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Strengthening Hip Rotators and Ankle Muscles Versus Knee Extensors on Knee Osteoarthritis: Randomized Controlled Trial with Triple Blindness

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ABSTRACT: Background: One of the leading causes of pain, functional limitations, and impairment in the elderly population is knee osteoarthritis (OA). The impact of strengthening hip rotators in conjunction with ankle muscles on individuals with knee OA has not been well studied. The current study aims to investigate the effect of adding strengthening exercises of hip rotators and ankle muscles to standard knee exercises on pain, function, and knee proprioception in patients with knee OA.

Methods: A triple-blinded, controlled, randomized trial was conducted with 40 patients with knee osteoarthritis, randomly divided into a control and experimental group. The control group underwent strengthening exercises for the knee extensors and stretching exercises for the hamstrings and calf muscles, three times per week for four weeks. The experimental group received the same previous exercises in addition to strengthening exercises for hip rotators and ankle muscles for the same period. Pain intensity during gait, stair climbing, and at night was assessed using a visual analogue scale, and functional disability was assessed using the Arabic version of the Knee Injury and Osteoarthritis Outcome Score questionnaire. Proprioception was assessed using a digital inclinometer by measuring absolute angular error. Finally, isometric muscle strength was measured using a handheld dynamometer for the Knee extensors, hip internal and external rotators, ankle dorsi- and plantar flexors, and ankle evertors and invertors. All measures were taken at baseline and the end of the trial.

Results: within- and between-group comparisons were measured through MANOVA, which revealed a significant reduction in pain intensity during gait ($p=0.004^*$) and significant improvement in knee functional level (pain ($p=0.015^*$), ADL ($p=0.017^*$) and QOL ($p=0.046^*$)) in the experimental group at the end of 4 weeks ($p<0.05$). There was no significant difference in knee proprioception and muscle strength improvement between groups.

Conclusion: Adding hip rotators and ankle muscle strengthening exercises to knee extensor exercises presented a significant improvement in pain intensity, as well as knee functional level, among patients with knee osteoarthritis.

INTRODUCTION

Knee osteoarthritis [OA] is a leading cause of pain, functional limitation and disability in the older population [1]. Its prevalence is estimated to reach 654.1 million patients, with a higher prevalence in females than males [21.7%], [11.9%], respectively. Furthermore, the incidence was approximately 203 per 10,000 persons per year. Knee OA affects health, social and economic sectors in societies [2,3].

Risk factors for OA vary between personal causes, such as age, sex, and race and joint-related causes such as deformities, joint injury and muscle weakness [3]. The weakness of muscles around the knee has been addressed in several studies to investigate its relationship with the progression of the disease, pain intensity, restrictions in daily living activities, and functional disability. These studies revealed weakness of the hip's internal and external rotators, as well as the ankle muscles [4–6]. Lun and his colleagues conducted a study to compare the effect of strengthening hip muscles and leg muscles (quadriceps, hamstring and calf on knee pain, functional level, and quality of life in knee OA patients; significant improvement was noticed in both groups [7].

Also, Neelapala and his colleagues in 2020 investigated the effectiveness of strengthening hip muscles in knee OA patients through a systematic review, and they concluded that significant benefits were gained in terms of knee pain, functional level, and hip muscle strength by applying hip strengthening exercises to the treatment program[8]. Regarding ankle muscle strengthening in knee osteoarthritis patients, a previous article studied the influence of strengthening ankle muscles in the form of heel raises and external ankle rotation in knee OA, improvement in pain, function, and cartilage volume was documented [9]. However, based on our current knowledge, no study has investigated the effect of combining exclusive strengthening for hip rotators and all muscles around the ankle together on pain, function, and proprioception in knee osteoarthritic patients. The purpose of the current study is to investigate the effect of adding strengthening exercises of hip rotators and ankle muscles to knee extensor exercises on pain, function, and knee proprioception in patients with knee OA.

METHODS

The current study is a triple-blind randomized controlled trial [patient, assessor, and statistician]. The study investigated the effect of adding strengthening exercises for hip rotators and ankle muscles to knee extensor exercises on pain, function, and knee proprioception in patients with knee OA. The study was approved by the institutional ethics committee of the Faculty of Physical Therapy, Cairo University [P. T. REC/012/004359] and registered at ClinicalTrials.gov [NCT05855681].

