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The effect of AposTherapy on pain and function in Knee Osteoarthritis population.

A randomized controlled trial

Clinical Study Protocol

Study Type: Randomized controlled trial

PI **Matthew N. Bartels, MD, MPH**

Professor and Chairman of Rehabilitation Medicine

Albert Einstein College of Medicine

Chairman, Department of Rehabilitation Medicine

Montefiore Medical Center

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Study Synopsis	
Title of the study	The effect of AposTherapy on pain and function in Knee Osteoarthritis (OA) population. A randomized controlled trial
Study objective	To evaluate the effect of AposTherapy on pain and function in knee OA population.
Outcome measures	<u>Primary outcome measures:</u> • Pain and function at 1-year post treatment initiation <u>Secondary outcome measure:</u> • Total healthcare utilization and costs of physical therapy and AposTherapy will be assessed, including physical therapy, ED visits, pharmacological pain treatments, injections, imaging studies, surgical procedures, physician visits related to knee pain and total physician visits • PROMIS Pain Interference and Physical Function • Pain medication consumption • Quality of life • Gait assessment • 6-min walk test • Blood pressure and resting heart rate • Adherence to treatment - AposTherapy (Patient to have step counter permanently attached to AposTherapy device, downloaded at each visit • Overall activity and sleep patterns, both groups. Will be measured via FitBit Charge HR

	(http://www.fitbit.com/chargehr#i.f9n1ye1ehxd30p) motion sensor worn for one week after each evaluation session, mailed back via prepaid mailer at the end of the week.
Study design	A randomized controlled trial (AposTherapy compared to traditional physical therapy)
STUDY POPULATION **Inclusion criteria**	Patients suitable for inclusion in this study will be those fulfilling the following: • Patients suffering from symptomatic knee OA (uni/bi lateral) for at least six months, fulfilling the ACR clinical criteria for OA of the knee, and having radiographically assessed OA of the knee according to the Kellgren and Lawrence scale. • Patients with VAS pain score of ≥3cm (measured at baseline). • Males and females between the ages of 40-75. • 17<BMI<40 • Ambulatory and active patients that can participate in a rehabilitation program that includes daily walking • Stable medical regimen (no recent changes to their pain medication within a month) • Able to walk at least 50 meters • Able to understand, read and sign the informed consent form • English or Spanish speaking
Exclusion Criteria	Patients with any of the following are to be excluded from the study:

	• Patients suffering from acute septic arthritis. • Patients suffering from inflammatory joint disease such as rheumatoid arthritis. • Patients who received a viscosupplementation /corticosteroid injection within 3 months of the study • Patients with diagnosis of avascular necrosis of the knee. • Patients with diagnosis of neuromuscular disease. • Patients with more than 3 falls in the last 12 months, OR any fall with an injury in the last 12 months. • Patients exhibiting a lack of physical or mental ability to perform or comply with the study procedure. • Patients with a history of pathological osteoporotic fracture • Patients with referred pain in the knees from back or hip joint symptoms. • Patients with severe back pain, ≥ 4 cm in visual analogue scale or radiating leg pain • Patients with generalized body pain (both upper and lower extremities, such as fibromyalgia • No major surgery to the affected limb and contralateral limb (e.g. no joint replacements or surgical fracture repair) • No major cardiovascular comorbidities (able to enroll in an active exercise program) • Patient started on lipid lowering medication in last 3 months • Any change in blood pressure medications • No recent physical therapy (no more recent than 6

	months) on the affected limb • No active heart disease (ischemia or heart failure admissions within 6 months) and no active COPD (exacerbation within 6 months) • No active malignancies on ongoing treatment • Patient with neurological gait pattern [2] • Patient requiring assistive device during gait analysis.
Total number of patients	One-hundred and forty-seven (147) individuals will be randomly assigned to one of two groups; traditional physical therapy or AposTherapy on a 1:2 ratio (49:98). A sample size of 147 will yield 80% power to detect an expected difference on the WOMAC pain scale, with components measured on VAS scales from 0 to 10 and a summary score standardized to also range from 0 to 10, of 1.5 at a 2-sided alpha of 0.05. The difference corresponds to a clinically meaningful moderate effect size of 0.4 standard deviation units assuming a typical standard deviation of 2.65. Anticipating an attrition rate of 10%, we aim at recruiting 162 patients for the trial.
Study groups	Patients will be randomly assigned to one of the following groups: • Patients with knee OA treated with AposTherapy • Patients with knee OA treated with traditional physical therapy
Assessment time points	Patients will be enrolled in the study and have clinical evaluations at the following time points: • Pre-treatment • 4 weeks following treatment initiation

