow-up without any case who dropped out.

3.4. Prediction of sample size for a large sample clinical trial

Based on the feasibility clinical trial results, we selected the change in OKS total score between baseline and 24-week follow-up to predict the minimum sample number for the next large-sample clinical trial with the potential to reveal differences between these two groups.

The standard deviation of the difference between the overall OKS scores of the two groups at 24 weeks and at baseline was 5.757869 when combined. With a confidence error of 1.6363684, using the standard deviation as the variability index and the confidence error as the allowable error, and with a test power of 0.9 and a group ratio of 1:1, the minimum required total sample size calculated was 524 (Supplementary Table 1).



Fig. 8. The number of swings for all participants as an average with associated 95% confident intervals, whereby across all KOAPT group participants, the target of 1000 swings per day was, on average, achieved by day 58, with a group average increase of 7.1 swings/day ($R^2 = 0.8068$).

Table 3
Demographic data (number or mean ± SD).

		Control (n = 24)	KOAPT (n = 26)
Age (years)		52.83 ± 1.84	57.35 ± 2.24
Gender	Male	9	6
	Female	15	20
KL	0	1	0
	1	11	13
	2	9	10
	3	3	1
	4	0	2
Side of KOA	Left	5	4
	Right	5	3
	Bilateral	16	17

4. Discussion

The knee joint intra-articular static pressures of both minipigs and healthy humans were found to be negative under normal conditions. However, they varied three-fold between healthy and KOA patients, with the value in healthy individuals being -11.32 ± 0.21 cmH₂O, whereas in KOA patients, it was -3.52 ± 0.34 cmH₂O ($p < 0.05$). During pendulum leg swing exercise, there were also dynamic intra-articular pressure changes in the knee joint in both humans and minipigs, demonstrated as oscillation between positive and negative pressure. In minipigs, both passive and active pendulum swings increased synovial local blood flow based on adjusted 0 points. Interestingly, pendulum swinging helped the depletion of synovial fluid content not only in the swing leg but also in the leg at rest. Thus, it supports the potential for our hypothesis that an altered mechanical environment in patients with OA is associated with clinical outcomes.

In the feasibility study there was excellent completion of measures and good adherence to the training program achieving our success targets. The feasibility clinical trial showed that both walking and KOAPT exercises significantly reduced the pain of KOA, even though there were no significant differences between the two groups in terms of the OKS

and most gait analysis parameters. However, the significant improvement of walking speed, step length and step time in the KOAPT group over the control group suggests the potential for a positive effect and highlights the need for a fully powered trial. Our findings are important as they provide evidence for a possible mechanism and support the potential use of this ancient approach for symptom management in OA.

The KOAPT group showed a steady step length and reduced step time over 12 weeks, while the control group showed reductions in both step length and step time, and consequently the walking speed in the control group decreased and ultimately was lower than the KOAPT group.

Pain is the most common symptom of KOA and is the key driver of disability and negative impact on quality of life [30]. However, the mechanism involved in OA pain is complex. It is well known that articular cartilage of the knee joint is not innervated; therefore, the pain more likely originates from subchondral bone [31,32] and surrounding soft tissue such as synovium [33].

Recently, inflammation-predominant OA has been recognised as an important clinical type of OA [34,35]. OA synovitis is found early in OA, and has been suggested as a cause of pain, structural damage, and progression of OA [36,37].

One important component of OA pain is mechanical pain [38,39]. Excessive mechanical loading, including intraarticular pressure within the joint and surrounding tissue is another cause of knee pain [38,40,41]. Cartilage, bone and synovial cells are all rich in mechanical sensor molecules [42] which can interact with sensory nerves [43].

The sensory nerves in the knee joint are believed to be free terminals of unmyelinated C fibres, and they are present in all structures of the joint except the cartilage. Mechanical and chemical stimuli activate these sensory nerves under pathological conditions such as inflammation. They are also sensitised by increased intra-articular pressure and local chemical changes [38].

Joint pain has a major effect in preventing patients from participating in weight-bearing activities and exercise. However, KOA patients may also experience pain, discomfort, and stiffness at rest. Previous research mostly focussed on mechanical loading from weight bearing and movement, and little attention has been paid to the effect of

Table 4

Data of the feasibility clinical trial at four time-points in the two groups (mean ± SD) and linear mixed model (LMM) statistical analysis.

