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Change in Knee Cartilage Volume in Individuals Completing a Therapeutic Exercise Program for Knee Osteoarthritis

STUDY DESIGN: Prospective cohort study.

OBJECTIVES: To characterize knee cartilage change in individuals with knee osteoarthritis (KOA) who have completed a therapeutic exercise program.

BACKGROUND: While therapeutic exercise is frequently used successfully to improve pain and function in individuals with KOA, no studies have reported the volume of cartilage change or individual factors that may impact volume of cartilage change in those completing an exercise program for KOA.

METHODS: Thirteen individuals with KOA underwent magnetic resonance imaging to quantify cartilage volume change in the weight-bearing regions of the medial and lateral femoral condyles and the entire surface of the tibial plateaus from baseline to 1-year follow-up. Body structure and function measures were taken for body mass index, knee axis alignment, knee motion, and knee strength. Activity limitations and activity levels were also measured prior to the therapeutic exercise program, using the Western Ontario and McMaster Universities Osteoarthritis Index and the Physical Activity Scale for the Elderly. At 6 months from baseline, follow-up clinical measurements of knee strength and motion were performed. At 1 year from baseline, imaging of the knee cartilage and knee alignment were performed, and participants completed the Western Ontario and McMaster Universities Osteoarthritis Index and Physical Activity Scale for the Elderly.

RESULTS: The central region of the medial femoral condyle (cMF) had a median volume of cartilage loss of 3.8%. The other 3 knee tibiofemoral articular surfaces had minimal median cartilage volume change. Individuals were dichotomized into progressors (n = 6) and nonprogressors (n = 7), based on the standard error of measurement of cartilage volume change for the cMF. Progressors were younger, had a larger body mass index, had a higher Kellgren-Lawrence grade in the medial compartment of the knee, and had a greater increase in knee varus alignment from baseline to 1-year follow-up. The progressors also had frontal plane hip and knee kinetics during baseline gait analysis that potentially increased medial knee joint loading.

CONCLUSION: The loss of cMF cartilage volume was highly variable and the median loss of cartilage was within the range previously reported. Seven of the 13 individuals did not have cMF cartilage volume loss greater than the standard error of measurement. Change in cartilage volume of the cMF may be influenced to a greater extent by personal factors than by completion of a therapeutic exercise program. Additional research is needed to decipher the interactions among therapeutic exercise and personal characteristics that impact knee cartilage loss. *J Orthop Sports Phys Ther 2011;41(10):708-722, Epub September 2011. doi:10.2519/jospt.2011.3633*

KEY WORDS: *arthritis, biomechanics, magnetic resonance imaging, MRI*

The prevalence of knee osteoarthritis (KOA) has been reported to be between 19% to 28% in adults older than 45 years of age, and as high as 37% in adults over the age of 60.[38] In total, over 9 million adults in the United States are believed to have symptomatic KOA.[38] A myriad of negative sequelae, including impairments of knee strength and motion, knee pain, knee instability, limited functional abilities, and increased disability have been well documented in individuals with KOA.[21,27,30,31,42,51,52] In addition to impairments and functional limitations associated with KOA, an increased rate of articular cartilage loss at the knee, as measured by quantitative magnetic resonance imaging (MR), has been shown to be a predictor of subsequent total knee arthroplasty.[14] Therefore, treatments that slow the rate of knee cartilage loss may delay or potentially prevent knee arthroplasty. Therapeutic exercise may be one such option to positively change the rate of knee cartilage loss in individuals with KOA.

To treat both the impairments and functional limitations that result from

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KOA, therapeutic exercise is often recommended. Therapeutic exercise has been shown to be effective in reducing pain and improving function in patients with KOA and is recommended by the American College of Rheumatology in its clinical guideline for treatment of individuals with KOA.[30,34,39,54] Although therapeutic exercise improves the functional abilities and symptomatology of those with KOA,[24] whether therapeutic exercise affects the rate of articular cartilage loss at the knee in persons with KOA is currently unknown.

While basic science research and animal studies have shown that cartilage synthesis responds favorably to loading,[25,26,43] human MR imaging studies investigating loss of knee cartilage in individuals with KOA have reported an increased loss of tibiofemoral cartilage with factors that increase loading.[19,48,49] Individuals with KOA have been shown to have an increased knee adduction moment during gait compared to those without KOA, even when gait speed is standardized.[5] While a predominantly weight-bearing therapeutic exercise program increases loading through the knee, it has also been shown to improve quadriceps strength, knee range of motion, and joint proprioception.[34,35] Improved quadriceps strength, increased knee joint motion, and heightened joint proprioception resulting from a therapeutic exercise program may have a protective effect on the cartilage of the knee and reduce the rate of cartilage loss. To determine if therapeutic exercise has a protective effect on knee cartilage, the changes in knee cartilage found in individuals with KOA completing a therapeutic exercise program must be compared to the natural rate of cartilage loss in individuals with KOA.[13,18,44-46]

Loss of knee joint cartilage may be influenced by many factors. Evidence of gender, age, body mass index (BMI), medial meniscal damage, and knee alignment as factors impacting the rate of cartilage loss has previously been reported.[18,19,44-46,48] Abnormal variations in gait pattern and resulting hip and knee kinetics may also serve as risk factors for knee cartilage loss in those with KOA. Gait analysis studies have shown that individuals with KOA exhibit biomechanical risk factors for knee cartilage loss, such as increased knee adduction moments, decreased hip adduction moments, and increased rates of loading across the knee joint.[5,9,12,32] Knee adduction moments are used as a surrogate measurement for loading of the medial compartment of the knee, with increased knee adduction moments equating to increased medial compartment loading.[33] At the hip, external hip adduction moments are maintained in equilibrium by contraction of the hip abductor musculature. In a prior study measuring hip adductor moments during gait, stronger hip abductor muscles were shown to slow the progression of medial joint space narrowing in individuals with medial KOA.[12] To our knowledge, there are currently no longitudinal studies that have examined both lower extremity gait kinetics and the rate of knee cartilage loss simultaneously in patients with KOA.

Despite the common prescription of exercise programs to individuals with KOA, there is a paucity of research investigating how completion of a therapeutic exercise program may affect knee cartilage volume loss. The main purpose of this study was to measure knee cartilage change in individuals with KOA who have completed a therapeutic exercise program and to compare their rate of cartilage loss to the currently known rates for individuals with KOA. It was also to explore the differences between those individuals who had a loss of cartilage volume greater than measurement error and those who had a cartilage volume loss within the SEM.

