

Original Article

Effect of the Frequency and Duration of Land-based Therapeutic Exercise on Pain Relief for People with Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract. [Purpose] This study aimed to investigate the influence of land-based exercise frequency and duration on pain relief for people with knee osteoarthritis (OA). [Subjects and Methods] The systematic review included randomized controlled trials that investigated this influence, which were identified by searches of PubMed, the Cochrane Central Register of Controlled Trials, the Physiotherapy Evidence Database, and the Cumulative Index to Nursing and Allied Health Literature. The exercise groups in the identified trials were categorized according to their type, frequency, and duration of exercise, and subgroup analyses were performed. [Results] Data integration of 17 studies (23 exercise groups) revealed a significant effect and a medium effect size. In subgroups involving strengthening exercise programs of ≥ 9 weeks duration, heterogeneity was found between subjects who performed up to 3 sessions/week and those who performed ≥ 4 sessions/week. In subgroups involving strengthening exercise programs of up to 3 sessions/week, there was heterogeneity between subjects who exercised for up to 8 weeks and those who exercised for ≥ 9 weeks. Heterogeneity was not confirmed in aerobic exercise subgroups. [Conclusion] Differences in exercise frequency and duration influence pain relief in effects of strengthening exercises but do not influence the effect size of aerobic exercise for people with knee OA.

Key words: Knee osteoarthritis, Exercise, Pain

(This article was submitted Nov. 20, 2013, and was accepted Jan. 8, 2014)

INTRODUCTION

Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder¹⁾ and it is a leading cause of disability, particularly in the elderly^{2, 3)}. It most commonly involves the hip and knee, and is characterized by progressive degeneration of the articular cartilage resulting in loss of joint space, and by marginal and central new bone formation⁴⁾. Pain and functional limitation are the main complaints of people with symptomatic OA^{4, 5)}. As pain affects the quality of life, pain relief should be the focus of OA treatment. Muscle-strengthening and aerobic exercises, classified as land-based therapeutic exercises, have almost similar effects on pain relief⁶⁾. Resistance training in a non-weight-bearing position^{7, 8)} and use of a leg press machine in a weight-bearing position as muscle-strengthening exercises^{9, 10)}, as well as walking^{11, 12)} and *tai chi* as aerobic exercises^{13, 14)} have been found to be effective for pain relief. Several systematic

reviews have also outlined the effectiveness of land-based exercise therapy on pain relief in OA populations^{15–17)}, and have reported the results of meta-analyses of clinical trials supporting the positive effects of exercise for people with knee OA^{6, 18, 19)}. However, the trials in these reviews had widely varying delivery modes, dosages, and types of exercises performed. Moreover, the impact of these factors on the ultimate effect of exercise was not determined. Fransen and McConnell showed a positive relation between the number of sessions directly supervised by a healthcare provider and the effect size; however, they did not control for the influence of exercise type, frequency, and duration on the effect size in their subgroup analysis¹⁸⁾. In fact, the factors influencing the effect of different exercise program elements are unknown. Moreover, the selection criteria for the type, intensity, and duration of exercises beneficial for patients with knee OA remain unclear²⁰⁾. This systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to investigate the influence of exercise frequency and duration on pain relief for people with knee OA.

SUBJECTS AND METHODS

RCTs comparing land-based therapeutic exercises with no intervention or psychoeducational intervention for people with knee OA were included. Jamtvedt et al.²¹⁾, in their

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systematic review, indicated that psychoeducational interventions improve psychological outcomes, but are not associated with a clinically important difference in pain. Trials including interventions with a combination of multiple exercise types, such as muscle-strengthening and aerobic exercises, were excluded from our review, as they would cause conceptual heterogeneity of exercise intervention. No restrictions with respect to publication date or publication status, and frequency, duration, or intensity of exercise were imposed. Observational studies such as cohort studies were excluded. All participants diagnosed with knee OA, except for those scheduled to undergo knee surgery (e.g., total knee arthroplasty), and those who had already undergone knee surgery, were considered. The primary outcome measure was pain.

