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Original Article

Long-Term Effects of High-Volume Resistance Training Combined with Pain Neuroscience Education on Pain, Physical Function, Muscle Strength, Pain Modulation, and Quality of Life in Individuals with Knee Osteoarthritis: A Randomized Controlled Trial

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ABSTRACT

Background: The optimal resistance-training volume and additional value of Pain Neuroscience Education in knee osteoarthritis rehabilitation remain uncertain. Objective: To compare high-volume resistance training combined with Pain Neuroscience Education, moderate-volume resistance training, and standard physiotherapy for symptomatic knee osteoarthritis. Methods: This multicentre, assessor-blinded, three-arm randomized controlled trial included 210 participants allocated equally among the three programmes. Supervised treatment was delivered three times weekly for 12 weeks. Pain, WOMAC, quadriceps strength, functional performance, psychosocial outcomes, pain modulation, biomarkers, and health-related quality of life were assessed at the specified intervention and follow-up time points. Longitudinal outcomes were analysed using linear mixed-effects models under the intention-to-treat principle. Results: At 12 months, NPRS scores were 2.1 ± 0.8, 3.8 ± 1.0, and 5.2 ± 1.3 in the combined, moderate-volume, and standard-physiotherapy groups, respectively ((F=28.64), ($p<0.001$)). Corresponding WOMAC scores were 26.2 ± 6.1, 39.6 ± 7.4, and 49.8 ± 8.5 ((F=31.27), ($p<0.001$)), while quadriceps strength was 26.9 ± 4.6, 23.8 ± 4.4, and 20.5 ± 4.1 kg ((F=24.83), ($p<0.001$)). Week 12 functional, psychosocial, pain-modulation, biomarker, and SF-36 findings also favoured the combined programme. Conclusion: HVRT + PNE was associated with greater and more sustained improvement in pain, WOMAC, and quadriceps strength, although its individual treatment components could not be separated. Keywords: Knee osteoarthritis; resistance training; Pain Neuroscience Education; physical function; pain modulation; randomized controlled trial.

INTRODUCTION

Knee osteoarthritis is a prevalent musculoskeletal disorder and a major cause of persistent pain, reduced mobility, and disability among middle-aged and older adults. Its clinical manifestations arise from interacting structural, inflammatory, neurological, and biomechanical processes, including articular cartilage deterioration, subchondral bone changes, synovial inflammation, muscle weakness, and altered joint loading (1,2). These impairments can restrict activities of daily living, reduce social and occupational participation, increase healthcare use, and adversely affect health-related quality of life.

The burden of knee osteoarthritis is expected to increase further with population ageing, obesity, physical inactivity, and the growing prevalence of chronic noncommunicable conditions.

International clinical practice guidelines recommend exercise as a core component of non-surgical knee osteoarthritis management (3,4). Exercise therapy can reduce pain and improve physical function, mobility, strength, and quality of life, although its effects vary according to participant characteristics, intervention design, treatment adherence, and exercise dose (5). Progressive resistance training is particularly relevant because quadriceps weakness is commonly associated with impaired knee stability, activity limitation, and reduced functional capacity. Strengthening the quadriceps and other lower-limb muscle groups may improve force production, movement control, walking performance, and independence in daily activities (5,6).

Resistance exercise may also affect pain through mechanisms extending beyond muscle strengthening. Exercise-induced hypoalgesia refers to a temporary reduction in pain sensitivity following physical activity and is thought to involve peripheral and central pain-regulatory pathways (7). However, individuals with chronic musculoskeletal pain may demonstrate altered endogenous pain inhibition or enhanced pain facilitation, which can influence their response to exercise (7,8). In knee osteoarthritis, pressure pain thresholds, conditioned pain modulation, and temporal summation may therefore provide useful complementary information about changes in pain processing. Nevertheless, the long-term effects of repeated resistance training on these measures remain insufficiently established.

The optimal volume of resistance training for knee osteoarthritis is also uncertain. Exercise volume generally reflects the number of sets and repetitions performed, whereas the total training stimulus is additionally influenced by exercise intensity, frequency, progression, rest intervals, and adherence. Resistance training performed at different volumes can improve pain and physical function, but available studies have not consistently demonstrated whether higher-volume programmes produce superior clinical outcomes (6). Increasing training volume may provide a greater stimulus for neuromuscular adaptation and exercise-induced hypoalgesia, but it may also increase fatigue, muscle soreness, transient symptom aggravation, and difficulty maintaining adherence. Exercise volume must therefore be evaluated in relation to both potential benefit and treatment tolerability.

Psychological and behavioural factors may further modify rehabilitation outcomes. Pain catastrophizing, fear of movement, anxiety, and low pain self-efficacy can contribute to activity avoidance, reduced exercise participation, and persistent disability. Pain Neuroscience Education is intended to improve patients' understanding of pain, address maladaptive beliefs, reduce the perceived threat associated with movement, and encourage active self-management (9,10). Evidence suggests that Pain Neuroscience Education may improve pain-related knowledge and psychological outcomes when incorporated into exercise-based rehabilitation, although its additional clinical benefit and the durability of its effects remain variable across populations and intervention designs (9–11).