TABLE 1 GROUP CHARACTERISTICS AT BASELINE

	Mean ± SD
Age, y	63.5 ± 11.4
Sex, n	
Female	3
Male	10
Body mass index, kg/m^2	28.0 ± 4.0
Kellgren-Lawrence grade of medial compartment, n	
Grade 1	2
Grade 2	4
Grade 3	5
Grade 4	2
Knee axial alignment, deg	175.8 ± 3.5
WOMAC total score (0-96)	17.9 ± 9.8
PASE (0-400)	137.5 ± 76.9
Quadriceps MVIC, Nm/kg	2.0 ± 0.4

Abbreviations: MVIC, maximum voluntary isometric contraction; PASE, Physical Activity Scale for the Elderly; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

METHODS

THE SUBJECTS OF A LARGER RANDOMIZED trial investigating the effectiveness of therapeutic exercise for knee OA[20] were invited to have imaging of both tibiofemoral joints performed prior to beginning the randomized trial and follow-up imaging performed 1-year after the baseline imaging. Consecutive subjects were invited to participate in the imaging arm of the study until 15 subjects were enrolled. One subject did not return for the follow-up imaging and 1 subject was

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TABLE 2 Subject Baseline Measurements and 1-Year Change in cMF Cartilage Volume

Group/Participant ID	Sex	Age, y	BMI, kg/m²	Treatment Group	KL Med MA	KL Lat MA	Initial cMF VC, mm³	cMF VC Change, mm³	Percent cMF VC Change
Progressors									
136	M	67	30.9	Agility	4	1	846	−422	−49.9
130	M	54	30.8	Agility	2	3	1841	−420	−22.8
149	F	49	29.4	Standard	3	0	1633	−335	−20.5
142	M	66	34.2	Agility	3	2	1056	−240	−22.7
148	M	59	25.7	Standard	3	4	2628	−153	−5.8
145	M	50	27.2	Standard	1	3	3975	−121	−3.1
Nonprogressors									
150	M	82	26.5	Agility	2	3	746	−86	−11.5
151	M	67	25.9	Standard	2	0	2073	−79	−3.8
135	M	71	33.0	Agility	3	1	1828	−53	−2.9
138	F	63	19.3	Standard	2	0	1857	−6	−0.3
153	F	83	24.1	Standard	1	2	1955	49	2.5
147	M	48	25.8	Agility	3	2	1269	67	5.2
131	M	66	30.6	Agility	4	2	1246	113	9.1
Median values by group									
Progressors	5 M, 1 F	57	30	3 agility, 3 standard	3	2.5	1737	−287	−22
Nonprogressors	5 M, 2 F	67	26	4 agility, 3 standard	2	2	1823	−6	0

Abbreviations: BMI, body mass index; cMF, central region of the medial femoral condyle; F, female; KL, Kellgren Lawrence grade (0 to 4); Lat, lateral tibiofemoral compartment; M, male; MA, most affected side; Med, medial tibiofemoral compartment; MVIC, maximum voluntary isometric contraction; VC, volume of cartilage.

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determined not to have met the inclusion criteria. This resulted in a sample size of 13 subjects for the imaging arm of the study. Inclusion criteria for the randomized trial required a Kellgren-Lawrence grade of 2 or greater in at least 1 compartment of the tibiofemoral joint and a diagnosis of KOA according to the criteria established by the American College of Rheumatology, which are 3 or more of the following: morning stiffness less than 30 minutes, crepitus with active motion of the knee, such as when squatting while weight bearing, tenderness on palpation of the bony margins of the joint, bony enlargement, and/or no palpable warmth.[1] Exclusion criteria were the following: less than 40 years of age; history of myocardial infarction, cerebral vascular accident or other neurological disorder; lower extremity joint arthroplasty; and the inability to walk without an assistive device. When both knees of a subject met the criteria for inclusion in the study, only the knee indicated by the subject as most affected by pain was used for analysis.

The group characteristics are presented in **TABLE 1**, and each individual's characteristics, as well as treatment group assignment, are presented in **TABLE 2**. All subjects signed an informed consent, approved by the University of Pittsburgh Institutional Review Board, and their rights were protected at all times.

Tests and Measures

Subjects underwent baseline testing prior to initiating the therapeutic exercise treatments. The baseline testing consisted of MR imaging of both knee joints, radiographs to measure varus/valgus knee alignment, gait analysis, testing of quadriceps strength, goniometric measurement of knee motion, and the completion of self-report questionnaires to measure physical activity and functional limitations. Following 12 clinical treatment sessions over 2 months, which were immediately followed by a 4-month home exercise program (HEP), clinical measurements of knee strength and motion were reassessed at a 6-month follow-up visit that coincided with the end of the monitored HEP. MR imaging, knee alignment radiographs, and self-report questionnaires were repeated 1 year after baseline, which coincided with a time frame of 6 months after completion of the HEP.

MR Imaging Assessments

A 3.0-T scanner (MAGNETOM Trio; Siemens Medical Solutions USA, Inc, Malvern, PA) was used to acquire a sagittal 3-D double-echo steady state with water excitation (SAG 3D-DESS WE) scan of both knee joints. Coronal multiplanar reformats were performed from the SAG 3D-DESS WE scans and used for segmentation of the femoral and tibial cartilage. The SAG 3D-DESS WE MR scan parameters were as follows: in-lane resolution,

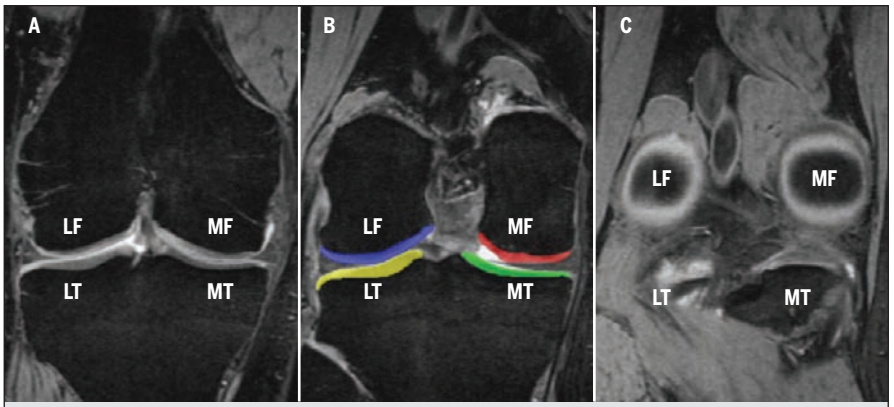

FIGURE. (A) Anterior landmark used to determine the central medial and lateral femoral regions of interests, (B) color maps displaying the tagged regions of interest over the femur and tibia cartilage, (C) posterior landmark used to determine the central medial and lateral femoral regions of interest (60% criterion between A and C). Abbreviations: LF, lateral femoral condyle; LT, lateral tibial plateau; MF, medial femoral condyle; MT, medial tibial plateau.