Studies were identified by a search of the electronic databases of PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), the Physiotherapy Evidence Database (PEDro), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) conducted by the first author (R.T.), who scanned the reference lists of the identified systematic reviews through December 30, 2010.

The following terms were used to search the trial registers and databases: osteoarthritis, knee; exercise; exercise therapy; and pain. The search strategy (Table 1) consisted of a combination of free text words and Medical Subject Headings (MeSH) terms. The publication language was restricted to English.

Study eligibility was determined by two of the authors (R.T. and J.O.) who read the titles and abstracts, and excluded obviously irrelevant trials. The inclusion and exclusion criteria were established a priori. Disagreements between reviewers were resolved by consensus. The two authors (R.T. and J.O.) then read the full-text articles and independently decided whether the retrieved trials met the inclusion criteria. The following data were then extracted from each trial: characteristics of trial participants; contents of exercise intervention and program design elements; and outcome scale. The primary outcome data were entered into Review Manager (RevMan) 5.1 software provided by the Cochrane Collaboration for statistical analysis. The risk of bias was determined using the PEDro scale²².

Since the outcomes consisted of continuous data standardized to the same scale, the standard mean difference (SMD) was used as the effect measure. The SMD values and their corresponding 95% confidence interval (95% CI) values were calculated, and the decision to use either a fixed-effect model²³ or a random-effect model²³ was made after examination of statistical heterogeneity among trials. If a standard deviation (SD) value was not given, it was calculated from the 95% CI or the standard error of the mean (SE) values. Trials that did not give means and SD, 95% CI, or SE values were excluded from the synthesis in our study. Positive values indicated that the control group showed a greater average improvement than the exercise group. An effect size of 0.2–0.5 was interpreted as small, 0.5–0.8 as medium, and >0.8 as large²⁴. Effects were considered significant at $p < 0.05$. Heterogeneity between trials was examined by the χ^2 test and the I^2 test²³. In cases of homogeneity

Table 1. Search strategy

(1) PubMed	#1 Osteoarthritis, knee [MeSH Terms] #2 Exercise [MeSH Terms] #3 Exercise therapy [MeSH Terms] #4 Pain #5 (#1 AND (#2 OR #3) AND #4) Limits: Randomized Controlled Trial
(2) CENTRAL	#1 Osteoarthritis, knee [MeSH Terms] #2 Exercise [MeSH Terms] #3 Exercise therapy [MeSH Terms] #4 Pain #5 (#1 AND (#2 OR #3) AND #4)
(3) PEDro	·Advance search Therapy: Strength training OR Fitness training Body Part: Lower leg or knee Problem: Pain Title or Abstract: Knee Osteoarthritis Method: Clinical trial
(4) CINAHL	#1 Osteoarthritis, knee [MeSH Terms] #2 Exercise+ [MeSH Terms] #3 Therapeutic Exercise+ [MeSH Terms] #4 Pain #5 (#1 AND (#2 OR #3) AND #4) Limits: Randomized Controlled Trial

($I^2 > 25\%$), a fixed-effects model was used, and in cases of heterogeneity, a random-effects model was used.

If heterogeneity between trials was significant, factors including type, frequency, and duration of exercise might influence its efficacy solely or interactively. To elucidate this possibility, the influence of these confounding factors on the efficacy of exercise was controlled. The exercise groups included in the trials were stratified according to type, frequency and duration of exercise, and subgroup analysis was performed. Stratification according to exercise frequency and duration was based on the median value to avoid the deviation of the number of trials in each subgroup. Stratification according to the delivery mode (e.g., individual treatments, exercise classes, or home program) was not performed because the mode of treatment delivery was not significantly associated with the magnitude of treatment benefit¹⁸.

RESULTS

Of the 424 citations identified by the search of the databases, 13 studies remained after adjusting for duplicates and excluding studies that did not meet the inclusion criteria. An additional 4 studies that met the criteria for inclusion were identified by checking the references of past systematic reviews. A total of 17 studies (23 exercise groups) were included in the meta-analysis.