Recent investigations have examined how exercise mode, training volume, and pain education influence exercise-induced hypoalgesia in individuals with knee osteoarthritis. A feasibility trial evaluating exercise modalities and additional pain education demonstrated the clinical relevance of investigating education alongside exercise-induced hypoalgesia (12). Sánchez-Sabater et al. subsequently reported that higher-volume resistance exercise produced a greater acute hypoalgesic response than a lower-volume protocol in individuals with severe knee osteoarthritis awaiting total knee arthroplasty (13). However, the latter study examined the immediate response to a single exercise session and did not establish whether repeated high-volume training produces sustained improvements in pain, disability, strength, psychosocial health, pain modulation, biomarkers, or quality of life. Its findings also cannot be assumed to apply to broader clinical populations or longer-term functional strengthening programmes.

Although education and structured exercise are established components of contemporary knee osteoarthritis care (14), evidence remains limited regarding the sustained effects of a comprehensive

programme combining progressive high-volume resistance training with Pain Neuroscience Education. In particular, few studies have simultaneously evaluated clinical symptoms, muscle strength, functional performance, psychosocial factors, experimental pain-modulation measures, inflammatory biomarkers, physical activity, and health-related quality of life over an extended follow-up period. Long-term assessment is important because the safety and sustainability of exercise-related benefits cannot be inferred solely from immediate post-treatment responses (15).

The present multicentre, assessor-blinded, three-arm randomized controlled trial therefore compared high-volume progressive resistance training combined with Pain Neuroscience Education, moderate-volume progressive resistance training, and standard physiotherapy in individuals with symptomatic knee osteoarthritis. The primary objective was to compare changes in pain intensity and physical function among the three rehabilitation programmes. The secondary objectives were to evaluate changes in quadriceps strength, functional performance, psychosocial outcomes, pain modulation, inflammatory and neuroplasticity biomarkers, physical activity, and health-related quality of life. It was hypothesized that participants allocated to the combined high-volume resistance-training and Pain Neuroscience Education programme would demonstrate greater improvements in pain and physical function than participants receiving moderate-volume resistance training or standard physiotherapy.

MATERIALS AND METHODS

This multicentre, assessor-blinded, three-arm, parallel-group randomized controlled trial compared three rehabilitation programmes for individuals with symptomatic knee osteoarthritis. The study was conducted in the outpatient physiotherapy departments of Lady Reading Hospital, Khyber Teaching Hospital, and Paraplegic Centre Peshawar in Khyber Pakhtunkhwa, Pakistan. Intervention sessions and outcome assessments were undertaken within the physiotherapy departments of the participating centres by licensed physiotherapists with at least five years of clinical experience in musculoskeletal rehabilitation.

Potential participants were recruited through referrals from orthopaedic surgeons and outpatient clinics and through community advertisements. Eligibility was assessed using the American College of Rheumatology clinical criteria for knee osteoarthritis (3). Individuals were eligible if they were 50–80 years of age; had unilateral or bilateral symptomatic knee osteoarthritis with Kellgren–Lawrence Grade II, III, or IV radiographic changes; had experienced knee pain for at least six months; reported an average pain intensity of at least 4 on an 11-point Numeric Pain Rating Scale; could walk independently with or without an assistive device; and had received medical clearance to participate in progressive resistance exercise. Individuals were excluded if they had undergone knee replacement surgery; had received an intra-articular corticosteroid or hyaluronic acid injection during the preceding three months; had inflammatory arthritis, a neurological disorder affecting lower-limb function, uncontrolled cardiovascular disease, severe cognitive impairment, or a recent lower-extremity fracture or operation; or were already participating in a structured resistance-training programme.

The sample size was estimated in G*Power version 3.1 for a repeated-measures comparison involving three intervention groups and five assessment occasions. The calculation used an effect size of (f=0.30), a two-sided alpha level of 0.05, 90% statistical power, and an assumed correlation of 0.50 among repeated measurements. The minimum estimated sample was 180 participants. The recruitment target was increased to 210 participants to allow for potential attrition, resulting in a planned allocation of 70 participants to each group.

After completion of the baseline assessment, participants were randomly assigned in a 1:1:1 ratio to high-volume resistance training combined with Pain Neuroscience Education, moderate-volume resistance training, or standard physiotherapy. An independent researcher who was not involved in recruitment, treatment delivery, or outcome assessment generated the computer-based allocation sequence using variable block sizes. Group assignments were placed in sequentially numbered, opaque, sealed envelopes

that were opened only after the corresponding participant had completed the baseline assessment. Because of the nature of the rehabilitation programmes, participants and treating physiotherapists could not be blinded. Outcome assessments were conducted by an experienced physiotherapist who remained unaware of group allocation, and the statistical analysis was undertaken by an independent biostatistician blinded to the assigned interventions.

Participants in all three groups attended three supervised physiotherapy sessions per week for 12 consecutive weeks. The programmes differed in resistance-training volume, exercise intensity, session duration, educational content, and accompanying physiotherapy components and were therefore treated analytically as three distinct multimodal rehabilitation programmes. The high-volume resistance-training and Pain Neuroscience Education programme lasted approximately 75–90 minutes per session. Each session included a 10-minute warm-up consisting of cycling and dynamic stretching, followed by progressive strengthening of the quadriceps, hamstrings, gluteal muscles, and calf muscles. Participants performed four or five sets of 10–15 repetitions of each exercise at approximately 60%–80% of their one-repetition maximum, with 60–90 seconds of rest between sets. Resistance was progressively increased according to pain tolerance, perceived exertion, and the participant's ability to complete the prescribed repetitions. The programme also incorporated progressive balance activities, step-ups, sit-to-stand practice, gait retraining, functional strengthening, and flexibility exercises for the quadriceps, hamstrings, calf muscles, and hip flexors.