0.365 × 0.456 mm; repetition time, 16.3 milliseconds; echo time, 2.8 milliseconds; flip angle, 25°; matrix, 384 × 384; field of view, 14 × 14 cm; slice thickness, 0.7 mm; scan time, 10 minutes 36 seconds.

Using a commercial software package (Sliceomatic; Tomovision, Montreal, Canada), the coronal MR images of the knee were manually segmented to distinguish the cartilage from the surrounding bone and soft tissues (**FIGURE**). Four regions of knee cartilage were segmented to quantify their cartilage volume. The cartilage coverings of the medial and lateral tibial plateaus were segmented in their entirety, while the medial and lateral femoral condyles were segmented into a central region for each condyle (central region of the medial femoral condyle [cMF] and central region of the lateral femoral condyle [cLF]). Calculating the volume of just the central region of the condyle has the advantage of measuring only the subregion of the condyle that is most subject to weight-bearing loads during ambulation.[37] To ensure that volumetric measurements were performed on the same region of the femoral condyles, baseline and 1-year follow-up image analyses for the cMF and cLF were performed on the same number of image slices, which constituted the anterior 60% of the distance between the image starting with the divergence of the trochlea into the femoral condyles (**FIGURE**) and the last image showing the circular structure of the posterior femoral condyles (**FIGURE**).[17] Measurement of this region has previously been shown to be reliable and to closely match the region of the femoral condyle determined to undergo the greatest amount of loading during normal walking.[37] Volumetric measurements were subsequently performed by multiplying the segmented surface areas on each image by the slice thickness (1.5 mm after multiplanar reformatting). All MR images were segmented by 1 of the investigators (S.F.), who was trained in the methods used to quantify cartilage morphology. In our laboratory, the SEM for quantifying cMF cartilage volume was calculated to be 120 mm^3. The coefficient of variation for intratester reliability of cMF cartilage volume quantification was 2.4%. The coefficient of variation for the cMF surface area digitized was calculated to be 6.9%. Both of these coefficients of variation are within acceptable limits.[17]

Knee Alignment and Kellgren-Lawrence Grade

Weight-bearing anterior-posterior long-cassette radiographs were taken and used to calculate the axial alignment of the tibiofemoral joint, as described by Moreland et al.[40] An axial alignment of 180° indicated a neutral alignment. Values of less than 178° indicated a varus alignment of the knee, while values greater than 182° indicated a valgus alignment.

A rheumatologist assigned a Kellgren-Lawrence grade to each subject's baseline knee radiographs, according to the guidelines established by Kellgren and Lawrence.[36]

Gait Analysis

Subjects ambulated on an 8.5-m-long vinyl-tiled walkway. A Vicon 612 motion analysis system (Vicon-UK, Oxford, UK) with 8 M2 cameras recorded 3-dimensional motion data at a sampling rate of 120 Hz from the Plug-in Gait marker set. Ground reaction forces were measured on 2 force plates (Bertec Corporation, Columbus, OH) embedded into the walkway. The force data were recorded at a sampling rate of 1080 Hz and synchronized with the motion data. Five walking trials, in which subjects contacted the force platforms without targeting, were collected and averaged. Marker trajectories and ground reaction force data were low-pass filtered (Butterworth, fourth order, phase lag) at 6 and 40 Hz, respectively. Data were analyzed using MatLab, Version 7.0 (The Mathworks, Inc, Natick, MA). External joint moments were derived using inverse dynamics and normalized to body mass (kg). Peak moments were calculated during the loading phase (from heel strike to the first peak of vertical ground reaction force).

Quadriceps Muscle Strength

Maximum voluntary isometric torque output for knee extension was measured using a Biodex System 3 dynamometer (Biodex Medical Systems, Inc, Shirley, NY). The subject was seated with the knee in 60° of flexion and instructed to extend the knee against the dynamometer with maximal effort for 5 seconds. A minimum of 3 trials and maximum of 6 trials were performed. After 3 trials, when a trial had a maximum torque output less than the previous trial, the strength testing was concluded. The highest maximum torque output from all trials was normalized to

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body weight (kg) and used in the analysis. This procedure has been shown to yield reliable quadriceps femoris torque measurements in our laboratory (intraclass correlation coefficient [$ICC_{2,1}$] = 0.96).

Self-Report Questionnaires

The Physical Activity Scale for the Elderly (PASE) was used to provide an estimate of each subject's level of physical activity. The PASE is a self-administered questionnaire that assesses an individual's level of leisure, occupational, and household activities, and has been shown to be reliable and valid in a sample of community-dwelling, older adults.[57] PASE scores can range from 0 to greater than 400, with higher scores indicating higher physical activity levels. Past studies have shown the average PASE score to be between 118 and 128 for older adults with arthritic or musculoskeletal conditions.[10,56] The Likert version of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to quantify self-reported functional limitations. The WOMAC is a disease-specific measure of pain, stiffness, and physical function for individuals with knee OA. The WOMAC includes 5 items related to pain, 2 items related to stiffness, and 17 items related to physical function. Each item is scored on a 5-point Likert scale (0 to 4), with a total maximum score of 96 points. Higher scores indicate greater functional limitations. The reliability and validity of the WOMAC have been established.[6,7,28]

Treatment Interventions

The exercise protocol used in this report has been published previously and is provided in the **APPENDIX**.[47] All subjects completed a 6-week, 12-session outpatient physical therapy program that included aerobic treadmill walking and lower extremity strengthening and flexibility exercises. The subjects randomized to the experimental treatment group also completed dynamic agility and perturbation training. Following completion of outpatient physical therapy, an HEP was completed 2 times per week for 4 months.

TABLE 3 Change in Cartilage Volume Over 12 Months by Tibiofemoral Articular Surface*

Articular Surface of the Tibiofemoral Joint	Median Cartilage Volume Change
Femur	
cMF	-3.8 (-50, +9)
cLF	0.0 (-17, +20)
Tibia	
Medial plateau	0.8 (-47, +19)
Lateral plateau	0.1 (-25, +18)

Abbreviations: cLF, central region of lateral femoral condyle; cMF, central region of medial femoral condyle.
**Values are median (minimum, maximum) percentage change.*

The 7 subjects randomized to the standard treatment group completed an exercise program consisting of muscle stretching (quadriceps, hamstrings, and calf musculature), muscle strengthening (single-leg leg presses, seated isometric knee extensions, standing hamstring curls, standing heel raises, prone hip extensions, supine straight leg raises, and quad sets), and treadmill walking. The 6 subjects who were randomized to the agility and perturbation treatment group received the same exercises as the standard treatment group, as well as the following agility exercises: sidestepping, braiding (lateral stepping combined with forward and backward crossover steps), forward crossover steps during forward ambulation, forward/backward shuttle walking, change-in-direction drill (the therapist provided hand signals that would require the subject to combine random forward/backward walking with lateral stepping and diagonal stepping). The perturbation techniques were done using foam surfaces, tilt boards, and roller boards. The subjects attempted to maintain balance while experiencing the destabilizing perturbations.