	• 8 weeks following treatment initiation • 12 weeks following treatment initiation • 24 weeks following treatment initiation • 52 weeks following treatment initiation

The effect of AposTherapy on pain and function in Knee Osteoarthritis (OA) population. A randomized controlled trial

1. Background

AposTherapy is a home-based exercise program utilizing footwear that causes exercise with normal daily activity that may significantly improve function in patients with knee pain in general, and specifically knee osteoarthritis (OA). Capitalizing on the reported excellent adherence and clinical benefit of Apos Therapy in patients with significant lower limb arthritis, we propose to evaluate this as a conservative treatment that may supplant/supplement traditional pain medications and physical therapy in knee OA population. [3-6]

A potential use of AposTherapy as a replacement for traditional physical therapy may yield a less costly, more effective therapy with better adherence. Problems with traditional therapy include poor patient adherence (patients often do not complete the sessions and have very poor adherence (about 50-60%) to home therapy programs [7]), added cost of travel (which may be more than $100 per session for ambulette or access-a-ride for eligible patients), and the lack of continuation in an ongoing exercise program, leading to relapse and need for retreatment. Additionally, access to physical therapy is limited for many patients since there are not enough available outpatient therapy services to meet the needs of all patients. Finding an alternative exercise program that will increase adherence, decrease total therapy visits, and improve patient's outcomes with decreased dependence on pain medications is a high priority from both patient care and cost management perspectives.

AposTherapy potentially overcomes many of these issues with improving/modifying abnormal biomechanics (therefore decreasing pain), and a home-based exercise program utilizing footwear that causes exercise with normal activity by promoting perturbation. This biomechanical approach may significantly reduce pain and improve function in patients with

knee OA. Capitalizing on the reported excellent adherence and clinical benefit of AposTherapy in patients with significant knee OA, we propose to evaluate the biomechanical exercise (wearing an appropriately calibrated shoe at home for a prescribed amount of time each day) as a conservative treatment that may supplement or supplant traditional pain medications, interventional pain procedures and physical therapy in an at-risk urban inner city population with knee OA.

2. Study objective

The purpose of the current study is to evaluate the effect of this home-based biomechanical device and treatment (AposTherapy) in knee OA population. This will be a randomized single blinded (evaluator) trial of conventional physical therapy versus AposTherapy in patients with knee OA treated for one year.

In order to assess the efficacy of the intervention with AposTherapy on our patient population, a set of primary and secondary outcome measures will be defined:

3. Outcome measures

3.1. Primary outcome measures:

- Pain and function at 1 year following treatment initiation

3.2. Secondary outcome measure:

- Total healthcare utilization and costs of physical therapy and AposTherapy will be assessed, including physical therapy, ED visits, pharmacological pain treatments, joint injections, imaging studies, surgical procedures, physician visits related to knee pain and total physician visits
- Pain medication consumption
- Quality of life
- Gait assessment
- 6-min walk test

- Blood pressure and resting heart rate
- Adherence to treatment - AposTherapy group (Patient to have step counter permanently attached to AposTherapy device)
- Overall activity and sleep patterns, both groups. Will be measured via FitBit Charge HR (http://www.fitbit.com/chargehr#i.f9n1ye1ehxd30p) motion sensor worn for one week after each evaluation session, mailed back via prepaid mailer at the end of that week.

4. Materials and Methods

4.1. Trial Design

Single blinded (evaluator), single-center, randomized controlled trial.

4.2. Recruitment

Recruitment will be at the Montefiore Medical Center Moses Campus with therapy being provided on site.

4.3. Randomization

Blocked randomization will be used to assign to their respective treatment arm. The assigning ratio will be one to two; The random method of selection will be through a computerized random number generator. The on-site coordinator will be responsible for entering and maintaining the subject randomization information.

4.4. Ethics approval

This study will start following the approval of the institutional review board.
All patients will be asked to read and sign an informed consent prior to their final recruitment to the study.