Participants allocated to the combined programme additionally received one 30-minute Pain Neuroscience Education session each week. The educational content addressed pain neurophysiology, central pain sensitization, fear avoidance, activity pacing, self-management, exercise adherence, and the relationship between pain and movement. Participants were encouraged to apply these concepts during supervised exercise and daily activities. They were also prescribed daily home-based strengthening and flexibility exercises and maintained exercise diaries that were reviewed weekly by the treating physiotherapists.

The moderate-volume resistance-training programme lasted approximately 60–75 minutes per session and used the same principal muscle-group exercises as the high-volume programme. Participants performed two or three sets of 10–12 repetitions at approximately 60%–70% of their one-repetition maximum, with 60–90 seconds of rest between sets. Resistance was progressed weekly using moderate increments according to exercise performance and tolerance. The programme included the same flexibility exercises and similar balance and functional activities, although these were delivered with less progression. Participants did not receive Pain Neuroscience Education but completed a daily home-exercise programme.

Standard physiotherapy sessions lasted approximately 45–60 minutes. Treatment consisted of a 10-minute warm-up involving gentle range-of-motion and stretching exercises, low- to moderate-intensity strengthening performed as two sets of 10 repetitions according to clinical tolerance, basic balance and gait exercises, and flexibility exercises for the principal lower-limb muscle groups. Soft-tissue mobilization and patellofemoral or tibiofemoral joint mobilization were provided when clinically indicated. Participants also received general advice concerning knee osteoarthritis and a standard home-exercise programme. Treatment progression was determined according to the participant's clinical tolerance and the treating physiotherapist's assessment.

Outcomes were assessed at baseline, during the intervention at Week 6, immediately after the 12-week intervention, and at 6- and 12-month follow-up. The primary outcomes were pain intensity and physical function. Pain intensity was measured using the 11-point Numeric Pain Rating Scale, with higher scores representing more severe pain. Physical function was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index, which measures knee osteoarthritis-related pain, stiffness, and functional limitation.

Secondary outcomes included quadriceps strength, functional performance, psychosocial characteristics, pain modulation, inflammatory and neuroplasticity biomarkers, physical activity, and health-related quality of life. Quadriceps strength was measured using a calibrated handheld dynamometer. Functional performance was evaluated using the 30-Second Chair Stand Test, Timed Up and Go Test, Six-Minute Walk Test, Stair Climb Test, and 40-Meter Fast-Paced Walk Test. Health-related quality of life was assessed using the 36-Item Short Form Health Survey. Pain catastrophizing, fear of movement, pain self-efficacy, anxiety, and depressive symptoms were evaluated using the Pain Catastrophizing Scale, Tampa Scale for Kinesiophobia, Pain Self-Efficacy Questionnaire, and Hospital Anxiety and Depression Scale.

Pressure pain threshold was measured over the affected knee and the contralateral tibialis anterior using a digital pressure algometer. Conditioned pain modulation and temporal summation procedures were used to evaluate endogenous pain inhibition and pain facilitation. In participants with bilateral knee osteoarthritis, the more symptomatic knee was treated as the index knee for knee-specific outcome assessment. Fasting venous blood samples were collected at baseline and Week 12 for analysis of C-reactive protein, interleukin-6, tumour necrosis factor-alpha, brain-derived neurotrophic factor, and serum cortisol. Physical activity was monitored using an ActiGraph accelerometer worn for seven consecutive days at baseline, Week 12, and the 6-month follow-up.

Attendance was recorded for every supervised treatment session, and home-exercise diaries were reviewed weekly. Satisfactory adherence was defined as completion of at least 80% of the prescribed supervised sessions. Adverse events, including increased knee pain, muscle soreness, falls, joint swelling, and other unexpected complications, were recorded throughout the intervention. Participants who experienced severe symptom exacerbation were reassessed by the study physician before resuming treatment.

Data were analysed using IBM SPSS Statistics version 27.0. The distribution of continuous variables was examined using the Shapiro–Wilk test and visual inspection of quantile–quantile plots. Continuous variables were summarized as mean and standard deviation or median and interquartile range, according to their distribution, whereas categorical variables were summarized as frequency and percentage. Baseline characteristics were described by randomized group without using baseline significance testing to determine the success of randomization.

The primary analysis followed the intention-to-treat principle. Missing outcome data were addressed using multiple imputation. Longitudinal changes were examined using linear mixed-effects models containing treatment group, assessment time, and the group-by-time interaction as fixed effects and participant as a random effect. The models estimated whether outcome trajectories differed among the three randomized groups across the assessment period. Where an overall interaction or group effect was identified, Bonferroni-adjusted pairwise comparisons were used to examine differences between intervention groups. Effect sizes were expressed as Cohen's (d) for within-group and between-group comparisons and partial eta squared for interaction effects.