Participants:

Forty patients with knee osteoarthritis [OA] were recruited for this study; however, thirty-three participants completed the study. The experimental group consisted of 19 patients and the control group consisted of 14 patients, as shown below in the flow chart [Figure 1]. They were referred to the Physical Therapy clinic of the Faculty of Physical Therapy, Cairo University, with a confirmed diagnosis of knee OA by an orthopedic surgeon according to the Kellgren/Lawrence grading system for osteoarthritis [Kellgren /Lawrence grade 1, 2 and 3][10]. The inclusion criteria included participants aged between 40 and 55, with BMI between 18.5 and 34.9, and having one or more of the following criteria: morning stiffness for less than 30 min, crepitus during movement, tenderness of the knee joint line, palpable or radiographic enlargement of bone [11,12]. Knee pain intensity was between 30 mm and 80 mm on VAS to reduce the wide range of variability and prevent overestimating baseline pain. Patients were excluded if they had received any physical therapy intervention for the hip, knee, or ankle within the last month, had a knee steroid injection within the previous 3 months, or had a hyaluronic acid intra-articular injection within the previous 6 months [13]. History of knee, ankle or hip surgery in the previous 2 years, severe knee deformity that requires the use of an assistive device, neurological disease in the lower limb, and inflammatory arthritis.

All participants were informed about the aim of the study, the entire tests, procedures, and interventions. They were then asked to sign the informed consent form, indicating their approval to participate in this study. All participants signed the consent to document their agreement to participate in the study. Participants were randomized to either the control or experimental group using a random generator link [<http://www.graphed.com/quickcalcs/randomize/>]. They were allocated by sequential numbering. Participants were blinded to group allocation and exercises for each group. The researcher who enrolled the participant had access to the allocation sequence.

Assessment procedures:

Pain intensity was assessed using the Visual Analogue Scale [VAS], which was classified as the most reliable measurement to assess knee OA pain, with excellent test–retest reliability [ICC = 0.97] and good to excellent validity [$r = 0.941$][14]. VAS represents a horizontal 10 cm line on which the patient was asked to mark their pain intensity in three situations: walking, stair climbing, and at night. The left end of the scale denotes no pain, and the right end represents intolerable pain [15–17].

The functional disability was assessed using the Arabic version of the KOOS questionnaire [Knee Injury and Osteoarthritis Outcome Score Questionnaire]. It has five subscales pain, signs and symptoms, Functional activities of daily living [ADL], Function in sport and recreation [Sport/Rec], and knee-related Quality of life [QOL]. It is a valid and reliable questionnaire for assessing knee OA patients. The Internal consistency [Cronbach's α] for each subscale are [Pain: 0.65–0.94, Symptoms: 0.56–0.83, ADL: 0.78–0.97, Sport/rec: 0.84–0.98, QOL: 0.71–0.85], and the test-retest ICC are [Pain: 0.8–0.97, Symptoms: 0.74–0.94, ADL: 0.84–0.94, Sport/rec: 0.65–0.92, QOL: 0.6–0.91][18]. It exhibits excellent internal consistency in the adapted Arabic version [Cronbach's $\alpha = 0.87$ –0.92], as well as excellent test-retest reliability [ICC_{2,1} = 0.92–0.94] [19].

Knee proprioception, mainly JPS was assessed using a digital inclinometer, which was proven to have excellent validity in obtaining joint position error [AAE: ICC = 0.981, and excellent inter-tester reliability [AAE: ICC = 0.967][20]. Evaluation of proprioception primarily depends on assessing Joint Position Sense [JPS] and finding Absolute angular error [AAE] [21]. The Absolute angular error [AAE] value was calculated by subtracting the reproduced angle from the target angle. Participants were seated with their knees flexed at 90 degrees, as measured by a universal goniometer. Their eyes were closed to eliminate visual input, and the digital inclinometer was secured to the middle third of the leg [15 cm below the head of the fibula] using a strap [20]. Participants actively moved their leg to 30 degrees of knee flexion and maintained the position for 5 Seconds, then moved it again to the starting point. The next step was reproducing this angle again, depending on their inner JPS. This procedure was repeated three times, and the average difference was calculated. The angle of 30° strongly correlated with proprioceptive feedback in normal gait and was assumed to be more accurate and reflect functional measurement [22].

Finally, isometric muscle strength has been measured using a handheld dynamometer, which is a valid [ICC > 0.9] and reliable tool [ICC > 0.75] used in clinical and research situations [23]. The used dynamometer was [Model 01165, Lafayette Instrument Company, Indiana, USA], which is a valid and reliable assessment of muscle strength [$r = 0.9$][24].