Variable	KOAPT (n = 26)				Control (n = 24)				P value
	0	6	12	24	0	6	12	24	
Oxford Knee Score Total	22.04 ± 7.7	19.92 ± 4.9	16.53 ± 3.5	17.38 ± 5.3	18.87 ± 6.1	16.91 ± 4.8	16.41 ± 4.2	16.21 ± 3.9	***
Pain	10.57 ± 3.2	8.08 ± 2.3	7.58 ± 1.6	7.96 ± 3.0	8.75 ± 3.0	8.00 ± 2.5	7.29 ± 2.0	7.25 ± 1.7	***
Daily Activity	11.46 ± 4.9	9.85 ± 2.9	8.96 ± 2.1	9.42 ± 2.6	10.12 ± 3.4	8.92 ± 2.6	9.12 ± 2.3	8.96 ± 2.5	***
Visual Analogue score - pain	4.12 ± 1.9	2.46 ± 1.0	1.96 ± 1.0	—	3.46 ± 1.9	2.46 ± 1.6	2.25 ± 1.5	—	***
Ten metre walk	—	—	—	—	—	—	—	—	—
Speed (m/s)	1.14 ± 0.2	1.23 ± 0.2	1.24 ± 0.3	—	1.29 ± 0.2	1.38 ± 0.3	1.24 ± 0.2	—	NS
Cadence Steps/minute	115.4 ± 21.2	136.8 ± 34.2	130.6 ± 39.0	—	127.5 ± 31.0	158.0 ± 43.2	142.3 ± 44.5	—	***
Walking Speed (m/s)	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.3	—	1.3 ± 0.2	1.4 ± 0.3	1.2 ± 0.2	—	&
Stride length (m)	1.30 ± 0.14	1.28 ± 0.13	1.29 ± 0.15	—	1.35 ± 0.17	1.31 ± 0.13	1.25 ± 0.14	—	NS
Step length Left (m)	0.665 ± 0.067	0.668 ± 0.085	0.686 ± 0.008	—	0.692 ± 0.083	0.713 ± 0.01	0.644 ± 0.056	—	@@
Step length Right (m)	0.685 ± 0.080	0.687 ± 0.061	0.682 ± 0.064	—	0.685 ± 0.09	0.692 ± 0.075	0.685 ± 0.107	—	NS
Step time average (milliseconds)	576.9 ± 74.4	529.0 ± 70.6	566.1 ± 234.0	—	529.7 ± 58.1	494.7 ± 104.0	512.4 ± 69.8	—	&
Muscle strength Left	130.9 ± 56.0	155.3 ± 59.7	145.7 ± 46.9	—	165.6 ± 73.6	171.2 ± 79.1	168.3 ± 64.8	—	*
Right	135.1 ± 62.7	165.8 ± 63.9	160.3 ± 55.6	—	165.9 ± 76.7	180.3 ± 72.5	170.6 ± 63.0	—	**
Sit to stand in 30 s	13.65 ± 3.4	16.46 ± 5.8	15.88 ± 3.4	—	16.17 ± 5.0	15.62 ± 5.9	17.46 ± 6.0	—	NS
Patient compliance score %	—	95.8 ± 11.4%	96.2 ± 8.0%	—	—	94.2 ± 15.3%	98.3 ± 4.9%	—	NS

No statistical significance: NS

Difference between groups: &, $p < 0.05$

Difference over time: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$

Mixed group*time: @@, $p < 0.01$

Table 5

Additional drug/intervention during the course of the clinical trial.

Drug/additional intervention	Baseline		6 weeks		12 weeks	
	KOAPT	Control	KOAPT	Control	KOAPT	Control
Acerein	12	3	6	3	3	0
Irecoxib	4	0	0	0	3	3
Etoricoxib	0	0	3	0	0	0
Glucosamine	7	11	6	3	0	0
Acupuncture	5	3	0	0	0	0
Physiotherapy	4	0	0	0	0	0

Table 6

Adverse events and treatment.