Multiple linear regression was planned to examine whether age, sex, body mass index, Kellgren–Lawrence grade, baseline pain intensity, pain catastrophizing, and baseline quadriceps strength predicted treatment response. Mediation analysis was planned to evaluate whether changes in psychosocial outcomes were associated with improvements in pain and physical function. All statistical tests were two-sided, and statistical significance was established at ($p<0.05$).

RESULTS

A total of 258 individuals were assessed for eligibility, of whom 210 met the eligibility criteria and were randomized in a 1:1:1 ratio to high-volume resistance training combined with Pain Neuroscience Education, moderate-volume resistance training, or standard physiotherapy, with 70 participants

assigned to each group. The randomized groups had similar baseline demographic and clinical profiles. Mean age ranged from 63.7 to 64.4 years, women comprised 58.6%–61.4% of each group, and mean body mass index ranged from 29.0 to 29.5 kg/m². Grade III knee osteoarthritis was the most frequent radiographic category, accounting for 47.1%–50.0% of each group. Baseline NPRS, WOMAC, quadriceps strength, PCS, TSK, and PSEQ values were also comparable across the three groups (Table 2).

Pain intensity decreased in all groups, with the greatest reduction observed in the HVRT + PNE group (Table 3). At Week 12, mean NPRS scores had decreased by 3.8 points in the HVRT + PNE group, 2.8 points in the MVRT group, and 1.8 points in the standard physiotherapy group. The corresponding Week 12 mean score was 1.2 points lower with HVRT + PNE than with MVRT and 2.1 points lower than with standard physiotherapy. At 12 months, reductions from baseline were 4.6, 3.1, and 1.6 points, respectively. The 12-month NPRS score was 1.7 points lower in the HVRT + PNE group than in the MVRT group and 3.1 points lower than in the standard physiotherapy group. The reported group-by-time interaction was statistically significant ((F=28.64), (p<0.001)).

WOMAC total scores decreased progressively during treatment and follow-up, with the largest reductions in the HVRT + PNE group (Table 4). From baseline to Week 12, WOMAC scores decreased by 28.8 points with HVRT + PNE, 18.1 points with MVRT, and 9.4 points with standard physiotherapy. At Week 12, the mean WOMAC score was 11.2 points lower in the HVRT + PNE group than in the MVRT group and 19.0 points lower than in the standard physiotherapy group. At 12 months, the reductions from baseline were 32.7, 19.8, and 8.7 points, respectively. The corresponding between-group differences favoured HVRT + PNE by 13.4 points compared with MVRT and by 23.6 points compared with standard physiotherapy. The reported group-by-time interaction was statistically significant ((F=31.27), (p<0.001)).

Table 1. Baseline Demographic and Clinical Characteristics of the Randomized Participants

Characteristic	HVRT + PNE (n = 70)	MVRT (n = 70)	Standard Physiotherapy (n = 70)
Age, years	64.4 ± 6.5	63.7 ± 7.2	64.1 ± 6.9
Female, n (%)	43 (61.4)	41 (58.6)	42 (60.0)
Body mass index, kg/m²	29.3 ± 3.6	29.0 ± 3.9	29.5 ± 3.4
Symptom duration, years	6.5 ± 2.3	6.0 ± 2.7	6.3 ± 2.5
Bilateral osteoarthritis, n (%)	45 (64.3)	46 (65.7)	44 (62.9)
Kellgren–Lawrence Grade II, n (%)	21 (30.0)	20 (28.6)	19 (27.1)
Kellgren–Lawrence Grade III, n (%)	33 (47.1)	34 (48.6)	35 (50.0)
Kellgren–Lawrence Grade IV, n (%)	16 (22.9)	16 (22.9)	16 (22.9)
NPRS score	6.7 ± 1.1	6.9 ± 1.0	6.8 ± 1.2
WOMAC total score	58.9 ± 8.3	59.4 ± 8.6	58.5 ± 8.1
Quadriceps strength, kg	18.7 ± 4.1	18.2 ± 4.3	18.5 ± 4.0
PCS score	27.2 ± 5.9	27.9 ± 6.0	27.6 ± 5.7
TSK score	39.5 ± 5.4	40.1 ± 5.3	39.8 ± 5.1
PSEQ score	31.8 ± 5.8	31.1 ± 6.2	31.5 ± 6.0

Values are mean ± standard deviation unless otherwise indicated. HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training; NPRS: Numeric Pain Rating Scale; PCS: Pain Catastrophizing Scale; PSEQ: Pain Self-Efficacy Questionnaire; TSK: Tampa Scale for Kinesiophobia; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 2. Pain Intensity Across the Assessment Period

Group	Baseline	Week 6	Week 12	6 Months	12 Months	Change at Week 12	Change at 12 Months
HVRT + PNE	6.7 ± 1.1	4.6 ± 1.1	2.9 ± 0.8	2.3 ± 0.9	2.1 ± 0.8	−3.8	−4.6
MVRT	6.9 ± 1.0	5.3 ± 1.0	4.1 ± 0.9	3.7 ± 0.9	3.8 ± 1.0	−2.8	−3.1
Standard physiotherapy	6.8 ± 1.2	5.8 ± 1.2	5.0 ± 1.1	4.9 ± 1.2	5.2 ± 1.3	−1.8	−1.6

Between-group contrast	Week 12 mean difference	12-month mean difference
HVRT + PNE versus MVRT	−1.2	−1.7
HVRT + PNE versus standard physiotherapy	−2.1	−3.1
MVRT versus standard physiotherapy	−0.9	−1.4

Values at each assessment are mean ± standard deviation. Change was calculated as follow-up minus baseline; negative values indicate reduced pain. The reported group-by-time interaction was (F=28.64), (p<0.001). HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training.