To account for a potential confounding effect of contact/treatment time between the 2 treatment groups, the subjects in the standard exercise group completed 10 to 15 minutes of upper extremity exercise on an arm bike. This additional treatment time approximated the time required for the subjects in the agility and perturbation group to complete their agility and perturbation activities.

For the HEP, the content was similar to the outpatient sessions, with modifications to the exercises that were done clinically using exercise machines. Wall squat exercises were substituted for the leg press, and gold Thera-Band was used to perform isometric quadriceps exercises similar to those performed clinically on the knee extension machine. All subjects were given a cuff weight adjustable from 1 to 10 lb (0.45-4.54 kg) for the straight leg raises, hip extensions, and hamstring curls.

Subjects in the agility treatment group performed all exercises completed by the standard group. All agility activities were completed at home, with the exception of the change in direction during walking activity and the roller board and tilt board exercises due to safety concerns and inability to provide this equipment. Therefore, single-leg balance on level surfaces and carpeted surfaces was included in the agility group's HEP to provide a balance/perturbation component to the program. Subjects in both groups were also encouraged to continue a walking program of 30 minutes a day for at least 3 days a week. The trial coordinator contacted each subject monthly to remind the subjects to complete their HEP and to discuss any barriers to completion of the HEP as instructed. At the midpoint of the HEP duration, each subject had a face-to-face visit with the trial coordinator to

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TABLE 4 WOMAC, PASE, and Self-Reported Pain Levels at Initial Visit and 12-Month Follow-up*

	WOMAC Physical Function Subscale (0-68)		WOMAC Pain Subscale (0-20)		WOMAC Knee Stiffness Subscale (0-8)		WOMAC Total Score (0-96)		PASE (0 to >400)		Worst Pain in Past 24 h (0-10)	
Group/Participant ID	Initial	12 mo	Initial	12 mo	Initial	12 mo	Initial	12 mo	Initial	12 mo	Initial	12 mo
Progressors												
136	12	12	4	4	3	2	19	18	138	184	4	4
130	10	5	3	3	1	0	14	8	347	295	4	3
149	29	5	4	1	6	4	39	10	181	174	4	4
142	10	8	0	3	3	0	13	11	109	120	1	2
148	12	5	3	2	2	0	17	7	202	211	2	1
145	2	0	1	0	2	2	5	2	104	94	1	1
Nonprogressors												
150	12	4	1	1	1	0	14	5	78	138	2	2
151	3	3	3	0	1	1	7	4	124	31	1	1
135	16	13	5	6	2	3	23	22	34	267	3	5
138	8	5	1	2	2	3	11	10	123	166	2	3
153	11	13	4	3	3	2	18	18	115	140	3	5
147	21	9	6	2	3	3	30	14	155	192	8	3
131	12	36	3	10	1	5	16	51	77	116	4	5
Median values by group												
Progressors	11	5	3	3	3	1	16	9	160	179	3	3
Nonprogressors	12	9	3	2	2	3	16	14	115	140	3	3

Abbreviations: 12 mo, 12-month follow-up visit; PASE, Physical Activity Scale for the Elderly; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
**Higher WOMAC values indicate greater functional deficits, pain, and stiffness. Higher PASE scores indicate increased physical activity.*

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review the HEP, to ensure that the exercises were being completed correctly, and to encourage compliance with the HEP.

RESULTS

Because this study included a relatively small sample of subjects, descriptive statistics were used to examine the data and inferential statistics were not performed. The annual percentage change in cartilage volume for the medial and lateral tibial and femoral articular surfaces was calculated by dividing the difference in cartilage volume from baseline to follow-up by the baseline volume. To explore the differences between subjects who had a loss of cartilage volume greater than the measurement error and those who had a cartilage volume loss within the SEM, the 13 subjects were dichotomized into progressors and nonprogressors using the standard error of the measure (SEM) for the cMF. The median values for each baseline factor were then calculated for the individuals that had a cartilage loss greater than the SEM (progressors) and for those who had a change within the SEM (nonprogressors). The decision to use change at the cMF region to examine factors that may impact cartilage volume loss was based on the recent work of Eckstein et al,[18] who found the cMF to be the most responsive region of the tibiofemoral joint in terms of change in cartilage volume. In addition, prior studies have found the central region of the medial femoral condyle to be the area of greatest cartilage loss over time in patients with KOA.[3,8]

The median percent changes in cartilage volume for the 4 articular surfaces of the tibiofemoral joint are shown in **TABLE 3**. The cMF had a median loss of 3.8%, while the other 3 articular surfaces had median changes in cartilage volume of less than 1%. When the SEM was used to dichotomize the loss of cMF cartilage volume, the progressors had a median cMF cartilage volume loss of 22%, while the nonprogressors had a median change of 0% (**TABLE 2**).

TABLE 2 presents the individual subject characteristics, treatment group assignment, and KL grade of the most affected knee, as well as the baseline, absolute change, and percentage change in cartilage volume for the cMF. In the progressor group, 3 subjects were assigned to the standard treatment group, while 3 were assigned to the agility treatment group. In the nonprogressors, 3 subjects were in the standard group, while 4 were in the agility group. Comparing the median values of the progressor group to the nonprogressor group, the progressors had a greater BMI (30 versus 26 kg/m^2),

TABLE 5 Knee ROM, Quadriceps Strength, and Knee Axis Alignment at Baseline and Follow-up

	Passive Knee ROM, deg		Quadriceps MVIC, Nm/kg		Knee Axis Alignment, deg	
Group/Participant ID	**Initial**	**6 mo**	**Initial**	**6 mo**	**Initial**	**12 mo**
Progressors						
136	14-114	20-117	1.8	1.7	170 varus	170 varus
130	4-0-118	0-126	2.2	2.4	173 varus	171 varus
149	8-124	12-131	1.9	1.8	176 varus	172 varus
142	3-139	6-135	2.1	2.1	177 varus	170 varus
148	8-0-112	10-0-117	2.5	2.6	179 neutral	182 neutral
145	8-127	9-130	2.2	2.2	180 neutral	182 neutral
Nonprogressors						
150	5-150	5-140	1.5	1.1	174 varus	175 varus
151	5-146	6-149	1.9	1.7	176 varus	176 varus
135	5-130	6-0-132	1.8	1.7	176 varus	178 neutral
138	2-0-146	1-146	2.4	2.4	179 neutral	180 neutral
153	4-130	12-140	1.4	0.7	181 neutral	183 valgus
147	4-128	8-136	1.7	1.6	174 varus	175 varus
131	13-130	17-135	2.3	2.1	170 varus	168 varus
Median values by group						
Progressors	121 flexion, 5 loss of extension	128 flexion, 7 loss of extension	2.1	2.2	177	172
Nonprogressors	130 flexion, 5 loss of extension	140 flexion, 6 loss of extension	1.8	1.7	176	176

Abbreviations: 6 mo, 6-month follow-up visit; 12 mo, 12-month follow-up visit; MVIC, maximum voluntary isometric contraction; ROM, range of motion.