4.5. Population

We will offer this option to patients at the general clinic sites, orthopedic clinics, and general medical and rehabilitation practices of the Montefiore Medical Group and Departments of Orthopedics and Rehabilitation Medicine Practices, who would normally be referred for physical therapy for their knee pain.

Inclusion Criteria:

- Patients suffering from symptomatic knee OA (uni/bi lateral) for at least six months, fulfilling the ACR clinical criteria for OA of the knee, and having radiographically assessed OA of the knee according to the Kellgren and Lawrence scale.
- Patients with VAS pain score of ≥3cm (measured at baseline).
- Males and females between the ages of 40-75.
- 17<BMI<40
- Ambulatory and active patients that can participate in a rehabilitation program that includes daily walking
- Stable medical regimen (no recent pain medication changes within a month)
- Able to walk at least 50 meters
- Able to understand, read and sign the informed consent form
- English or Spanish speaking

Exclusion Criteria:

- Patients suffering from acute septic arthritis.
- Patients suffering from inflammatory joint disease such as rheumatoid arthritis.
- Patients who received a viscosupplementation/corticosteroid injection within 3 months of the study.
- Patients with diagnosis of avascular necrosis of the knee.
- Patients with diagnosis of neuromuscular disease.

- Patients with more than 3 falls in the last 12 months, OR any fall with an injury in the last 12 months.
- Patients exhibiting a lack of physical or mental ability to perform or comply with the study procedure.
- Patients with a history of pathological osteoporotic fracture
- Patients with referred pain in the knees from back or hip joint symptoms.
- Patients with severe back pain, ≥ 4 cm in visual analogue scale or radiating leg pain
- Patients with generalized body pain (both upper and lower extremities, such as fibromyalgia
- No major surgery to the affected limb and contralateral limb (e.g. no joint replacements or surgical fracture repair)
- No major cardiovascular comorbidities (able to enroll in an active exercise program)
- Patient started on lipid lowering medication in last 3 months
- Any change in blood pressure medications
- No recent physical therapy (no more recent than 6 months) on the affected limb
- No active heart disease (ischemia or heart failure admissions within 6 months) and no active COPD (exacerbation within 6 months)
- No active malignancies
- Patient with neurological gait pattern [2]
- Patient requiring assistive device for gait analysis

4.6. Sample size

Our target recruitment is 147 individuals randomly assigned to one of two groups; traditional physical therapy or AposTherapy, on a 1:2 ratio. A sample size of 147 patients will yield 80% power to detect an expected difference on the WOMAC pain scale, with components measured on VAS scales from 0 to 10 and a summary score standardized to also range from 0 to 10, of 1.5 at a 2-sided alpha of 0.05. The difference corresponds to a

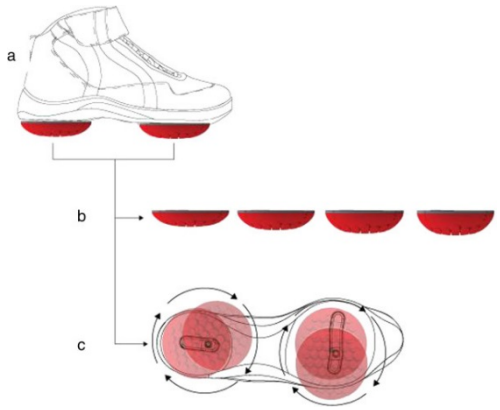
clinically meaningful moderate effect size of 0.4 standard deviation units assuming a typical standard deviation of 2.65. Anticipating an attrition rate of 10%, we aim at recruiting 162 patients for the trial (54 patients will be assigned to traditional physical therapy and 108 patients will be assigned to AposTherapy)

4.7. Treatment protocol

Group 1: AposTherapy

AposTherapy is a biomechanical therapy that has the ability to combine the two well-established treatment strategies for knee OA: reducing loads from the affected joint by altering joint kinematics and training of the neuromuscular system by perturbation. The AposTherapy device is comprised of convex adjustable biomechanical elements ('pertupods') placed under the hind-foot and fore-foot regions of each foot. The elements are attached via a platform in the form of a shoe. This platform enables a trained physiotherapist to calibrate the biomechanical elements to a customized configuration for each patient (Figure 1).

Figure 1. The biomechanical device



The AposTherapy Device. (*a*) A biomechanical device comprising two individually calibrated elements and a foot-worn platform. The elements are attached to a platform under the hind-foot and forefoot regions. **(*b*)**The biomechanical elements are available in different degrees of convexity and resilience. **(*c*)** The specially designed sole of the platform includes two mounting rails and a positioning matrix to enable flexible positioning of each biomechanical element. [Elbaz, 2014].