Table 3. WOMAC Total Score Across the Assessment Period

Group	Baseline	Week 6	Week 12	6 Months	12 Months	Change at Week 12	Change at 12 Months
HVRT + PNE	58.9 ± 8.3	44.5 ± 7.4	30.1 ± 6.7	27.4 ± 6.3	26.2 ± 6.1	−28.8	−32.7
MVRT	59.4 ± 8.6	49.2 ± 7.8	41.3 ± 7.3	38.9 ± 7.1	39.6 ± 7.4	−18.1	−19.8
Standard physiotherapy	58.5 ± 8.1	53.0 ± 8.3	49.1 ± 7.9	48.5 ± 8.2	49.8 ± 8.5	−9.4	−8.7

Between-group contrast	Week 12 mean difference	12-month mean difference
HVRT + PNE versus MVRT	−11.2	−13.4
HVRT + PNE versus standard physiotherapy	−19.0	−23.6
MVRT versus standard physiotherapy	−7.8	−10.2

Values at each assessment are mean ± standard deviation. Change was calculated as follow-up minus baseline; negative values indicate improvement. The reported group-by-time interaction was (F=31.27), (p<0.001). HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Table 4. Quadriceps Strength Across the Assessment Period

Group	Baseline	Week 6	Week 12	6 Months	12 Months	Change at Week 12	Change at 12 Months
HVRT + PNE	18.7 ± 4.1	22.3 ± 4.4	26.4 ± 4.7	27.2 ± 4.5	26.9 ± 4.6	7.7	8.2
MVRT	18.2 ± 4.3	20.6 ± 4.2	23.4 ± 4.4	24.1 ± 4.3	23.8 ± 4.4	5.2	5.6
Standard physiotherapy	18.5 ± 4.0	19.3 ± 4.1	20.7 ± 4.2	20.9 ± 4.0	20.5 ± 4.1	2.2	2.0

Between-group contrast	Week 12 mean difference, kg	12-month mean difference, kg
HVRT + PNE versus MVRT	3.0	3.1
HVRT + PNE versus standard physiotherapy	5.7	6.4
MVRT versus standard physiotherapy	2.7	3.3

Values at each assessment are mean ± standard deviation in kilograms. Change was calculated as follow-up minus baseline; positive values indicate increased strength. The reported group-by-time interaction was (F=24.83), (p<0.001). HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training.

Table 5. Functional Performance at Week 12

Outcome	HVRT + PNE	MVRT	Standard Physiotherapy	HVRT + PNE versus MVRT	HVRT + PNE versus Standard Physiotherapy	p-value
Timed Up and Go Test, seconds	8.4 ± 1.1	9.7 ± 1.2	11.0 ± 1.4	−1.3	−2.6	<0.001
30-Second Chair Stand Test, repetitions	17.3 ± 2.5	15.1 ± 2.4	13.6 ± 2.2	2.2	3.7	<0.001
Six-Minute Walk Test, m	491 ± 48	451 ± 46	417 ± 44	40	74	<0.001
Stair Climb Test, seconds	9.1 ± 1.2	10.4 ± 1.3	11.9 ± 1.5	−1.3	−2.8	<0.001

Values are mean ± standard deviation or unadjusted mean difference. The p-values represent the reported overall between-group comparisons. HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training.

Table 6. Psychosocial Outcomes Across the Reported Assessment Period

Outcome	Group	Baseline	Week 12	12 Months	Change at Week 12	Change at 12 Months
PCS	HVRT + PNE	27.2 ± 5.9	13.8 ± 4.6	12.4 ± 4.3	−13.4	−14.8
	MVRT	27.9 ± 6.0	19.6 ± 5.1	18.8 ± 4.9	−8.3	−9.1
	Standard physiotherapy	27.6 ± 5.7	24.5 ± 5.6	24.0 ± 5.4	−3.1	−3.6
TSK	HVRT + PNE	39.5 ± 5.4	26.8 ± 4.8	25.3 ± 4.7	−12.7	−14.2
	MVRT	40.1 ± 5.3	31.9 ± 5.1	31.2 ± 4.9	−8.2	−8.9
	Standard physiotherapy	39.8 ± 5.1	36.7 ± 5.4	36.3 ± 5.2	−3.1	−3.5
PSEQ	HVRT + PNE	31.8 ± 5.8	46.9 ± 6.2	48.2 ± 6.0	15.1	16.4

Values at each assessment are mean ± standard deviation. Change was calculated as follow-up minus baseline. Lower PCS and TSK scores and higher PSEQ scores indicate improvement. The manuscript reported group-by-time differences of (p<0.001) for the psychosocial outcomes. HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training; PCS: Pain Catastrophizing Scale; PSEQ: Pain Self-Efficacy Questionnaire; TSK: Tampa Scale for Kinesiophobia.