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a lower age (57 versus 67 years), and a higher KL grade for the medial compartment (3 versus 2). The initial cMF cartilage volumes for the groups were similar at baseline, with a median of 1737 mm^3 for the progressors and 1823 mm^3 for the nonprogressors.

TABLE 4 presents the baseline and 1-year scores for the WOMAC and its 3 subscales, the PASE, and the worst pain level, as reported with the numerical pain rating scale.

The baseline and follow-up values for knee range of motion, quadriceps strength, and knee axis alignment are presented in **TABLE 5**. Both groups showed a modest improvement in knee flexion and a slight worsening in knee extension range of motion. Change in quadriceps maximum voluntary isometric contraction was minimal in both groups from baseline to 6-month testing. There was a 5° increase in the knee varus angle of the progressors, while the nonprogressors had no change in alignment.

TABLE 6 presents frontal plane kinetic data collected at baseline for the hip and knee joints during the loading phase of gait. The progressors had a 13% greater median peak knee adduction moment than the nonprogressors (0.61 versus 0.54 Nm/kg). At the hip joint, the nonprogressors had a 12% greater median peak hip adduction moment than the progressors (1.0 versus 0.89 Nm/kg).

Compliance for the treatment sessions completed in the clinic and the HEP is listed in **TABLE 7**. All 13 subjects completed all 12 treatment sessions that occurred in the clinic. The progressors completed 94% of their HEP sessions, while the nonprogressors completed 66%.

DISCUSSION

To our knowledge, this is the first report to present the rate of change of tibiofemoral cartilage volume in subjects enrolled in a therapeutic exercise program for treatment of KOA. The 3.8% median loss of cMF cartilage volume is within the range of 2% to 7.5% per year reported in prior studies.[16,18,44-46] However, it must be noted that some earlier studies measured all cartilage of the femoral condyle, while the current study, and 2 previously published studies, measured only the weight-bearing central aspect of the femoral condyles. Weight-bearing region of the condyle has been shown to experience greater changes than non–weight-bearing regions.[3,8] Therefore, the data from this study is most appropriately compared to those of studies which measured cartilage change in the cMF rather than in the entire femoral condyle. The 2 studies that quantified change in the weight-bearing cMF reported annual cartilage volume losses of 1.5% and 6%.[18,44] The lateral femoral condyle and both tibial plateaus experienced cartilage loss at a decreased

TABLE 6 Individual Values and Group Median Values (Range) for Baseline Hip and Knee Frontal Plane Gait Kinetics

Group/Participant ID	Peak Hip Adduction Moment During Loading, Nm/kg	Peak Knee Adduction Moment During Loading, Nm/kg
Progressors		
136	0.91	0.70
130	0.46	0.88
149	0.87	0.30
142	1.14	0.73
148	0.78	0.52
145	1.16	0.30
Nonprogressors		
150	0.62	0.40
151	1.10	0.98
135	0.76	1.10
138	1.13	0.54
153	1.00	0.31
147	1.03	0.46
131	0.80	0.62
Median values by group		
Progressors	0.89 (0.46 to 1.16)	0.61 (0.30 to 0.88)
Nonprogressors	1.00 (0.62 to 1.13)	0.54 (0.31 to 1.10)

rate compared to prior studies.[16] The median cMF cartilage volume loss was within previously reported ranges, in spite of the increased severity of radiographic KOA as measured using the KL scale. An increasing rate of cMF cartilage volume loss with a higher KL grade has been reported.[18] In the current study, 7 out of 13 (54%) subjects had a KL grade of 3 or 4 in the medial compartment of the knee. In the study by Eckstein et al,[18] only 34% of the knees had a KL grade of 3 or 4. The study by Pelletier et al[44] excluded those with a KL grade of 4, and 53% and 47% of the study's subjects had KL grades of 2 and 3, respectively. It has previously been shown that a higher KL grade is indicative of more extensive cartilage loss and a smaller baseline cartilage volume.[15] Mathematically, as the baseline cartilage volume decreases, a given absolute amount of cartilage loss results in a higher percentage cartilage volume loss.

The large variability of cMF cartilage loss found in this report (ranging from 50% loss to 9% gain) and by other researchers underscores the importance of understanding mediating factors that impact the rate of loss of articular cartilage. For instance, Raynauld et al[45] determined KOA subgroups by rate of cartilage loss and found a fast progressor group that lost 21.5% of its medial tibiofemoral articular cartilage volume over 2 years and a slow progressor group that lost just 3.2%. Likewise in our study, the progressor group lost a median cMF cartilage volume of 22%, while the nonprogressor group had a median cMF cartilage volume change of 0%. Though both groups improved their total WOMAC scores from baseline to 1-year follow-up, the progressor group actually had a greater improvement compared to the nonprogressor group. Both groups demonstrated the greatest change in the physical function subscale of the WOMAC but showed little overall change on the WOMAC pain and stiffness subscales. As expected, given the minimal change in the WOMAC pain subscale, the numeric pain rating scale did not indicate any significant change from baseline to 1-year follow-up in the subjects' worst level of knee pain, whether or not they had cMF cartilage volume loss.