The included studies (Table 2) involved 1,816 participants (890 comparisons and 926 interventions). The exercise groups included in trials were categorized based on the type of exercise into 2 groups: strengthening exercise, and aerobic exercise. Of the 23 exercise groups, 17 exercise groups^{1, 7–10, 25–31} were examined for the effect of strength-

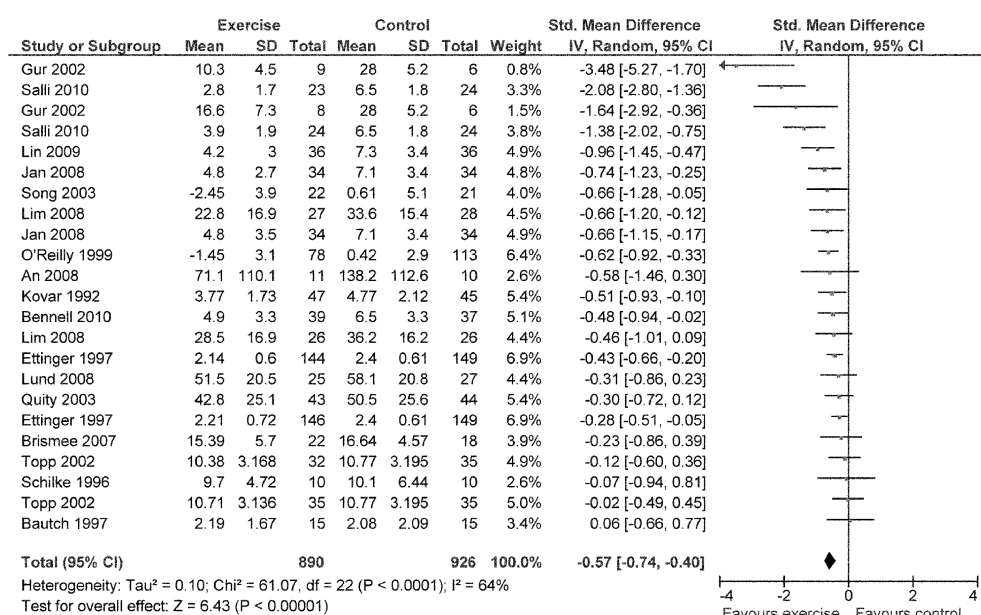


Fig. 1. Forest plots for RCTs on the effect of land-based therapeutic exercise on pain

ening exercise (e.g., resistance-training exercises performed by using Thera-Band[®] elastic bands and exercise with a leg press machine). Six exercise groups^{11–14, 31, 32} were examined for the effect of aerobic exercise (walking, Baduanjin, or *tai chi* exercise). The median number of exercise sessions/week was 3. All included exercise groups were categorized into 2 subgroups according to the median number of weekly sessions: up to 3 sessions^{1, 7–14, 27–29, 31} and more than 4 sessions^{25, 26, 30, 32}. The median exercise duration was 8 weeks. All included exercise groups were categorized into 2 subgroups according to the median duration: up to 8 weeks^{7–11, 13, 27, 29, 32}, and 9 or more weeks^{1, 12, 14, 25, 26, 28, 30, 31}. Measurement scales for pain were the visual analogue scale (VAS)^{1, 8, 10, 12, 25}, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)^{9, 13, 14, 26–28, 30, 32}, the arthritis impact measurement scale (AIMS)¹¹, the osteoarthritis screening index (OASI)²⁹, the numerical rating scale (NRS)⁷, or an original scale³¹. Of 17 studies, 15 studies had a PEDro score of at least 5 (88%). Of the 17 studies, however, 5 studies^{7, 11, 28, 29, 32} (29%) had no concealed allocation, no blind assessors, and no intention-to-treat analysis.

The means of original data, SDs, sample sizes, and the SMD (95% CI) values of each trial are presented in the forest plots of Fig. 1. Of the 23 exercise groups, 22 showed a better effect than the control group. Pooled SMD values of all trials can be seen in the forest plots of Fig. 1. The integrated effect of all trials was significant, and the effect size was medium. There was significant statistical heterogeneity between all the included trials.

All exercise groups included in the trials were stratified according to the type, frequency and duration of exercise, and subgroup analysis was performed. The results for the exercise frequency are shown in Table 3. In subgroups of strengthening exercise of ≥ 9 weeks, heterogeneity was found between subjects who performed up to 3 sessions/

week and those who performed ≥ 4 sessions/week. In subgroups of aerobic exercise as exercise type, heterogeneity between subgroups was not observed.