Table 7. Pain-Modulation Outcomes at Week 12

Outcome	HVRT + PNE	MVRT	Standard Physiotherapy	HVRT + PNE versus MVRT	HVRT + PNE versus Standard Physiotherapy	p-value
Pressure pain threshold, kPa	409 ± 47	371 ± 45	334 ± 42	38	75	<0.001
Conditioned pain modulation, %	30.8 ± 7.4	24.2 ± 6.7	17.3 ± 6.0	6.6	13.5	<0.001
Temporal summation, %	15.1 ± 3.9	21.0 ± 4.4	26.8 ± 5.3	−5.9	−11.7	<0.001

Values are mean ± standard deviation or unadjusted mean difference. The p-values represent the reported overall between-group comparisons. HVRT + PNE: high-volume resistance training combined with Pain Neuroscience Education; MVRT: moderate-volume resistance training.

Quadriceps strength increased in all three groups (Table 5). At Week 12, mean strength had increased from baseline by 7.7 kg in the HVRT + PNE group, 5.2 kg in the MVRT group, and 2.2 kg in the standard physiotherapy group. Week 12 strength was 3.0 kg greater with HVRT + PNE than with MVRT and 5.7 kg greater than with standard physiotherapy. These differences were retained at 12 months, when the mean increases from baseline were 8.2, 5.6, and 2.0 kg, respectively. At that assessment, quadriceps

strength was 3.1 kg greater in the HVRT + PNE group than in the MVRT group and 6.4 kg greater than in the standard physiotherapy group. The reported group-by-time interaction was statistically significant ((F=24.83), (p<0.001)).

Table 8. Biomarker Concentrations at Week 12

Biomarker	HVRT + PNE	MVRT	Standard Physiotherapy	HVRT + PNE versus MVRT	HVRT + PNE versus Standard Physiotherapy	p-value
C-reactive protein, mg/L	2.4 ± 0.8	3.2 ± 0.9	3.9 ± 1.1	−0.8	−1.5	<0.001
Interleukin-6, pg/mL	3.7 ± 1.1	4.8 ± 1.3	5.6 ± 1.5	−1.1	−1.9	<0.001
Tumour necrosis factor-alpha, pg/mL	7.1 ± 1.4	8.3 ± 1.6	9.4 ± 1.9	−1.2	−2.3	<0.001
Brain-derived neurotrophic factor, ng/mL	28.1 ± 4.9	24.7 ± 4.4	21.2 ± 4.0	3.4	6.9	<0.001
Cortisol, µg/dL	11.7 ± 2.7	13.4 ± 2.9	14.8 ± 3.2	−1.7	−3.1	<0.001

Table 9. Health-Related Quality of Life at Week 12

SF-36 component	HVRT + PNE	MVRT	Standard Physiotherapy	HVRT + PNE versus MVRT	HVRT + PNE versus Standard Physiotherapy	p-value
Physical component score	71.6 ± 8.4	65.2 ± 7.8	58.1 ± 7.4	6.4	13.5	<0.001
Mental component score	74.9 ± 7.6	68.7 ± 7.3	62.0 ± 7.2	6.2	12.9	<0.001

At Week 12, functional performance differed across all reported measures (Table 6). Compared with MVRT, participants receiving HVRT + PNE completed the Timed Up and Go Test 1.3 seconds faster, performed 2.2 additional repetitions during the 30-Second Chair Stand Test, walked 40 m farther during the Six-Minute Walk Test, and completed the Stair Climb Test 1.3 seconds faster. Compared with standard physiotherapy, the corresponding differences were 2.6 seconds for the Timed Up and Go Test, 3.7 chair-stand repetitions, 74 m for the Six-Minute Walk Test, and 2.8 seconds for the Stair Climb Test. The reported overall between-group comparison was (p<0.001) for each measure.

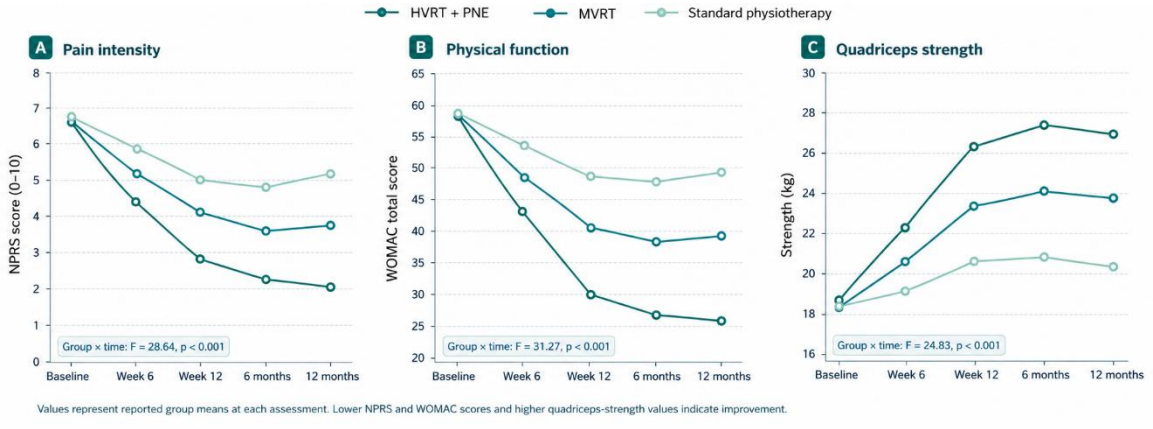
Pain catastrophizing and fear of movement decreased across the reported assessment period, with the largest numerical reductions in the HVRT + PNE group (Table 7). At Week 12, PCS scores had decreased by 13.4 points with HVRT + PNE, 8.3 points with MVRT, and 3.1 points with standard physiotherapy. At 12 months, the respective reductions were 14.8, 9.1, and 3.6 points. TSK scores decreased by 12.7, 8.2, and 3.1 points at Week 12 and by 14.2, 8.9, and 3.5 points at 12 months, respectively. In the HVRT + PNE group, the PSEQ score increased by 15.1 points at Week 12 and by 16.4 points at 12 months. The manuscript reported statistically significant group-by-time differences for the psychosocial outcomes ((p<0.001)).