During the first assessment the biomechanical device (AposTherapy device) will be individually calibrated to each patient by a physiotherapist certified in AposTherapy treatment methodology. The principle of device calibration is to achieve minimal pain while walking. For example, in knee OA with medial compartment disease, the pod-element under the hindfoot is shifted laterally from the neutral position. This shifts the center of pressure (COP) in the foot laterally, thereby reducing the magnitude of the knee adduction moment acting on the knee joint. This is done until the patient reports minimal pain during initial contact. The forefoot pod-element is shifted medially from the baseline position until the patient reports minimal pain during mid-stance to toe-off. Once the desired alignment is achieved, the patient should report immediate pain relief while walking. Following calibration patients will receive home-based exercise guidelines. During the first three weeks patients will be instructed to wear the calibrated biomechanical device for 30 minutes, while doing their daily activities (overall accumulating 10-15 minutes' walk). Patients will be instructed to gradually increase their wearing time reaching 2 hours a day following 3 months of treatment. After three months, patients will be encouraged to add outdoor walking, starting with 10 minutes and reaching 30 minutes a day. Patients will be asked to come back to follow-up meetings at the clinical center after 4 weeks, 8 weeks, 12 weeks, 24 weeks and 52 weeks. During these follow-up meetings patients will be re-assessed by the Apos therapist and, if needed, the biomechanical device will be re-calibrated.

<u>Group 2: Traditional physiotherapy</u>

Physical therapy for knee osteoarthritis is provided at Department of Rehabilitation Medicine, Moses Division, three times a week for 4 to 8 weeks (up to 20 sessions) depending on the progression of the subject. Each session takes about 1 hour. Physical therapist will follow the standard of care protocol available at our institution with minor adjustment as needed (Appendix 1).

Typical physical therapy regimen for knee OA includes strengthening, stretching exercise, therapeutic modality and education.

4.8. Assessment time points

Visits for evaluation will be done in a blinded fashion with independent evaluators who will perform all follow-up evaluations. Patients will have all outcome measures on initial entry into the study (pre-treatment), at 4 weeks, 8 weeks, 12 weeks, 24 weeks and 52 weeks after entry into the study.

4.9. Outcome measures

Primary study outcome:

- Western Ontario and McMaster Universities (WOMAC) pain scale at one year.
- WOMAC function scale at one year

Secondary study outcome: at: Pre-treatment, 4 weeks, 8 weeks, 12 weeks, 24 weeks, 52 weeks.

- WOMAC pain and function subscale
- PROMIS Pain Interference and Physical Function
- Costs: Assessment of total utilization and cost from resource utilization monitored via the CMO
- MOS item of the Short Form (SF)-36
- Spatio-temporal gait assessment including gait velocity, step length, single limb support and limb symmetry measured by Zeno Walkway ®
- 6-min walk test
- Blood pressure and resting heart rate

- Treatment adherence: Measured via attendance at sessions of therapy (conventional therapy), hours of use of AposTherapy (Patient to have step counter)
- Overall activity and sleep patterns (both arms (via FitBit Charge HR (http://www.fitbit.com/chargehr#i.f9n1ye1ehxd30p) motion sensor worn for one week after each evaluation session, mailed back via prepaid mailer at the end of the week.)

5. Statistical analysis

All demographic data will be reported as mean standard deviations and average. Data from primary and secondary outcome measures will be checked for skewness using Fisher-Pearson coefficient of skewness. ANOVA or Kuskal- Wallis test will be applied depending normality of data. All statistical analysis will be conducted using IBM SPSS Statistics Ver.24.

6. Benefits

- Participants will all have physical therapy for their knee
- AposTherapy involves fewer visits to the physical therapy center thus allowing individuals more time at home and lower transportation costs
- AposTherapy is done at home and more convenient
- AposTherapy will be provided for free for participants.

7. Risks

- Muscle soreness associated with exercise
- Minimal fall risk with use of new footwear device and exercise

8. Subject Reimbursement

Participants will be reimbursed a total of $40 at each assessment point (pre-treatment, at 4 weeks, 8 weeks, 12 weeks, 24 weeks and 52 weeks after entry into the study). Participants will

receive $95 reimbursement for their time at the completion of the study after return of all devices and materials. This will apply to all arms of the study.