Knee extensors, hip internal and external rotators, ankle dorsi and plantar flexors, and ankle evertors and invertors have been assessed in the following manner: for knee extensor participants seated with hip in neutral position without rotation, knee flexed to 60 degrees determined by universal goniometer, then the handheld dynamometer stabilized by the assistant researcher [N.A] 2.5 cm proximal to ankle joint[25,26].

To test internal and external rotators, participants were seated with the knee flexed 90 degrees and hip in neutral rotation and the hand-held dynamometer was placed 2.5 cm above the medial malleolus to assess external rotators, and 2.5 cm above the lateral malleolus to assess internal rotators [23,26]. To assess ankle muscle strength, participants were seated with the knee flexed 90 degrees and the assessor placed the dynamometer on the dorsal surface of the foot to evaluate dorsiflexors, on the plantar surface of the foot to assess plantar flexors, at the base of the 5th metatarsal to assess foot evertors and finally near the head of the 1st Metatarsal to assess foot invertors [23,25,27]. All these tests and procedures were done at baseline and at the end of the interventions after 4 weeks.

Rehabilitation procedures:

Strengthening exercises for all patients in both groups were loaded at 50% of the one-repetition maximum for each patient in the first 2 weeks, and then progressed to 70% of the one-repetition maximum in the last 2 weeks. Also, progress from mild and moderate Thera-band resistance in the first 2 weeks to maximum resistance in the last 2 weeks.

The Control Group received knee extensor exercises [7,28].

Short arch knee extension exercise: patient lies supine with a towel placed below the treated knee to produce 25 degrees of flexion and a sandbag secured above the malleolus level.

The patient was then asked to extend the knee and maintain the contraction for five seconds.

Straight leg raising exercise: patient lies supine, flexing the non-involved knee to support the lower back. The treated knee was extended, with a sandbag secured above the malleolar level. The patient was asked to lift it off the plinth by 25-30 cm and sustain this position for 5 seconds.

Knee extension from sitting against TheraBand: the patient was seated in a chair with a supported back, their knee flexed to 90 degrees. One end of the Thera-band was secured around the malleolus, and the other end was secured around the chair leg. The patient was then asked to slowly extend their knee until it reached complete extension and maintain this position for 5 seconds. All previous exercises were repeated for three sets. Each set consisted of 10 repetitions [7,28].

At the end of each session, patients applied self-stretches for the hamstring and calf muscles under the supervision of the therapist. For each muscle, three repetitions of 30 Seconds Were Performed with 10 seconds of rest in between. For the hamstring stretch, the patient was seated in a long sitting position, maintaining both legs straight, and then bent forward at the waist until they felt a stretch at the back of the thigh and knee. Calf muscle stretching was performed with the patient standing facing a wall, hands on the wall. The stretched leg was moved about a step behind the other leg, with the heel kept on the floor. Then, the front knee was bent until a stretch was felt in the back leg [29]. The experimental group received hip internal and external rotator strengthening exercises, in addition to ankle muscle strengthening exercises, as in the control group, and self-stretching for the hamstring and calf muscles.

Hip rotator strengthening exercises: the patient was seated at the end of the plinth with feet off the ground. One end of the Thera band was attached to the leg of the plinth and the other

end looped around the patient's ankle; the lower leg was kept vertical and the knee at 90 degrees. The patient moved the leg out for internal rotation and inward for external rotation against the elastic resistance; this position was held for 5 seconds, then returned to the starting position [7].

Ankle strengthening exercises: the patient was seated in a long sitting position with one end of the Thera-band on the dorsal surface for dorsiflexion and the plantar surface for plantar flexion. The therapist then stabilized the other end. The patient pulled against the Thera-band for 5 seconds [23]. The patient was seated in a long-sitting position with their feet over the edge of the plinth. The Thera-band was positioned against the lateral border of the foot, distal to the base of the 5th metatarsal, for foot evertors, and against the medial border of the foot, near the base of the 1st metatarsal head, for foot invertors. The patient then pulled against the Thera-band for 5 seconds [27]. All previous exercises consisted of 3 sets, each set consisting of 10 repetitions. Exercises were conducted for 30 to 45 minutes per session, 3 times per week, over 4 weeks, totalling 12 sessions.

Outcome measures: The primary outcomes of this study were pain intensity, functional disability, and proprioception. On the other hand, muscle strength was considered a secondary outcome of this study.