As for physical activity, the PASE scores of the progressors were slightly higher at baseline and 1 year than those of the nonprogressors. This was expected, given the younger age of the progressors as compared to the nonprogressors. Prior research has shown that PASE scores decrease with increasing age, and the differences in activity levels between our 2 groups could have been the result of a difference in age.[10] In addition, both groups had an approximately 20-point increase in the PASE scores from baseline to 1 year. Physical activity levels may be an important mediator of cartilage volume loss; but, to our knowledge, there are currently no longitudinal MR studies considering this relationship in individuals with KOA. Amin et al[2] conducted a cross-sectional study that reported an increased risk of worse patellofemoral whole-organ MRI cartilage scores (WORMS) in workers with self-reported occupational exposure to kneeling/squatting and heavy lifting. Their research demonstrates the potentially deleterious effect of repeated, stressful activities on the articular cartilage of the knee. Foley et al,[22] in a sample of healthy subjects, found greater quadriceps strength and higher levels of fitness to be associated with less knee cartilage loss. However, their findings of a positive relationship between activity and knee cartilage response cannot be assumed to occur in individuals with KOA. In fact, Andriacchi et al[4] have shown that healthy knees appear to respond favorably to loading by increasing the thickness of articular cartilage in response to increased loading, while the opposite is true of arthritic knees. The lack of studies examining the impact of physical activity levels on knee cartilage loss in individuals with KOA makes it difficult to prescribe the proper therapeutic dosage of physical activity and knee joint loading. Making it even more difficult to assess the impact of physical activity on cartilage loss are

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TABLE 7 Compliance With Clinic Sessions and Home Exercise Program

Group/Participant ID	Compliance With Clinic Sessions*	Compliance With HEP†
Progressors		
136	100	100
130	100	34
149	100	100
142	100	88
148	100	100
145	100	100
Nonprogressors		
150	100	100
151	100	100
135	100	56
138	100	44
153	100	97
147	100	66
131	100	56
Median values by group		
Progressors	100	94
Nonprogressors	100	66

Abbreviations: HEP, home exercise program.
**Percent of clinic sessions completed.*
†Percent of HEP sessions completed.

the limitations of self-report measures of physical activity, such as the PASE.[23] Additional research is required to more precisely capture activity levels, given the potentially large impact of physical activity on outcomes in a myriad of disease processes, including KOA.

The changes in impairment measures of knee motion and knee strength paralleled those between the progressors and nonprogressors in self-reported pain and activity levels. Both groups had a modest improvement in passive knee flexion and a slight worsening in the loss of terminal knee extension. Despite the inclusion of stretching exercises to improve knee extension, both groups failed to improve terminal knee extension. Similarly, despite a thorough strengthening program, both groups showed minimal change in quadriceps strength.

The strengthening program used in this study utilized 1-repetition maximum strength testing to prescribe at least 70% of the 1-repetition maximum as dosage for the single-limb leg press. Knee extension exercises were performed isometrically at maximum effort. This dosage for the leg press and knee extension strengthening exercises should have provided adequate stimulus for strengthening of the hip and knee extensor musculature. While the individuals in this study showed no significant change in their maximum quadriceps strength, the larger sample from the full randomized trial did demonstrate an improvement in knee extension strength.[47] Therefore, the minimal change in strength was unexpected. Potential explanations for a lack of strength gain in individuals with KOA are that pain during exercise may limit the ability of the treating therapist to increase the dosage of the exercises, and individuals may limit their force output in response to pain. Future studies should consider collecting pain data during exercises to determine if pain during exercise can affect lower extremity strength changes.

Although the self-reports and measures of knee impairment demonstrated similar changes between the groups, with the exception of the progressors having a greater improvement in the physical function subscale of the WOMAC, there were several factors that differed between the progressors and nonprogressors. Age, BMI, severity of KOA, progression of knee varus alignment, and gait kinetics all differed between the progressors and nonprogressors. These factors, with the exception of age, have been previously shown to impact the rate of knee cartilage loss in KOA.

As to the role of age in cMF cartilage volume loss, 2 previous studies failed to find a statistically significant association between cMF cartilage volume loss and age.[18,44] In the current report, the progressors had a median age of 57 years and the nonprogressors had a median age of 67 years. Despite this difference, age may not greatly impact cMF cartilage loss when other factors that more directly affect loading are taken into account.

In the current study, progressors had a BMI of 30 kg/m^2, while nonprogressors had a BMI of 26 kg/m^2. BMI has been shown to have a significant association (r = 0.21, P = .03) with cMF cartilage volume loss.[44] In addition, Eckstein et al[18] reported a trend of a faster rate of cartilage loss in cMF subjects with a BMI greater than 30 kg/m^2 compared to those with a BMI of less than 30 kg/m^2. These findings support the deleterious effect of increasing BMI on cMF cartilage loss in those with KOA.

Progressors also had more severe radiographic KOA and a greater progression towards varus alignment of the knee compared to nonprogressors. While the progressors had a median KL grade of 3 in the medial compartment of the knee, the nonprogressors had a median of 2. Eckstein et al[18] have shown that knees with a KL grade of 3 tend to have a higher rate of cMF cartilage volume loss than knees with a KL grade of 2. It has also been shown that increased KOA severity increases the knee adduction moment during gait.[41] An increased knee adduction moment is believed to result in greater loading across the medial com-

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partment of the knee.

While the groups had nearly identical alignment of the knee at baseline, at 1 year the progressor group had a median knee alignment of 172°, while the nonprogressors had a median of 176°. Therefore, the progressor group median alignment became more varus while the nonprogressors median alignment remained at 176°. The deleterious effect of varus alignment on the cartilage of the medial compartment of the tibiofemoral joint has been well established by previous research.[19,48]

In the gait analysis data the progressors showed a 13% higher median external knee adduction moment and a 12% lower median hip adduction moment compared to the nonprogressors. While higher than normal knee adduction moments, similar to the magnitudes found between our progressors and nonprogressors, have been shown to be common in those with medial KOA,[5,41,53,58] there are currently no studies that have examined the relationship between external knee adduction moment during gait and the rate of cMF cartilage volume loss. However, the differences between our groups were small, and the ranges of both knee and hip adduction moments in the progressors and nonprogressors were quite similar. These results suggest, therefore, that larger studies investigating these relationships are warranted.

The slightly larger external hip adduction moment found in the nonprogressors appears to be in agreement with the results reported by Chang et al.[12] In fact, in their study, the 12% difference in the frontal plane hip moment between those who lost knee joint space and those who did not closely matches the difference observed between the 2 groups in the current report. Using inverse dynamics to equate internal hip abduction moments created by the gluteus medius with the external hip adduction moment, Chang et al[12] suggested that higher internal hip abduction moments during loading of the lower extremity should decrease the load through the medial compartment of the knee. Strong hip abductors that could prevent contralateral rotation of the pelvis and a shift of the center of mass away from the hip joint axis during stance would accomplish a lower external knee adduction moment.[9,11]

In support of Chang's[12] findings, Mundermann et al[41] found smaller external hip adduction moments in subjects with more severe KOA when compared to those with less severe KOA. From these findings, the authors suggested hip abductor strengthening may reduce the knee adduction moment. However, a recent trial examining the impact of a hip abductor strengthening on the knee adduction moment during gait found no change in the knee adduction moment after 8 weeks of hip abductor strengthening, despite a 33% gain in hip abductor strength.[50] Also calling into question the role of hip abductor strength in reducing the knee adduction moment, Henriksen et al[29] reported that experimentally induced hip abductor weakness did not result in an increased knee adduction moment. However, this study was completed in a small sample of young, healthy individuals. The lack of agreement as to whether or not hip abductor strength deficits impact the external adduction moment at the knee requires additional research to not only examine the role of strength but also of hip muscle activation patterns. The potentially beneficial effects of hip abductor strength may be mitigated if muscle activation patterns are not properly coordinated during the stance phase of gait. Finally, actual hip abductor strength may have a weaker association with hip and knee moments compared to other factors, such as gait compensations, hip muscle activation patterns, and alignment of the lower extremity.