Symptoms	Cases	Causes	treatment	Outcomes
Lower back pain	6	Sports injury, cycling, mountain climbing, history of previous low back pain, lumbar spine surgery, self-increasing exercise. Not directly caused by the trial.	Rest, adjusting exercise plan, seen by doctor or physiotherapists	Some were cured, some improved
Base of thigh pain	2	Occurred during leg swing, Relieved with rest	Rest, more frequent change of legs	Recovered
Knee pain worsened	3	Occurred after climbing, overwork and exercise	Rest, change of legs, reduced exercise, seen by doctor	Some were cured, some improved
Buttock soreness	2	Occurred during exercise, after increasing the strength of exercise, after physiotherapy	Rest	Recovered
Hip soreness	1	Occurred during exercise	Rest, reduced load to the support leg	Recovered
Hip pain	1	Occurred before and after exercise, worsened after exercise	Rest, reduced exercise	Improved
Instep redness	1	Consistent before and after exercise	Temporary cessation of exercise, rest	Improved
Ankle discomfort	1	Occurred after carrying heavy objects	Rest, reduced weight bearing	Recovered
Calf cramps	1	Occurred at night	Rest, hot pad	Recovered
Calf soreness	1	Occurred after leg swing	Massage, stretching after exercise	Recovered

hydrostatic/hydrodynamic pressure within the articular joint on pain and joint function [44].

The knee is a major synovial joint and contains synovium fluid to maintain normal function. Over 80% of KOA patients experience knee effusions [45]. The increase in volume of synovial fluid may result in intraarticular pressure change. Our study shows that in healthy volunteers, the intraarticular joint pressure is negative, whereas intraarticular

pressure in KOA patients is three-fold higher than that in healthy volunteers ($p < 0.05$).

This result is consistent with previous studies in the literature on intraarticular pressure at rest and during exercise; it has been shown that normal peripheral synovial joints have a sub-atmospheric pressure, commonly -2 to -4 mm Hg at rest [46,47]. Negative pressure maintains nutritional supply to articular cartilage, and maintains joint stability

during rest and exercise [47].

This negative pressure may be lost in KOA patients with effusion. Unlike during weight-bearing and exercise when the mechanical loadings are temporary, such hydrostatic pressure changes are constant and long-term. The effect of long-term exposure to high intraarticular pressure on cartilage and synovium is not fully understood; however, clinical evidence has shown that KOA patients with effusion have a high risk of losing muscle mass from muscles such as the quadriceps and consequently suffering reduced knee function [48].

The early literature showed clearly that an increase in intraarticular pressure of as little as 20 mm Hg in patients with effused knees can significantly decrease synovial blood flow [49]. High intraarticular pressure due to effusion may reduce cartilage waste product depletion, increase chondrocyte apoptosis, and stimulate sensory nerves in synovial tissue. Therefore, we hypothesise that changing the hydrostatic/hydrodynamic pressure environment through exercise may help reduce pain in the joint.

We noticed that pendulum swinging of the leg could have several advantages in altering the joint mechanical environment. First, as patients stand on a 15 cm block during exercise, the swinging leg is suspended, which may reduce the impact of weight bearing during exercise, as non-weight loading can provide fundamental benefits for patients with OA [41,50]. Secondly, the oscillation of leg movement may produce a pump effect to change the hydrodynamic environment of the joint, increasing local blood flow and helping depletion of synovial contents, such as cartilage metabolic waste, debris from wear and tear, and potential inflammatory molecules.

It is difficult to perform such tests in human subjects; therefore, we used miniature pigs as a model for this study. As expected, miniature pigs also demonstrated negative intraarticular pressure of the knee. By performing active and passive leg swinging in the miniature pigs, we detected similar intraarticular dynamic pressure changes to those observed in healthy human volunteers. By using a miniature pig model, we revealed that not only does leg swinging increase blood flow of the leg during exercise, but it also increases blood flow in the opposite leg. More interestingly, we showed that leg swinging can help rapid depletion of synovial fluid content, in this case, gadopentetate dimeglumine injected into the joint.

Gadopentetate dimeglumine (also known by the brand name Magnevist) is an extracellular intravenous contrast agent used in magnetic resonance imaging [51]. This compound can be quantitatively detected using inductively-coupled plasma mass spectrometry. By using this method, we successfully showed the depletion of gadopentetate dimeglumine from the joint. However, this result is still preliminary and requires further assessment.