Statistical analysis:

The sample size was calculated using the free software G*Power 3.1.9, estimating the effect size at [Cohen = 0.50], α error probability 0.05, with power [$1 - \beta$ error probability] 80%. The total sample size was 34, and we recruited 40 cases to compensate for potential dropouts. Data analysis was performed using SPSS version 27. The data were screened for normality assumptions using the Shapiro–Wilk test. Since most data were normally distributed, parametric tests were used. Independent t-tests and Chi-square tests were used to compare patients' demographic outcomes between groups. MANOVA tests were used to compare the effects of each prescribed exercise protocol on pain, functional ability, knee proprioception, and hip, knee, and ankle muscle strength. All values were presented and tabulated as mean $\pm$ SD. The level of significance was set at $p < 0.05$ for all analyses.

RESULTS

A total of 62 participants were screened for eligibility criteria; 40 participants [2 male, 38 female] were enrolled and randomized into the trial groups, with 20 subjects per group, as presented in the CONSORT diagram [Figure 1]. Thirty-three patients completed the study. The demographic data for the groups were collected and recorded as illustrated in Table 1. No Significant difference was found in age [$p = 0.113$], weight [$p = 0.829$], Height [$p = 0.381$], and BMI [$p = 0.507$]. A significant difference was noticed in gender [$p < 0.001$], dominant leg [$p = <0.001$], and unilateral/bilateral affection [$p = 0.003$].

Table 1: Demographic data of the study population

Variable		Control group N =14 Mean $\pm$ SD	Experimental group N = 19 Mean $\pm$ SD	t-value	Sig.
Age [years]		47.07 $\pm$ 4.531	47.42 $\pm$ 5.670	-0.190	0.113
Weight [kg]		79.6 $\pm$ 14	83.55 $\pm$ 10.94	-0.908	0.829
Height [cm]		159.29 $\pm$ 13.40	164.89 $\pm$ 6.8	-1.574	0.381
BMI [kg/m ²]		31.026 $\pm$ 2.84	30.655 $\pm$ 3.247	0.342	0.507
Variable		Control group N =14 Count [%]	Experimental group N = 19 Count [%]	Chi-square	
Gender	Male	0	1 [5.3]	29.121	<0.001
	Female	14 [100]	18 [94.7]		
Dominant leg	Rt	11 [78.6]	15 [79]	10.939	<0.001
	Lt	3 [21.4]	4 [21]		
Unilateral/bilateral	Unilateral	2 [14.3]	6 [31.6]	8.758	0.003
	Bilateral	12 [85.7]	13 [68.4]		

Repeated-measures MANOVA was conducted to study the effect of rehabilitation timing on all dependent variables in groups. A significant main effect of time on all dependent variables of pain intensities and functional disabilities was noticed [$p < 0.005$], with no significant main effect of time observed on knee proprioception and muscle strength. A significant interaction effect of group and time was noticed only for hip internal and external rotation strength [$p = 0.040$, $p = 0.027$], respectively, as illustrated in Table 2.