The fact that all the subjects in this study completed the therapeutic exercise program, yet cartilage loss varied greatly, suggests that the exercise program itself might not have altered the rate of cartilage loss. Undeniably, therapeutic exercise has shown itself to be an effective treatment for improving pain and function in those with KOA.[24] In the current study, both groups demonstrated improved WOMAC total scores, WOMAC physical functioning scores, and PASE scores. By better understanding how individual factors impact cartilage loss, researchers may be able to refine and assess therapeutic exercise programs for those at risk for rapid cMF cartilage loss. Programs that limit loading, such as non–weight-bearing exercise and aquatic therapy, may be better suited to improve function and pain and limit cartilage loss in a subset of individuals with KOA who are at greatest risk for rapid cartilage loss.

Limitations

As this research report includes only a small number of subjects, it serves to provide preliminary evidence that larger trials are needed to more accurately determine the effects of exercise, physical activity, gait kinetics, and anthropometrics on knee cartilage loss in individuals with KOA. Although we performed MR scans, our MR scans did not examine the condition of the medial meniscus, which has previously been shown to be a strong predictor of change in knee cartilage morphology.[45,48] Physical activity was quantified using the PASE. While this self-report questionnaire has undergone psychometric testing to demonstrate its reliability and validity, it is unable to capture temporal changes in level of physical activity over the course of a year or the amount of impact imparted to the knee cartilage during physical activities. It has also correlated only modestly with accelerometer data used to measure physical activity levels.[55] Additionally, a recent systematic review of self-administered physical activity scales concluded that additional high-quality validation studies are needed to support the use of these instruments.[23] Due to the potentially large but currently unproven influence of physical activity on cartilage loss in those with KOA, we advocate that future studies examine the interaction between physical activity levels and knee cartilage loss in this population.

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CONCLUSION

While 6 subjects had a loss of cMF cartilage volume greater than the SEM, 7 subjects had a loss within the SEM, indicating no loss of cMF cartilage volume beyond measurement error. The median absolute volume loss for the cMF of 86 mm^3 was within the SEM. Expressed as a percent change, the median loss of 3.8% of cartilage volume at the cMF was within the range published by previous authors who have quantified volume at the weight-bearing region of the medial femoral condyle. The large variability in cMF cartilage change may potentially be mediated by individual factors, especially those that have the potential to increase loading at the medial compartment of the knee, rather than the common factor of completing a therapeutic exercise program. In spite of differences in the amount of cMF cartilage volume loss between the groups, changes in physical activity levels, as well as impairments of knee motion and strength, were similar between the progressors and nonprogressors. The scores on the physical functioning subscale of the WOMAC improved for both groups, with the progressors having a slightly more robust improvement in that subscale. ◉

KEY POINTS

FINDINGS: In individuals with KOA, the completion of a therapeutic exercise program resulted in a rate of cMF cartilage loss within ranges previously reported. Factors that increase loading across the knee joint may increase the rate of cMF cartilage loss.

IMPLICATION: Since knee cartilage loss is a predictor of eventual knee arthroplasty, rehabilitation programs that improve symptoms and function, while limiting cartilage loss, would be optimal. This study is to serve as an impetus for studies that will compare rehabilitation protocols and their effects on symptoms, function and cartilage loss in individuals with KOA.

CAUTION: Due to the nature of this study design and the small sample size, future studies are required to elucidate optimal rehabilitation strategies for preserving cartilage while also improving symptoms and function.

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APPENDIX

EXERCISE THERAPY PROCEDURES

Standard Exercise Program

Exercise	Description	Dosage/Progression
Calf stretching	Subject stands in front of wall with hands supporting body against the wall. For the limb being stretched, the hip is extended, the knee is extended, and the foot is placed flat on the floor. The contralateral limb rests on the floor for stability, with the hip and knee comfortably flexed and the foot resting comfortably on the floor. The patient slowly leans forward toward the wall, keeping the foot flat and maintained in slight supination, and keeping the knee extended, until a stretch discomfort is felt by the subject in the calf muscles. The exercise should be repeated on the other limb.	2 repetitions, each 30 seconds in duration. Performed on both limbs. Range can be increased during 30-second period, if subject reports stretch discomfort has decreased.
Hamstring stretching	The therapist stabilizes the contralateral limb on the plinth and moves the stretching limb in a straight leg raise position, flexing the hip until a stretch discomfort is felt by the subject in the hamstrings, while keeping the knee in full extension. The exercise should be repeated on the other limb.	2 repetitions, each 30 seconds in duration. Performed on both limbs. Range can be increased during 30-second period, if subject reports stretch discomfort has decreased.
Prone quadriceps stretching	The subject lies on the treatment table in prone. The therapist stabilizes the contralateral limb on the plinth. The knee of the stretching limb is placed in 90° of flexion, then the therapist extends the hip until a stretch discomfort is felt by the subject in the quadriceps. The exercise should be repeated on the other limb.	2 repetitions, each 30 seconds in duration. Performed on both limbs. Range can be increased during 30-second period, if subject reports stretch discomfort has decreased.
Long-sitting knee flexion and extension	The subject is positioned in long-sitting on the treatment table. The therapist instructs the subject to flex the knee as far as possible, by sliding the foot along the treatment table toward the pelvis. The subject holds the flexed position for 3 to 5 seconds. A belt, towel, or a strap may be used by the subject to assist with bending the knee. The therapist then instructs the subject to extend the knee by sliding the foot along the treatment table toward the end of the table. The subject holds the fully extended position for 3 to 5 seconds. The exercise should be repeated on the other limb.	Repetitions are progressed from a minimum of 10 to a maximum of 30 repetitions
Quadriceps setting	The subject is positioned in long-sitting, with the knee extended. Therapist instructs the subject to isometrically contract the quadriceps muscles bilaterally as vigorously as possible, without reproducing pain. The subject is instructed to hold the contraction for 3 to 5 seconds. The exercise should be repeated on the other limb.	Exercise is progressed from 10 contractions to 30 contractions, as tolerated.
Supine straight leg raises	The subject is positioned in supine on the treatment table. The contralateral knee is flexed so that the foot is resting comfortably in a foot-flat position on the table. The therapist instructs the subject to raise the exercise limb with the knee maintained in full extension to the height of the contralateral flexed knee position, then lower the limb back to the table. The exercise should be repeated on the other limb.	Exercise is progressed from 10 to 30 repetitions. When the subject can do 30 repetitions without added weight, a 1-lb (0.45 kg) cuff weight is added. Resistance is progressed by adding 1 lb (0.45 kg), when the subject can do 30 repetitions at the current resistance.
Prone straight leg raises/ hip extensions	The subject is positioned in prone on the treatment table. The therapist instructs the subject to raise the exercise limb, with the knee maintained in full extension, as high as possible, then to lower the limb back to the table. The exercise should be repeated on the other limb.	Exercise is progressed from 10 to 30 repetitions. When the subject can do 30 repetitions without added weight, a 1-lb (0.45 kg) cuff weight is added. Resistance is progressed by adding 1 lb (0.45 kg) when the subject can do 30 repetitions at the current resistance.