One important aspect of any clinical study is to select a suitable control group. There are many exercises which are recommended for KOA; however, so far, no exercise therapy has proved superior to others. We chose walking as the control group exercise for the following reasons: 1) walking has been proven to be beneficial to KOA [52,53]; 2) walking involves very similar movement to KOAPT, the only difference is that walking involves weight bearing to the joint during exercise, whereas KOAPT may reduce weight bearing to the joint during exercise; 3) cycling may also provide similar movement, but the use of a device in a gym limits its use for easy access.

In the current clinical trial no significant differences were shown between the groups undertaking walking and KOAPT exercises. Since this was a feasibility study with limited sample size, increasing the sample size may provide comprehensive information. Power analysis shows that increasing the sample size to over 524 participants is likely to reveal the differences suggested using the current setting.

As KOA is a degenerative condition in the elderly population, long-term therapy is needed. Twelve weeks of intervention may not be sufficient to fully achieve a beneficial effect. We hypothesised that over 1000 swings/leg/day would be necessary, whereas in this 12-week intervention, it took nearly 7 weeks for the participants to reach the

target. The next trial should aim for a 6-month intervention.

There are several limitations of this study. Firstly, the *in vivo* tests used minipig model were performed only on health animal without knee OA. In order to further reveal the mechanism, a minipig or rabbit model with knee OA should be used. Secondly, this is a feasibility study, the assigned participant number may not be sufficient to demonstrate statistical significance between groups. Thirdly, the control walking exercise was mixed up with daily activity making it difficult to extract data for comparison. Finally, the understanding of the KOAPT is still preliminary. The supporting frame, monitoring of exercise, length of the therapy, and feedback collection are yet to be optimised.

In conclusion, this study highlighted the potential effect of the hydrostatic and hydrodynamic environment on KOA and its intervention. Both KOAPT and walking showed beneficial effects on KOA and there were no significant differences between these two groups. However, due to the nature of a feasibility study, there is not a sufficient powder to demonstrate differences between these two groups. A minimum of 524 cases are required for a further large sample clinical trial to confirm whether the pendulum therapy is a better exercise intervention for KOA. To understand the mechanism further, animal experiments using knee OA models should be performed.

Declaration of competing interest

Dr. JiuHong Song is a director of Wuhan FL Medical Science & Technology Ltd. All other authors declare that they have no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jot.2024.02.008>.

References

- [1] Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* 2008;58(1):26–35.
- [2] Nelligan RK, Hinman RS, Kasza J, Crofts SJC, Bennell KL. Effects of a self-directed web-based strengthening exercise and physical activity program supported by automated text messages for people with knee osteoarthritis: a randomized clinical trial. *JAMA Intern Med* 2021;181(6):776–85.
- [3] Fang L, Xia C, Xu H, Ge Q, Shi Z, Kong L, et al. Defining disease progression in Chinese mainland people: association between bone mineral density and knee osteoarthritis. *J Orthop Translat* 2021;26:39–44.
- [4] Daugaard R, Tjur M, Slieden M, Lipperts M, Grimm B, Mechlenburg I. Are patients with knee osteoarthritis and patients with knee joint replacement as physically active as healthy persons? *J Orthop Translat* 2018;14:8–15.
- [5] Wellsandt E, Golithly Y. Exercise in the management of knee and hip osteoarthritis. *Curr Opin Rheumatol* 2018;30(2):151–9.
- [6] Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. *J Sci Med Sport* 2011;14(1):4–9.
- [7] Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Cochrane Database Syst Rev* 2015;1:CD004376.
- [8] Becker BE. Aquatic therapy: scientific foundations and clinical rehabilitation applications. *Pm&r* 2009;1(9):859–72.
- [9] Salacinski AJ, Krohn K, Lewis SF, Holland ML, Ireland K, Marchetti G. The effects of group cycling on gait and pain-related disability in individuals with mild-to-moderate knee osteoarthritis: a randomized controlled trial. *J Orthop Sports Phys Ther* 2012;42(12):985–95.
- [10] Nicolson PJA, Hinman RS, French SD, Lonsdale C, Bennell KL. Improving adherence to exercise: do people with knee osteoarthritis and physical therapists agree on the behavioral approaches likely to succeed? *Arthritis Care Res* 2018;70(3):388–97.
- [11] Marks R. Knee osteoarthritis and exercise adherence: a review. *Curr Aging Sci* 2012;5(1):72–83.
- [12] Bartels EM, Juhl CB, Christensen R, Hagen KB, Danneskiold-Samsøe B, Dagfinrud H, et al. Aquatic exercise for the treatment of knee and hip osteoarthritis. *Cochrane Database Syst Rev* 2016;3(3):CD005523.
- [13] Briggs AM, Houlding E, Hinman RS, Desmond LA, Bennell KL, Darlow B, et al. Health professionals and students encounter multi-level barriers to implementing high-value osteoarthritis care: a multi-national study. *Osteoarthritis Cartilage* 2019;27(5):788–804.