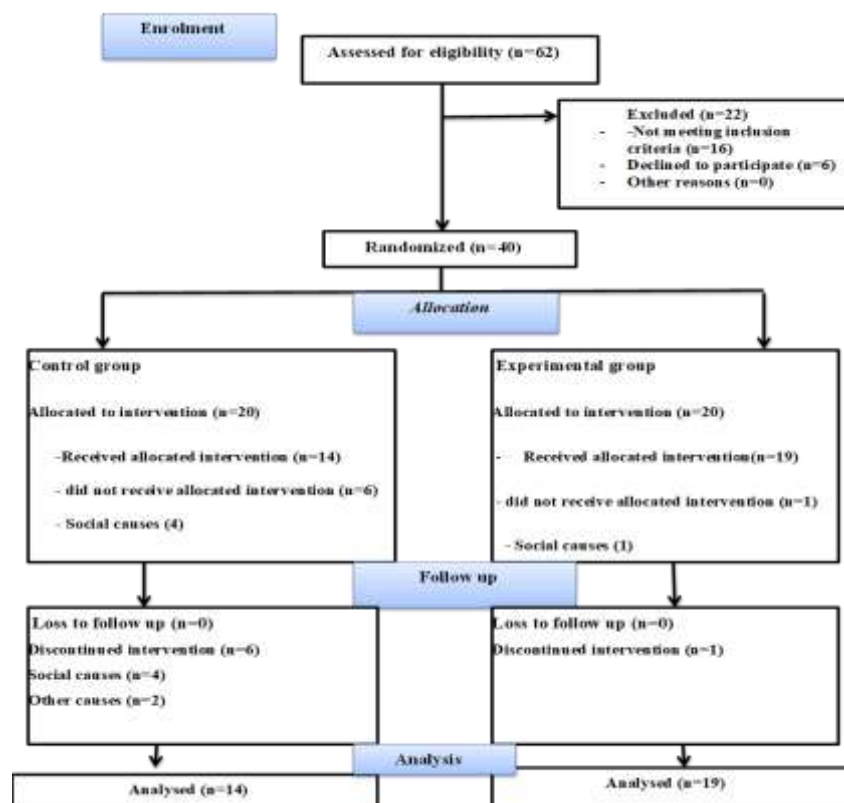


Figure 1. CONSORT flow chart

Table 2: MANOVA test results

Repeated-measures MANOVA		
Effect of Time		
Variable	F-value	p-value
Walking VAS	41.965	<0.001*
Climbing stair VAS	34.357	<0.001*
Night VAS	4.937	0.034*
KOOS signs and symptoms	24.479	<0.001*
KOOS pain	36.646	<0.001*
KOOS ADL	50.800	<0.001*
KOOS Sport	22.068	<0.001*
KOOS QOL	14.228	<0.001*
Joint position sense	.886	0.354
Knee extensor strength	.287	0.596
Hip internal rotator strength	.002	0.963
Hip external rotator strength	.213	0.648
Plantarflexor strength	.006	0.939
Dorsiflexor strength	.331	0.569
Evertors strength	.937	0.341
Invertors strength	1.278	0.267
Time*group		
Variable	F-value	p-value
Walking VAS	.941	0.339
Climbing stair VAS	1.566	0.220
Night VAS	.988	0.328
KOOS signs and symptoms	.222	0.641
KOOS pain	3.761	0.062
KOOS ADL	2.133	0.154
KOOS Sport	1.048	0.314
KOOS QOL	.996	0.326
Joint position sense	.620	0.437
Knee extensor strength	2.002	0.167
Hip internal rotator strength	4.576	0.040*
Hip external rotator strength	5.369	0.027*
Plantarflexor strength	2.747	0.108
Dorsiflexor strength	1.584	0.218
Evertors strength	1.546	0.223
Invertors strength	1.700	0.202

Pain Intensity

A significant reduction in pain intensity during walking and stair climbing in both groups, and at night in the experimental group, was noticed. Furthermore, a significant difference between groups in the post-measure of pain intensity during walking was noticed. On the other hand, no significant differences between groups in the post-measures of pain intensity during stair climbing and at night were noticed. Although both groups experienced improvement in pain, the percentage of change was almost double in the experimental group, as illustrated in Table 3.

Table 3: Mean values, within- and between-group comparison for VAS

		Control Group N = 14	Experimental Group N =19	Between-group comparison		
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	MD	p-value	Sig
Walking VAS	Pre	70.57± 23.36	55.63± 19.03	14.94	0.052	NS
	post	45.43±22.83	21.63±20.53	23.79	0.004*	S
	%of change	35.62	61.11			
	MD	25.14	34			
	p-value	0.002*	<0.001*			
	Sig	S	S			
Stair climbing VAS	Pre	71.71± 27.12	65.21± 18.61	6.50	0.420	NS
	post	51.21±27.71	33.58±27.45	17.63	0.079	NS
	%of change	28.58	48.5			
	MD	20.5	31.63			
	p-value	0.022*	<0.001*			
	Sig	S	S			
Night VAS	Pre	56.71±35.76	49.95±35.46	6.76	0.593	NS
	post	48.71±32.02	29±35.76	19.714	0.112	NS
	%of change	14.1	41.9			
	MD	8	20.95			
	p-value	0.459	0.019*			
	Sig	NS	S			