The results of subgroup analysis according to exercise duration are shown in Table 4. In subgroups of strengthening exercise up to 3 sessions/week, there was heterogeneity between subjects who exercised for up to 8 weeks and those who exercised for ≥ 9 weeks. However, in subgroups of aerobic exercise as the type, heterogeneity between subgroups was not observed.

DISCUSSION

In this study, the influence of frequency and duration of exercise therapy on pain of people with knee OA was investigated. The results of trial data synthesis suggested statistical heterogeneity among trials ($I^2 = 64\%$; Fig. 1). Subgroup analysis was performed after stratification of the exercise groups included in the trials according to exercise type, frequency and duration.

First, the difference in the effect due to the difference in exercise frequency between the subgroups was confirmed. In the category of strengthening exercise and ≥ 9 weeks' exercise duration, the effect of trials involving ≥ 4 sessions/week was larger than that of trials involving up to 3 sessions per week ($I^2 = 84.0\%$; Table 3). However, heterogeneity was not confirmed in the category including the trials of aerobic exercise. These results indicate no consistent influence of exercise frequency on efficacy within each category classified by the type of exercise. In the guidelines^{20, 33, 34}, no recommendation of exercise frequency has been emphasized. In the case of strengthening exercise, however, our findings raise the possibility that exercise frequency influences pain. Strengthening exercise for ≥ 4 sessions/week would be moderately effective for pain relief for people with knee OA even after 9 weeks from the start of exercise.

Table 2. Summary of included studies

Study (Year)	Participants			Exercise intervention			Outcome scale	PEDro score	
	Size	Age (Average)	Sex (% Female)	Contents	Type	Frequency (per a week)			Duration (week)
Gür et al. (2002)	E1: 8	E1: 55	Not reported	E1: Concentric-eccentric exercise	E1: SE	3	8	NRS	5
	E2: 9	E2: 56		E2: Concentric exercise	E2: SE				
	C: 9	C: 57							
Salli et al. (2010)	E1: 25	E1: 55.7	E1: 83%	E1: Combined concentric-eccentric exercise	E1: SE	3	8	VAS	7
	E2: 25	E2: 57.1	E2: 83%	E2: Isometric exercise	E2: SE				
	C: 25	C: 58.3	C: 79%						
Lin et al. (2009)	E: 36	E: 61.6	E: 67%	Strength training in a non-weight-bearing position	SE	3	8	WOMAC	8
	C: 36	C: 62.2	C: 72%						
Jan et al. (2008)	E1: 34	E1: 68.3	E1: 79%	E1: Leg press machine, high-resistance exercise (60% of 1RM)	E1: SE	3	8	WOMAC	7
	E2: 34	E2: 61.8	E2: 79%	E2: Leg press machine, low-resistance exercise (10% of 1 RM)	E2: SE				
	C: 34	C: 62.8	C: 83%						
Lund et al. (2008)	E: 25	E: 68	E: 88%	Strengthening/endurance exercise, balance exercise and stretching exercise	SE	2	8	VAS	8
	C: 27	C: 70	C: 66%						
Schilke et al. (2006)	E: 10	E: 64.5	Not reported	Isokinetic strength testing was performed on a Cybex	SE	3	8	OASI	4
	C: 10	C: 68.4							
Quilty et al. (2003)	E: 43	E: 66.8	Not reported	Patella taping, 7 exercises, posture correction, and footwear advice	SE	9 sessions / 10 week	10	VAS	8
	C: 44	C: 66.7							
Ettinger et al. (1997)	E1: 146	E1: 68	E1: 73%	E1: Leg extension, leg curl, step up, chest fly, upright row, military press, biceps curl, and pelvic tilt	E1: SE	3	72	Original scale	6
	E2: 144	E2: 69	E2: 69%	E2: Walking	E2: AE				
	C: 149	C: 69	C: 69%						
Topp et al. (2002)	E1: 35	E1: 65.6	E1: 71%	E1: Resistance-training exercise performed using Thera-Band elastic bands	E1: SE	3	16	WOMAC	5
	E2: 32	E2: 63.5	E2: 66%	E2: Resistance-training exercise using standard isometric training techniques	E2: SE				
	C: 35	C: 60.9	C: 80%						
Lim et al. (2008)	E1: 26	E1: 67.2	E1: 50%	E1: Quadriceps strengthening exercise (for participants with more varus malalignment)	E1: SE	5	12	WOMAC	8
	E2: 26	E2: 64.1	E2: 63%	E2: Quadriceps strengthening exercise (for participants with more neutral alignment)	E2: SE				
	C1: 27	C1: 66.6	C1: 46%						
	C2: 28	C2: 60.8	C2: 61%						