- [14] Egerton T, Diamond LE, Buchbinder R, Bennell KL, Slade SC. A systematic review and evidence synthesis of qualitative studies to identify primary care clinicians' barriers and enablers to the management of osteoarthritis. *Osteoarthritis Cartilage* 2017;25(5):625–38.
- [15] Hurley M, Dickson K, Hallett R, Grant R, Hauari H, Walsh N, et al. Exercise interventions and patient beliefs for people with hip, knee or hip and knee osteoarthritis: a mixed methods review. *Cochrane Database Syst Rev* 2018;4(4):CD010842.
- [16] Li R, Sun P, Zhan Y, Xie X, Yan W, Luo C. Efficacy of leg swing versus quadriceps strengthening exercise among patients with knee osteoarthritis: study protocol for a randomized controlled trial. *Trials* 2022;23(1):323.
- [17] Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Pilot Feasibility Stud* 2016;2:64.
- [18] Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- [19] Kohn MD, Sasso AA, Fernando ND. Classifications in brief: Kellgren-Lawrence classification of osteoarthritis. *Clin Orthop Relat Res* 2016;474(8):1886–93.
- [20] Alghadir AH, Anwer S, Iqbal A, Iqbal ZA. Test-retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res* 2018;11:851–6.
- [21] Dawson J, Fitzpatrick R, Murray D, Carr A. Questionnaire on the perceptions of patients about total knee replacement. *J Bone Joint Surg Br* 1998;80(1):63–9.
- [22] Harris KK, Dawson J, Jones LD, Beard DJ, Price AJ. Extending the use of PROMs in the NHS—using the Oxford Knee Score in patients undergoing non-operative management for knee osteoarthritis: a validation study. *BMJ Open* 2013;3(8):e003365.
- [23] A.C.o.P.S.f.C.P.F. Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166(1):111–7.
- [24] McAllister LS, Palombaro KM. Modified 30-second sit-to-stand test: reliability and validity in older adults unable to complete traditional sit-to-stand testing. *J Geriatr Phys Ther* 2020;43(3):153–8.
- [25] Chopp-Hurley JN, Wiebenga EG, Gatti AA, Maly MR. Investigating the test-retest reliability and validity of hand-held dynamometry for measuring knee strength in older women with knee osteoarthritis. *Physiother Can* 2019;71(3):231–8.
- [26] Esser P, Dawes H, Collett J, Feltham MG, Howells K. Assessment of spatio-temporal gait parameters using inertial measurement units in neurological populations. *Gait Posture* 2011;34(4):558–60.
- [27] Sim J, Lewis M. The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *J Clin Epidemiol* 2012;65(3):301–8.
- [28] Browne RH. On the use of a pilot sample for sample size determination. *Stat Med* 1995;14(17):1933–40.
- [29] Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. *Stat Methods Med Res* 2016;25(3):1057–73.
- [30] Aw NM, Yeo SJ, Wylde V, Wong SB, Chan D, Thumboo J, et al. Impact of pain sensitisation on the quality of life of patients with knee osteoarthritis. *RMD Open* 2022;8(1).
- [31] Zhu S, Zhu J, Zhen G, Hu Y, An S, Li Y, et al. Subchondral bone osteoclasts induce sensory innervation and osteoarthritis pain. *J Clin Invest* 2019;129(3):1076–93.
- [32] Zhen G, Fu Y, Zhang C, Ford NC, Wu X, Wu Q, et al. Mechanisms of bone pain: progress in research from bench to bedside. *Bone Res* 2022;10(1):44.
- [33] Benito MJ, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. *Ann Rheum Dis* 2005;64(9):1263–7.
- [34] Lee JH, Kim K, Chung SG. Intra-articular pressure characteristics of the knee joint: an exploratory study. *J Orthop Res* 2022;40(9):2015–24.