Knee Functional disability

Table 3: Mean value, within, and between-group comparison for KOOS questionnaire

		Control Group N = 14	Experimental Group N = 19	Between-group comparison		
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	MD	p-value	Sig
KOOS Signs and Symptoms	Pre	41.06± 16.91	47.17± 20.29	-6.108	0.367	NS
	post	58.92± 19.34	68.79± 17.89	-9.86	0.140	NS
	%of change	43.48	45.82			
	MD	-17.85	-21.61			
	p-value	0.010*	<0.001*			
	Sig	S	S			
KOOS Pain	Pre	37.30± 13.89	42.02± 20.95	-4.72	0.470	NS
	post	51.18± 18.22	69.00± 20.56	-17.81	0.015*	S
	% of change	37.23	64.20			
	MD	-13.8879	-26.98			
	p-value	0.010*	<0.001*			
	Sig	S	S			
KOOS ADL	Pre	34.97± 19.07	43.35± 18.99	-8.38	.220	NS
	post	51.25± 17.34	68.02± 19.86	-16.77	0.017*	S
	% of change	46.55	56.91			

	MD	-16.28	-24.67			
	p-value	<0.001*	<0.001*			
	Sig	S	S			
KOOS Sport	Pre	22.85± 20.91	20.52± 21.91	2.33	.760	NS
	post	38.57± 22.56	45± 27.88	-6.42	.484	NS
	% of change	68.75	119			
	MD	-15.7143	-24.4737			
	p-value	.019*	<0.001*			
	Sig	S	S			
KOOS QOL	Pre	27.67± 18.29	34.86± 20.12	-7.18	.300	NS
	post	39.73± 24.46	55.59± 19.42	-15.85	.046*	S
	% of change	43.54	59.43			
	MD	-12.0535	-20.7237			
	p-value	0.082	0.002*			
	Sig	NS	S			

Significant improvement in signs and symptoms, pain, ADL, and sports activities in the Arabic KOOS questionnaire in both groups was noticed; quality of life showed significant improvement in the experimental group. Furthermore, the experimental group showed a significant difference between groups for post-measurements of pain, ADL, and quality of life. On the other hand, no significant differences between groups in the post-measures of signs and symptoms and sports activities were noticed. Although both groups showed an improvement in functional level, the percentage of change was higher in the experimental group, as illustrated in Table 4.

Proprioception [JPS]

There was no significant change observed in proprioception errors within the range [90°-30°] in the control and experimental groups or between groups. The results are presented in Table 5.

Table 4: Mean value, within- and between-group comparison for JPS

		Control Group N = 14	Experimental Group N =19	Between-group comparison		
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	MD [CI 95%]	p-value	Sig
JPS	Pre	5.4464±5.98	5.2768±3.31	0.169	0.918	NS
	post	3.8057±3.04	5.1311±3.53	-1.325	0.268	NS
	% of change	30.12	2.76			
	MD	1.6407	.1457			
	p-value	0.345	0.893			
	Sig	NS	NS			

Muscle strength

A Significant improvement in hip external rotator strength was documented in the experimental group. On the other hand, no significant differences between groups were observed at the post-measures of hip external rotator strength. Although no significant difference was observed within each group or between groups in knee extensor strength, hip internal rotator strength, dorsiflexor strength, plantar flexor strength, evertor strength, and invertor strength, the percentage of improvement was almost double in the experimental group compared to that in the control group, as illustrated in Table 6.

Table 5: Mean value, within- and between-group comparison for muscle strength

		Control Group N = 14	Experimental Group N = 19	Between-group comparison		
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	MD	p-value	Sig
Knee extensor strength	Pre	20.73±10.65	17.42± 7.20	3.31	.295	NS
	post	17.82± 5.51	18.72± 5.68	-.90	.650	NS
	%of change	-14.02	7.517			
	MD	2.9	-1.3			
	p-value	.373	.250			
	Sig	NS	NS			
Hip Internal Rotator strength	Pre	15.02± 6.53	10.63± 3.93	4.93	0.022*	S
	post	12.89± 3.81	12.66± 4.48	.225	.880	NS
	%of change	-14.16	19.17			
	MD	2.12	-2.03			
	p-value	.268	0.054			
	Sig	NS	NS			
Hip External Rotator strength	Pre	12.64± 6.86	9.71± 2.94	2.92	.105	NS
	post	10.33± 2.56	11.25± 3.44	-.91	.407	NS
	%of change	-18.24	15.84			
	MD	2.30	-1.54			
	p-value	.202	0.033*			
	Sig	NS	S			
Plantar flexor strength	Pre	15.22± 8.55	12.24± 3.44	2.79	.177	NS
	post	13.48± 1.83	14.14± 5.17	-.66	.652	NS
	%of change	-11.39	15.55			
	MD	1.73	-1.9			
	p-value	.439	.074			
	Sig	NS	NS			
Dorsi flexor strength	Pre	17.40± 10.04	15.05± 7.98	2.35	.459	NS
	post	15.01± 4.18	15.94± 6.14	-.93	.626	NS
	%of change	-13.76	5.93			
	MD	2.39	-.89			
	p-value	.302	.567			
	Sig	NS	NS			
Evertor strength	Pre	9.07± 3.41	7.35± 2.52	1.71	.106	NS
	post	8.90± 2.26	8.74± 2.87	.15	.867	NS
	%of change	-1.9	18.87			
	MD	.17	-1.38			
	p-value	.843	.130			
	Sig	NS	NS			
Invertor strength	Pre	10.83± 5.97	9.27± 2.81	1.55	.326	NS
	post	8.98± 2.57	9.41± 3.40	-.43	.694	NS
	%of change	-17.11	1.4			
	MD	1.85	-.13			
	p-value	.189	.880			
	Sig	NS	NS			