Pain-modulation measures at Week 12 favoured the HVRT + PNE group (Table 8). Pressure pain threshold was 38 kPa higher than in the MVRT group and 75 kPa higher than in the standard physiotherapy group. Conditioned pain modulation was higher by 6.6 percentage points compared with MVRT and by 13.5 percentage points compared with standard physiotherapy. Temporal summation was lower by 5.9 percentage points compared with MVRT and by 11.7 percentage points compared with standard physiotherapy. The reported overall between-group comparison was (p<0.001) for each pain-modulation measure.

At Week 12, the HVRT + PNE group had lower concentrations of C-reactive protein, interleukin-6, tumour necrosis factor-alpha, and cortisol and a higher concentration of brain-derived neurotrophic factor than the other groups (Table 9). Compared with MVRT, the mean differences were −0.8 mg/L for C-reactive protein, −1.1 pg/mL for interleukin-6, −1.2 pg/mL for tumour necrosis factor-alpha, 3.4 ng/mL for brain-derived neurotrophic factor, and −1.7 µg/dL for cortisol. Compared with standard physiotherapy, the corresponding differences were −1.5 mg/L, −1.9 pg/mL, −2.3 pg/mL, 6.9 ng/mL, and −3.1 µg/dL. All reported overall between-group comparisons had (p<0.001).

Health-related quality-of-life scores at Week 12 were highest in the HVRT + PNE group (Table 10). The SF-36 physical component score was 6.4 points higher than in the MVRT group and 13.5 points higher than in the standard physiotherapy group. The mental component score was higher by 6.2 points

compared with MVRT and by 12.9 points compared with standard physiotherapy. The reported overall between-group comparison was ($p<0.001$) for both component scores.



The figure 1 illustrates changes in pain intensity, physical function, and quadriceps strength across baseline, Week 6, Week 12, and the 6- and 12-month follow-ups. All groups improved during the intervention; however, the HVRT + PNE group demonstrated the greatest and most sustained reductions in NPRS and WOMAC scores and the largest increase in quadriceps strength. The MVRT group showed moderate improvement, whereas standard physiotherapy produced comparatively smaller changes, with slight deterioration in pain and function between 6 and 12 months.

DISCUSSION

This multicentre randomized controlled trial compared high-volume resistance training combined with Pain Neuroscience Education, moderate-volume resistance training, and standard physiotherapy in individuals with symptomatic knee osteoarthritis. All three groups demonstrated numerical improvement in pain, physical function, and quadriceps strength, but the greatest changes occurred in participants receiving the combined HVRT + PNE programme. Differences in NPRS, WOMAC, and quadriceps strength remained evident at 12 months. At Week 12, the combined programme was also associated with better functional performance, psychosocial outcomes, experimental pain-modulation measures, biomarker concentrations, and health-related quality of life than the comparator programmes. These findings should be interpreted as the effect of the complete HVRT + PNE programme because the study design did not isolate the independent contributions of training volume and Pain Neuroscience Education.

The reductions in pain and WOMAC scores are consistent with clinical guidelines and systematic-review evidence supporting structured exercise as a principal component of non-surgical knee osteoarthritis management (3–5). Exercise may reduce symptoms by improving lower-limb strength, joint stability, movement confidence, and tolerance of functional loading. Previous evidence indicates that resistance exercise can improve pain and physical function, although the magnitude of benefit may depend on programme volume, duration, progression, adherence, and participant characteristics (6). The larger improvements observed with HVRT + PNE may therefore reflect the cumulative influence of greater training volume, higher exercise intensity, structured progression, longer treatment contact, functional training, and pain education rather than exercise volume alone.

Quadriceps strength increased most prominently in the combined-intervention group and remained higher at the 12-month assessment. This finding is clinically relevant because quadriceps weakness can contribute to reduced knee control, impaired mobility, and difficulty performing weight-bearing activities. The accompanying differences in chair-stand performance, walking distance, stair climbing, and Timed Up and Go performance at Week 12 were directionally consistent with the strength findings. Nevertheless, the absence of reported long-term functional-performance values means that sustained improvement in these performance tests cannot be inferred from the available results. Previous reviews have similarly shown that resistance exercise can improve strength and function, but the optimal dose

and the extent to which greater training volume produces additional clinical benefit remain uncertain (5,6).