- [35] Mapp PI, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol* 2012;8(7):390–8.
- [36] Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SM. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. *Arthritis Res Ther* 2015;17(1):152.
- [37] Mathiessen A, Conaghan PG. Synovitis in osteoarthritis: current understanding with therapeutic implications. *Arthritis Res Ther* 2017;19(1):18.
- [38] Perrot S. Osteoarthritis pain. *Best Pract Res Clin Rheumatol* 2015;29(1):90–7.
- [39] Chen L, Zheng JJY, Li G, Yuan J, Ebert JR, Li H, et al. Pathogenesis and clinical management of obesity-related knee osteoarthritis: impact of mechanical loading. *J Orthop Translat* 2020;24:66–75.
- [40] Zhu J, Zhu Y, Xiao W, Hu Y, Li Y. Instability and excessive mechanical loading mediate subchondral bone changes to induce osteoarthritis. *Ann Transl Med* 2020;8(6):350.
- [41] He Z, Nie P, Lu J, Ling Y, Guo J, Zhang B, et al. Less mechanical loading attenuates osteoarthritis by reducing cartilage degeneration, subchondral bone remodelling, secondary inflammation, and activation of NLRP3 inflammasome. *Bone Joint Res* 2020;9(10):731–41.
- [42] Zhao Z, Li Y, Wang M, Zhao S, Zhao Z, Fang J. Mechanotransduction pathways in the regulation of cartilage chondrocyte homeostasis. *J Cell Mol Med* 2020;24(10):5408–19.
- [43] Malfait AM, Miller RE, Miller RJ. Basic mechanisms of pain in osteoarthritis: experimental observations and new perspectives. *Rheum Dis Clin N Am* 2021;47(2):165–80.
- [44] Rutherford DJ. Intra-articular pressures and joint mechanics: should we pay attention to effusion in knee osteoarthritis? *Med Hypotheses* 2014;83(3):292–5.
- [45] Krasnokutsky S, Belitskaya-Levy I, Bencardino J, Samuels J, Attur M, Regatte R, et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. *Arthritis Rheum* 2011;63(10):2983–91.
- [46] Blake DR, Merry P, Unsworth J, Kidd BL, Outhwaite JM, Ballard R, et al. Hypoxic-reperfusion injury in the inflamed human joint. *Lancet* 1989;1(8633):289–93.
- [47] Jawed S, Gaffney K, Blake DR. Intra-articular pressure profile of the knee joint in a spectrum of inflammatory arthropathies. *Ann Rheum Dis* 1997;56(11):686–9.
- [48] Chiba D, Ota S, Sasaki E, Tsuda E, Nakaji S, Ishibashi Y. Knee effusion evaluated by ultrasonography warns knee osteoarthritis patients to develop their muscle atrophy: a three-year cohort study. *Sci Rep* 2020;10(1):8444.
- [49] Geborek P, Forslind K, Wollheim FA. Direct assessment of synovial blood flow and its relation to induced hydrostatic pressure changes. *Ann Rheum Dis* 1989;48(4):281–6.
- [50] Goh EL, Lou WCN, Chidambaram S, Ma S. The role of joint distraction in the treatment of knee osteoarthritis: a systematic review and quantitative analysis. *Orthop Res Rev* 2019;11:79–92.
- [51] Wei B, Du X, Liu J, Mao F, Zhang X, Liu S, et al. Associations between the properties of the cartilage matrix and findings from quantitative MRI in human osteoarthritic cartilage of the knee. *Int J Clin Exp Pathol* 2015;8(4):3928–36.
- [52] Voinier D, White DK. Walking, running, and recreational sports for knee osteoarthritis: an overview of the evidence. *Eur J Rheumatol* 2022;1:1. <https://doi.org/10.5152/eurjrh.2022.21046> (early view articles).
- [53] Lo GH, Vinod S, Richard MJ, Harkey MS, McAlindon TE, Kriska AM, et al. Association between walking for exercise and symptomatic and structural progression in individuals with knee osteoarthritis: data from the osteoarthritis initiative cohort. *Arthritis Rheumatol* 2022;74(10):1660–7.