DISCUSSION

The current study aimed to investigate the impact of combining hip rotator and ankle muscle strengthening exercises with knee extensor strengthening exercises on pain, function, proprioception, and muscle strength in patients with knee osteoarthritis. To the best of our knowledge, there are no previous studies assessing the effect of this combined exercise on the outcomes mentioned above. The results revealed that completion of 4 weeks of hip rotators and ankle muscle strengthening in addition to knee extensor exercise resulted in significant improvement in pain and functional level [KOOS], which makes this exercise an alternative option for patients who can't tolerate excessive exercise load on the knees or who suffer from stability issues, especially since all our exercises were performed in a sitting position.

The reduction in pain intensity in the current study is in line with previous studies' results that examined the effectiveness of adding ankle muscle strengthening exercises [9,13] or hip muscle strengthening on clinical outcomes of patients with knee OA [7,30]. The biomechanical effects of exercises that enhance the general fitness level, as well as psychological and neurophysiological status[31]. Although KOA is considered a peripheral joint lesion, it has a central component that is reflected by hyper-sensitization, which may explain pain in KOA patients[32]. However, exercise induces hypoalgesia, even in small amounts, as evidenced by a single session. Furthermore, pain thresholds in exercising patients were elevated in both exercising and non-exercising body parts, with greater hypoalgesic responses observed near the exercising muscle [33]. In the current study, exercises were performed on all muscles close to the knee [hip, knee, and ankle muscles] in the experimental group, which provided an even larger accumulated effect of hypoalgesic response, resulting in a greater reduction in pain level in this group. As well as the effect of the isotonic resisted exercise in decrease pain, stiffness and improve function must be taken in account[34]. Also, it is important not to eliminate the placebo effect of training. However, regardless the mechanism of action our result support strongly the effect of exercise in modulating pain in KOA patient which is the main goal of any treatment program.

Functional abilities are assessed by the KOOS, which is a self-reported questionnaire. It has five subscales that assess: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. The KOOS contains necessary items of outcome measures and can be used to assess the course of knee disease and treatment outcome in the short to long term [1 week to decades]. The KOOS is reported to be responsive to change in knee OA patients who received physical therapy treatment; large effect sizes are seen at 4 weeks on the pain, symptoms, and ADL subscales, while the sport/recreation and QOL subscales show moderate effects [18]. The current treatment program was practiced for 4 weeks, which had a positive impact on all KOOS subscales within each group, except for QOL in the control group. This may be attributed to the emotional factor related to the QOL subscale [18]. The significant improvement in the experimental group in pain, ADL activities and the QOL subscale over the control group could be explained by the better modulation of pain by the exercise program of the experimental group, which allows a higher degree of pain-free activities and improves the quality of life and activities, achieved by training hip rotators, which are responsible for pelvic stability in the transverse plane, and allow better dynamic alignment of the lower limbs, which in turn decreases knee adduction moment and improves capacity to practice ADL activities [35]. Additionally, strengthening ankle muscles supports the stability of the frontal plane [shank-foot-ground interactions], providing more foot joint mobility and a greater ability to absorb shock during daily activities, which also provides more confidence to meet different life requirements [13].