Pain-related psychological outcomes also favoured the HVRT + PNE programme. Participants in this group demonstrated larger reductions in pain catastrophizing and kinesiophobia, while the reported PSEQ values indicated increased pain self-efficacy. Pain Neuroscience Education is intended to reduce the perceived threat of pain, correct unhelpful beliefs, and support confident participation in movement and exercise (9,10). Systematic-review evidence suggests that education may improve pain-related knowledge and psychological outcomes when incorporated into active rehabilitation, although its additional effect on pain and disability varies among studies (9). The present findings are therefore compatible with a biopsychosocial interpretation, but they do not establish that PNE independently caused the observed psychosocial or clinical differences because PNE was delivered only as part of the high-volume programme.

At Week 12, participants receiving HVRT + PNE had higher pressure pain thresholds and conditioned pain modulation values and lower temporal summation values than participants in the comparator groups. Exercise-induced hypoalgesia and adaptations in endogenous pain regulation provide plausible explanations for these findings (7). Altered pain inhibition and enhanced pain facilitation have previously been described in osteoarthritis and other persistent-pain populations (7,8). The results also accord with emerging evidence that exercise modality, volume, and pain education may influence acute hypoalgesic responses in people with knee osteoarthritis (12,13). However, only Week 12 pain-modulation values were reported; consequently, changes from baseline and persistence beyond the intervention period cannot be established.

The Week 12 biomarker profile was more favourable in the HVRT + PNE group, including lower C-reactive protein, interleukin-6, tumour necrosis factor-alpha, and cortisol concentrations and higher brain-derived neurotrophic factor concentrations. These between-group differences may reflect variations in exercise exposure, metabolic adaptation, stress responses, physical activity, or baseline biological characteristics. Because baseline biomarker values, adjusted changes, and longer-term measurements were not presented, these findings should be interpreted as cross-sectional differences at Week 12 rather than evidence that the intervention reduced inflammation, altered neuroplasticity, or modified osteoarthritis progression. Mechanistic conclusions would require complete longitudinal biomarker analyses and formal evaluation of their relationship with clinical outcomes.

The higher Week 12 SF-36 physical and mental component scores in the HVRT + PNE group indicate that the observed benefits extended beyond pain and muscle performance to broader perceptions of physical and psychological health. These differences are compatible with the combined improvements in pain, mobility, movement confidence, and self-efficacy. Education and supervised exercise programmes are already central to structured osteoarthritis-management models (14), and sustained engagement in appropriately prescribed physical activity is generally considered safe for older adults with knee pain (15). However, baseline and long-term SF-36 values were not reported, preventing conclusions regarding change from baseline or maintenance of quality-of-life benefits.

The study has several strengths, including its multicentre randomized design, concealed allocation, blinded outcome assessment, three-group comparison, relatively large randomized sample, supervised intervention, and assessment of clinical, functional, psychosocial, pain-processing, biological, and quality-of-life domains. The 12-month assessment of pain, WOMAC, quadriceps strength, PCS, and TSK provided useful information concerning the persistence of these reported outcomes beyond the supervised treatment period. The inclusion of both patient-reported and performance-based measures also enabled the intervention programmes to be evaluated across complementary dimensions of knee osteoarthritis.

Several limitations require consideration. Participants and treating physiotherapists could not be blinded, creating potential performance and expectation effects. The intervention groups differed not only in resistance-training volume but also in education, intensity, session duration, manual therapy, functional progression, and treatment content. The design consequently cannot determine whether the observed differences were attributable to training volume, PNE, contact time, another programme component, or their combined effects. Long-term values were unavailable for functional performance, pain modulation, biomarkers, physical activity, and SF-36 outcomes, while complete comparative PSEQ and HADS results were not presented. The available results also did not provide follow-up denominators, adjusted confidence intervals, adherence findings, adverse-event frequencies, protocol deviations, regression estimates, or mediation results. The large number of secondary outcomes increases the possibility of chance findings despite the reported adjustment procedure. Finally, the supervised, resource-intensive programme and the inclusion of participants with Grade II–IV radiographic disease may limit generalizability to unsupervised, community-based, or lower-resource settings.

These findings support further evaluation of combined progressive resistance training and pain education as a comprehensive rehabilitation strategy for knee osteoarthritis. Future trials should use designs capable of separating the effects of exercise volume and PNE, such as factorial or carefully matched treatment-arm designs with equal contact time. Complete reporting of intervention fidelity, adherence, harms, cointerventions, adjusted between-group estimates, and confidence intervals is required. Longer-term assessment of performance, psychosocial, pain-modulation, biomarker, physical-activity, and quality-of-life outcomes would help determine whether the Week 12 differences represent durable treatment effects.

CONCLUSION

High-volume resistance training combined with Pain Neuroscience Education was associated with greater reductions in pain and functional limitation and greater improvement in quadriceps strength than moderate-volume resistance training and standard physiotherapy, with differences in these outcomes remaining evident at 12 months. The combined programme was also associated with more favourable functional-performance, psychosocial, pain-modulation, biomarker, and health-related quality-of-life findings at Week 12. Because the intervention combined several treatment components, the observed effects cannot be attributed independently to training volume or Pain Neuroscience Education. The findings support further evaluation of integrated, progressively loaded rehabilitation programmes for knee osteoarthritis using designs that isolate treatment components and report complete long-term effectiveness and safety outcomes.

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