Next, the influence of different exercise durations on pain relief was examined. For strengthening exercise performed for up to 3 sessions per week, subgroup analysis showed that the trials involving ≥ 9 weeks of exercise had a lesser

effect than those involving up to 8 weeks of exercise ($I^2 = 91.3\%$; Table 4). Furthermore, in the case of aerobic exercise performed for up to 3 sessions/week, the effect size for trials involving 8 weeks of exercise was the same as that of

Table 2. Continue

O'Reilly et al. (1999)	E: 78	E: 61.9	E: 64.8%	1) Isometric quadriceps contraction in full extension held for five seconds, 2) Isotonic quadriceps contraction held in mid flexion for five seconds, 3) Isotonic hamstring contraction, 4) Isotonic quadriceps contraction with resistance band held for five seconds, 5) Dynamic stepping exercise	SE	7	24	WOMAC	7
	C: 113	C: 62.2	C: 68.1%						
Bennell et al. (2010)	E: 45	E: 64.5	E: 48.9%	Resistance-training exercise performed in side-lying and standing with ankle cuff weights or elastic bands	SE	5	12	VAS	8
	C: 44	C: 64.6	C: 54.5%						
Kovar et al. (1992)	E: 52	E: 70.4	E: 77%	Walking and patient education	AE	3	8	AMS	5
	C: 50	C: 68.5	C: 90%						
Brismee et al. (2006)	E: 22	E: 70.8	E: 86.4%	Tai chi training	AE	3	6	WOMAC	5
	C: 19	C: 68.8	C: 78.9%						
Song et al. (2003)	E: 38	E: 64.8	E: 100%	Sun-style tai chi exercise	AE	3	12	K-WOMAC	5
	C: 34	C: 62.5	C: 100%						
Bautch et al. (1997)	E: 17	E,C: 69	Not reported	Walking	AE	3	12	VAS	5
	C: 17								
An et al. (2008)	E: 14	E: 65.4	E: 100%	Baduanjin	AE	5	8	WOMAC	4
	C: 14	C: 64.6	C: 100%						

SE: Strengthening exercise, AE: Aerobic exercise, E: Exercise group, C: Control group. Some studies had multiple exercise or control groups, their groups are shown as E1, E2, C1, or C2 in this Table.

Table 3. The results of subgroup analysis according to exercise frequency

Type of exercise	Exercise duration (weeks)	Exercise frequency (sessions per week)	Number of trials	Effect size [95% CI]	Heterogeneity within subgroup	Heterogeneity between subgroups
					(I^2 value)	(I^2 value)
SE	Up to 8	Up to 3	9	-1.06 [-1.50, -0.61]	74%	Not applicable
		More than 4	0	Not estimable	Not applicable	
	More than 9	Up to 3	4	-0.23 [-0.40, -0.06]	0%	84%
		More than 4	4	-0.58 [-0.78, -0.37]	0%	
AE	Up to 8	Up to 3	2	-0.43 [-0.77, -0.08]	0%	0%
		More than 4	1	-0.58 [-1.46, 0.30]	Not applicable	
	More than 9	Up to 3	3	-0.41 [-0.62, -0.21]	13%	