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Seated knee extension isometrics	The subject is seated on a leg extension exercise device, with the knee positioned in a comfortable flexed position between 90° and 60° of flexion. The subject is instructed to push against the force pad of the extension device as vigorously as possible, without reproducing pain symptoms. The subject is instructed to hold the contraction for 3 to 5 seconds. The exercise should be repeated on the other limb.	Exercise is progressed from 10 contractions to 30 contractions as soon as possible (by the third treatment visit).
Single-limb seated leg press	The subject is positioned in sitting on a leg press machine, with the exercise limb fixed to the foot platform. The subject is instructed to extend and flex knees in a range of motion from 0° to 45° of flexion against the resistance. The exercise should be repeated on the other limb.	A resistance equivalent to 70% of the 1-repetition maximum should be used for training. The subject attempts to perform 3 sets of 10 repetitions at this resistance. When the subject can perform 3 sets of 10 repetitions, resistance should be advanced 1 plate (4.54 kg). Additional plate is added when 3 sets of 10 repetitions are achieved with current resistance. A new 1-repetition maximum should be established every 2 weeks (every fourth visit). The minimum resistance is then 70% of the newly established 1-repetition maximum.
Standing hamstring curls with cuff weights	A 1-kg cuff weight is wrapped around the subject's ankle. The subject faces a wall or door. Keeping the thigh of the exercise leg even with the thigh from the support leg, the knee of the exercise leg is flexed to 90° then slowly lowered back to the start position. The exercise should be repeated on the other limb	The subject attempts to perform 3 sets of 10 repetitions. When subject can perform all 3 sets at 10 repetitions, another kg of resistance is added.
Standing calf raises	The subject is positioned in standing, with both feet flat on the floor. The subject is instructed to rise up on the toes as high as possible, hold for 1 to 2 seconds, then return to the foot-flat position.	When the subject can perform 30 repetitions with body weight, the exercise is performed on a calf machine, starting with 1 plate of resistance (4.54 kg). The resistance should be advanced 1 plate when the subject can perform 30 repetitions.
Treadmill walking	Subjects walk on a treadmill at a self-selected pace beginning at 1 to 5 minutes duration and progress to 15 minutes as tolerated.	When the subject reaches 15 minutes on the treadmill, the walking speed should be increased as tolerated.

Balance and Agility Activities for the Experimental Group

Activity	Description	Dosage/Progression
Sidestepping	Subjects step sideways, moving right to left then left to right, approximately 3 to 7 m, repeating 2 times in each direction for a total of 4 times.	The width of steps and the speed of steps are progressed every 1 to 2 sessions. The activity is initiated on a level surface and progressed to sidestepping over low obstacles when the subject performs sidestepping on level surfaces without difficulty.
Braiding activities	Subjects combine front and back crossover steps, while moving laterally (walking carioca). During each activity subjects will be moving right to left then left to right, approximately 3 to 7 m, repeating 2 times in each direction for a total of 4 times.	The activity is progressed by increasing the width of steps and the speed of steps every 1 to 2 sessions.

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Front and back cross-over steps during forward ambulation	The subject crosses one leg in front of the other, alternating legs with each step, while walking forward approximately 3 to 7 m. The subject then walks backwards to the start position, while crossing one leg behind the other, alternating legs with each step.	Two repetitions are performed. Begin with tandem crossover steps and progress to full crossover steps when the subject's performance improves. The width of steps and the speed of steps can also be progressed every 1 to 2 sessions.
Shuttle walking	Plastic pylon markers are placed at distances of 1.52 m (5 ft), 3.05 m (10 ft), and 4.57 m (15 ft). The subject walks forward to first marker, then returns to the start by walking backward. Subject then walks to 10-ft marker forward, then returns to 5-ft marker walking backward. The subject then walks to 15-ft marker, returns to 10-ft marker walking backward, then finishes by walking to 15-ft marker.	The activity is progressed by increasing the width of steps and the speed of steps every 1 to 2 sessions.
Multiple changes in direction during walking at the therapist's command	Therapist directs the subject to either walk forward, backward, sideways, or on diagonal by cueing patient with hand signals. Changes in direction are cued randomly by the therapist.	Duration of exercise bout is approximately 30 seconds.
Double-leg foam balance activity	Subject stands on a soft foam surface with both feet on the ground. Therapist attempts to perturb patient balance in random fashion.	The duration of the activity is approximately 30 seconds. The difficulty is progressed as the patient improves, by progressing to ball catching while the therapist provides perturbations to the patient. Progress to single-leg support, if tolerated without knee pain, swelling, buckling.
Tilt board balance training	The subject stands on a tilt board with both feet on the board. The therapist perturbs the tilt board in forward and backward and side-to-side directions for approximately 30 seconds each.	The difficulty of the activity is progressed by adding ball catching during the perturbations, and progressing to single-limb support perturbations if the subject tolerates single-limb weight bearing without knee pain, swelling, buckling.
Roller board and platform perturbations	The subject stands with one limb on a stationary platform, the other limb on a roller board. Therapist perturbs roller board in multiple directions, at random, and the subject attempts to resist the perturbations. The activity lasts approximately 30 seconds. The activity is repeated by changing the limbs on the platform and the roller board.	The activity may begin with subject in the semi-seated position, with hips resting on plinth if the subject has difficulty doing the activity in full standing. The activity is progressed to the full standing position when the subject is able to tolerate this position without pain.

Home Exercise Program

Subjects were encouraged to perform their exercises independently at home, at least 2 times per week, on days when they were not coming to therapy. The program was essentially the same, with some modifications for home. The modifications were as follows:

- For the standard program, wall squats were substituted for the seated leg press. Isometric knee extensions were performed against heavy resistance elastic bands that were secured to a chair.
- For the experimental program, subjects performed all standard home program activities. In addition, they performed all agility training, with the exception of the multiple changes in direction during walking on therapist command activity. They also did not perform tilt board and roller board activities. They performed single-leg standing balance instead.

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