Proprioception plays a significant role in controlling balance and enhancing functional ability. Proprioception is a combination of the threshold to detect passive movement [kinaesthesia] and joint position sense, which is the ability to determine extremities' positions in space [21]. Several studies imply JPS as a predictor of proprioception in knee osteoarthritis patients [36–39]. Proprioception in KOA patients was deteriorated, which restricted their abilities, decreasing their balance and increasing the risk of falls [40]. Thus, clinical management of proprioception is a must in KOA patients. In the current study, the effect of non-weight-bearing isotonic strengthening exercise on knee JPS was assessed. The results are surprising and present no significant difference in JPS value within groups or between groups. This finding is consistent with the results of a previous study that evaluated the effect of proprioception training exercise versus strengthening exercises on proprioception acuity in KOA patients; the results revealed significant improvement in proprioception [JPS] in the proprioception training group with no difference in the strengthening group[41]. On the other hand, Lai and his colleagues reported that strengthening exercise in weight-bearing form [static squat] provides significant enhancement in knee flexor proprioception but not in knee extensor detection of motion sense[42]. In the current study. We can attribute this finding to the non-weight-bearing mode of assessment

that was used in the current study and previous studies, which did not simulate the usual form of proprioceptive input but allowed the evaluation of JPS without the interface of pain [43,44].

The last outcome of the study was muscle strength. Strengthening exercises are recommended to be an important element in modulating pain and controlling functional disabilities associated with KOA [34,45]. The results revealed an improvement in strength among the experimental group in all muscles that underwent strengthening exercises, as indicated by an increasing percentage of change that did not reach the statistical significance level. This finding is consistent with the result of a previous study, which showed a significant improvement in muscle strength after 5 weeks of isometric resistance exercise for the quadriceps. However, the method of assessing muscle strength used in this study was a manual muscle test [46], which is less objective than a hand-held dynamometer. Additionally, a recent systematic review and meta-analysis conducted by Androulakis and his colleagues found that a period of 8-12 weeks of strengthening exercise is necessary to achieve a significant increase in muscle strength, as measured by one repetition maximum [47]. Also, evidence suggested that the form of strengthening exercise [isometric, eccentric, concentric, or isokinetic] didn't impact program outcomes [45].

To our knowledge, this is the first study to investigate the effect of combined hip rotators, ankle muscles and knee extensors strengthening exercises on pain, function and proprioception in knee OA patients. Many previous studies mention weakness in hip rotators or ankle muscles in KOA patients in cross-sectional or observational studies, but not in an intervention study. The sample size was determined based on a calculation. Finally, triple blinding was applied [patients, assessors and statistician]. However, a few limitations existed. First, the majority of participants were female, affecting the ability to generalize. Second, the experimental and control groups were not matched according to basic demographics; however, between-group comparisons showed no significant differences in all measured variables. Third, due to the type of intervention [physical exercise], it was impossible to blind the researcher who provided the intervention. However, the researcher responsible for assessment and data analysis, as well as the patients, were blinded to the group allocation throughout the study to improve the study's quality.

In conclusion, adding strengthening exercises for hip rotators and ankle muscles to the knee extensor exercise provides a significant improvement in pain during gait and stair climbing, as well as functional abilities, as reflected in the scores of pain, ADL activities, and the quality of life sub-scale of the KOOS questionnaire, among patients with knee osteoarthritis. The finding suggests that hip rotator and ankle muscle strengthening exercises could be effective treatment programs to reduce pain and increase functional levels in osteoarthritic patients. A larger study with more categories for age and severity of knee OA is needed to confirm the efficacy of this exercise combination.

Trial registration: ClinicalTrials.gov [NCT05855681]. It was a prospective registration. <https://register.clinicaltrials.gov/prs/beta/studies/S000D6I500000062/recordSummary>

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the Declaration of Helsinki and approved by the institutional ethics committee of the Faculty of Physical Therapy, Cairo University [P. T. REC/012/004359] and registered at ClinicalTrials.gov [NCT05855681]-4 2023-5.

Human Ethics and Consent to Participate declarations: Not Applicable

Consent to Publish declaration: Not applicable.

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Data sharing: The data that support the findings of this study are available from the corresponding author, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the corresponding author.

LIST OF ABBREVIATIONS

OA: osteoarthritis

BMI: Body Mass Index

VAS: Visual Analogue Scale

KOOS: The knee Injury and Osteoarthritis Outcome Score Questionnaire

QOL: Quality Of Life

ADL: Activities Of Daily Living

AAE: Absolute Angular Error

JPS: Joint Position Sens

AUTHORS' CONTRIBUTIONS

B.S.: Participated in study design, enrolment and randomization of patients, treatment application, and wrote the manuscript. E.F.: Participated in study design and supervision of manuscript. M.M.: Participated in study design, statistical analysis, interpretation of the data and supervision of the manuscript. All authors read and approved the final manuscript.

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