SE: Strengthening exercise, AE: Aerobic exercise, CI: Confidence interval

trials involving ≥ 9 weeks of exercise. This finding suggests that the effect on pain relief does not increase with time. In a previous systematic review, long-term effectiveness (>6 months after treatment) of exercise therapy for patients with

hip or knee OA was examined⁵). That review showed that positive post-treatment effects (at least 6 months after the end of the treatment) of exercise therapy on pain of patients with hip and/or knee OA are not long-term⁵). However, ad-

Table 4. The results of subgroup analysis according to exercise duration

Type of exercise	Exercise duration (weeks)	Exercise frequency (sessions per week)	Number of trials	Effect size [95% CI]	Heterogeneity within subgroup (I^2 value)	Heterogeneity between subgroups (I^2 value)
SE	Up to 3	Up to 8	9	-1.06 [-1.50, -0.61]	74%	91%
		More than 9	4	-0.23 [-0.40, -0.06]	0%	
	More than 4	Up to 8	0	Not estimable	Not applicable	Not applicable
		More than 9	4	-0.58 [-0.78, -0.37]	0%	
AE	Up to 3	Up to 8	2	-0.43 [-0.77, -0.08]	0%	0%
		More than 9	3	-0.41 [-0.62, -0.21]	13%	
	More than 4	Up to 8	1	-0.58 [-1.46, 0.30]	Not applicable	Not applicable

SE: Strengthening exercise, AE: Aerobic exercise, CI: Confidence interval

ditional booster sessions after the treatment period positively influenced the long-term maintenance of beneficial post-treatment effects on pain. These findings indicate that the efficacy of exercise on pain relief disappears after exercise discontinuation, but continuous exercise might maintain the efficacy. Our results are in agreement with these findings. More specifically, in the case of aerobic exercise, the small effect of exercise on pain relief might be significant and stable even after 9 weeks from the start of exercise. However, in the case of strengthening exercise, the effect size of pain relief decreases in spite of continuous exercise. These new findings in the field of exercise science will prove useful in clinical practice.

The major strength of our study is its design, which controls for the influence of confounding factors on the efficacy of exercise. There are several systematic reviews which have conducted meta-analyses of exercise for knee OA^{6, 19, 35}, which support the effect of exercise on pain relief. However, the influence of confounding factors on efficacy was not controlled in the meta-analyses of these reviews. In our study, all exercise groups included in the trials were stratified into subgroups, categorized according to the type, frequency and duration of exercise, and the effect size between the subgroups was compared. As a result, it was possible for us to show an indirect causal relationship between exercise frequency and duration, and the effect of exercise therapy on pain relief.

Our study, however, had several limitations. The first limitation of our study was the dissimilar protocol designs employed in the trials. The exercise intensity, session duration, and the number of sets in all trials were not always in the same. Although SMD was used as the summary measure, high statistical heterogeneity was observed within particular subgroups in trials of strengthening exercise ($I^2 = 74%$; Tables 3 and 4); the reason for this could not be determined. Meta-analyses in the future should be performed for RCTs with similar exercise protocols to decrease the variance of the effect at the study level. A second limitation of

our study was the risk of bias. All articles included in our study were in English and as language bias involving the investigation of the effect of exercise on people with knee OA has not been reported thus far, the degree to which language bias affected the results of our study is not known. The influence of bias risk estimates at the study level on the results of meta-analysis has been reported¹⁸. Some of the trials included in our meta-analysis had a high risk of bias^{7, 11, 28, 29, 32}. Therefore, the risk of bias at the study level might not have been excluded from our study. Furthermore, publication bias could not be tested. Thus, our present findings might not be high-quality evidence. The third limitation of our study was the availability and inclusion of only a limited number of trials in the meta-analysis. As a result of this subgroup analysis could not be performed for some of the categories. Future research should involve a higher number of trials to confirm the consistency of our present findings.

Our results showed that differences in frequency and duration of strengthening exercise possibly ameliorate pain of patients with knee OA. Although the effect size did not increase over time, continuous strengthening exercise or aerobic exercise intervention had a significant effect on knee pain of people with knee OA after 9 weeks. Our findings in this review may be biased and should be interpreted with caution. Future studies involving meta-analysis to examine the effect of exercise on pain of people with knee OA should consider the influence of the design elements of exercise programs such as exercise frequency and duration, and publication bias.

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