Study schedule:

Study Periods	Screening						
Visit	1	2	3	4	5	6	7
Time (week)	-2	0	4	8	12	24	52
Patient Information and Informed Consent	X						
Demographics	X						
Medical History	X						
In- /Exclusion Criteria	X						
Radiography	X						
Randomization	X						
Administer traditional physical therapy	Physical Therapy is administered according to the protocol for the duration of enrollment in the study						
Administer Biomechanical Device		X					
Adjustment Biomechanical Device			X	X	X	X	
VAS and ODI		X	X	X	X	X	X
Secondary outcome measures		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X

Resources

AposTherapy	Montefiore
• Training for Montefiore PTs • Full-time Apos resource to manage program on-site at Montefiore • AposTherapy devices	• Clinical Principle Investigator Lead • Research staff – 2 coordinators • Data informatics, including patient population, demographics, historical costs, etc. • Research infrastructure including IRB, recruitment, clinical expertise • Study materials • Step counter/Fitbit monitors

Staff	Salary - Rate/Hr	Fringe	FTE or Hours	Total Cost
Attending Physician Supervision	$165,000	30.5%	0.2	$43,065
Study coordinator	$0	0.0%	2	$0
These will be Everest individuals				
Informatics costs	$75		100	$7,500
Biostatistical support	$150		100	$15,000
CMO staff support	$65,000	30.5%	0.5	$42,413
Total Staffing Cost				**$107,978**
Materials	**Cost per Unit**	**# of Patients**	**Qty**	**Subject Costs**
Step counters:				
25% of Patients and 10% loss	$50	37	41	$2,050
Fitbit HR Monitors:				
25% of Patients	$150	37	41	$6,150
Mailing to Recover ste counter/Fitbit:*	$10	37		$14,800

Transportation costs:	$100	147		$14,700
Subject Complete Reimbursement	$100	147		$14,700
Zeno Walkway	$20,000		1	$20,000
Total Materials				**$72,400**
Total cost of the study				**$180,378**

Appendix 1. Brief description of the physical therapy intervention [8-13]

Physical Therapy

Three times per week up to 20 sessions

Reassessment by physiatrist after 8 sessions

Mandatory interventions:

1. Aerobic exercise: up to 10 minutes erogometer cycle or walk on the treadmill with Borg scale of perceived exertion: fairly light to somewhat hard
2. Strengthening: 3 sets of 10 repetitions of:
   Knee extension; hip abduction, adduction, extension; knee flexion.

   Resistance adjusted using Theraband® as appropriate.
3. Stretching exercise: up to 10 minutes: 60 seconds passive stretch of:
   Rectus femoris, iliopsoas, adductor muscle, ilioitibial band and hamstring muscle, gastrocnemius with subtalar neutral
4. Neuromuscular coordination control exercises: 3 sets of 2 minutes of (choose from): standing weight-shifting exercises; standing balance on uneven surfaces; balance (wobble) board, side-stepping, forward-backward and shuttle-walking drills; or stair walking

Non-mandatory interventions, prescribed as needed after mandatory exercise

Modality: transcutaneous electrical stimulation (100Hz, 50 μ secs) or ultrasound (1.5 W/cm2) on the knee for 10 minutes

Home exercise program:

Perform walking on comfortable walking speed for 10 minutes and following exercise on both legs for approximately 10-15 minutes at a time, five days a week

EXERCISE PROGRAM

Perform these exercises on both legs for approximately 10-15 minutes at a time, five days a week.

Lying on your back with one leg straight and the other leg bent.

Exercise your straight leg by pulling the toes up, straightening the knee and lifting the leg 20 cm off the bed. Hold approx 5 secs. - slowly relax.

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Lying on your back. Bend one leg and put your foot on the bed and put a cushion under the other knee.

Exercise your straight leg by pulling your foot and toes up, tightening your thigh muscle and straightening the knee (keep knee on the cushion). Hold approx. 5 secs. and slowly relax.

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Sit on a chair.

Pull your toes up, tighten your thigh muscle and straighten your knee. Hold approx. 5 secs. and slowly relax your leg.

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Stand.

Hold onto a support and bring one leg slightly backwards.

Bend your knee and lift your foot off the floor. Hold approximately 5 secs.

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