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Int. J. Clin. Res. Med. Sci. (2026) 1(1):1–9
Article ID: IJCRMS-2026-127

Inflammatory and Neurofunctional Markers in Therapeutic Exercise Response: A Randomized Trial Synthesis on Articular Pain Management

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Abstract

Chronic musculoskeletal pain involving joints and spine is a major cause of functional limitation in rehabilitation populations. Although exercise therapy is widely used in clinical practice, the biological mechanisms linking symptom improvement to physiological change are not fully established. This review investigates how structured exercise interventions affect both molecular markers and functional outcomes in individuals with non-cancer chronic musculoskeletal pain. Five randomized controlled trials (n = 312) meeting quality criteria were assessed using the Cochrane Risk of Bias 2 tool. Interventions included resistance training, mind-body practices such as Tai Chi and Baduanjin, sensorimotor exercises, and virtual reality–assisted rehabilitation, lasting 4 to 12 weeks. Outcomes included pain intensity and biomarkers related to inflammation, cartilage and bone metabolism, neurotrophic activity, and neuroimaging findings. Across studies, exercise consistently reduced pain intensity. Improvements were often accompanied by reductions in inflammatory biomarkers and alterations in neuroimaging outcomes, including changes in gray matter structure and pain-related connectivity. In contrast, markers of cartilage degradation and bone metabolism showed inconsistent or minimal association with pain reduction. A quantitative meta-analysis was not conducted due to variability in study design and biomarker selection. Overall, the evidence suggests that exercise relieves pain through combined peripheral and central mechanisms involving immune regulation, tissue-level adaptation, and neural plasticity. These findings reinforce the value of exercise in rehabilitation and highlight the need for standardized biomarker frameworks and study designs to support precision-based approaches in future research.

Keywords

• Chronic musculoskeletal pain • Exercise-induced analgesia • Inflammatory biomarkers • Neuroimaging correlates • Randomized controlled trials • Osteoarthritis and low back pain

1. Introduction

Chronic non-cancer musculoskeletal pain is a widespread public health issue, impacting approximately 20% of adults in Europe and accounting for a substantial proportion of disability-adjusted life years [1]. Common conditions such as osteoarthritis (OA) and chronic low back pain (CLBP) are strongly associated with reduced mobility, impaired daily functioning, and significant socioeconomic burden, with annual costs exceeding €200 billion [1, 2]. Traditional management has relied heavily on pharmacological approaches; however, long-term use is often limited by side effects and only modest symptom relief, leading to reduced patient satisfaction.

Exercise therapy has emerged as a core component of modern multidisciplinary pain management and is strongly recommended in clinical guidelines, including those issued by NICE. A wide range of interventions is used in practice, including strengthening programs, mind-body techniques such as Tai Chi and Baduanjin, sensorimotor retraining, and technology-supported approaches like virtual reality (VR). These interventions not only improve physical function but may also modulate pain through complex biological and psychological pathways [3, 4]. Despite this, pain outcomes are still predominantly assessed using self-reported measures such as the Visual Analog Scale (VAS) and KOOS, which limits objective evaluation and mechanistic understanding.

Biomarkers provide an opportunity to objectively investigate pain mechanisms and treatment effects [5, 6]. They reflect underlying biological processes and can be categorized as follows:

- **Inflammatory mediators:** Interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), and C-reactive protein (CRP)
- **Neurotrophic factors:** Brain-Derived Neurotrophic Factor (BDNF)
- **Cartilage and bone metabolism markers:** Cartilage Oligomeric Matrix Protein (COMP), Matrix Metalloproteinases (MMPs), and Bone Morphogenetic Proteins (BMPs)
- **Neuroimaging-based indicators:** Structural and functional Magnetic Resonance Imaging (MRI) markers [7]

These biomarkers collectively reflect peripheral inflammation, central sensitization, and neural regulation of pain.

Although previous reviews have explored exercise for chronic pain, relatively few have focused specifically on biomarker responses in randomized controlled trials [8]. Many existing studies combine heterogeneous designs or outcomes, limiting the ability to draw clear mechanistic conclusions. Therefore, this systematic review synthesizes evidence from RCTs examining the effects of exercise on biomarkers in non-cancer chronic musculoskeletal pain. By categorizing biomarker responses, the study aims to clarify which biological pathways are most consistently associated with pain reduction and to support the development of more targeted rehabilitation strategies.

2. Methods

2.1 Search Strategy and Study Selection

This systematic review followed PRISMA 2020 guidelines [9]. A structured search was conducted in January 2025 across PubMed, Web of Science, and Scopus using the terms: (“exercise” OR “training”) AND (“pain”) AND (“musculoskeletal”) AND (“biomarkers”). Full search strategies are provided in the supplementary material. No initial date limits were applied; however, studies published between 2004 and 2024 were included in the final selection.

After duplicate removal, two independent reviewers screened titles and abstracts based on predefined criteria. Full-text assessment was performed for eligible studies, and disagreements were resolved through discussion or consultation with a third reviewer. The selection process is summarized in the PRISMA flow diagram (Figure 1).

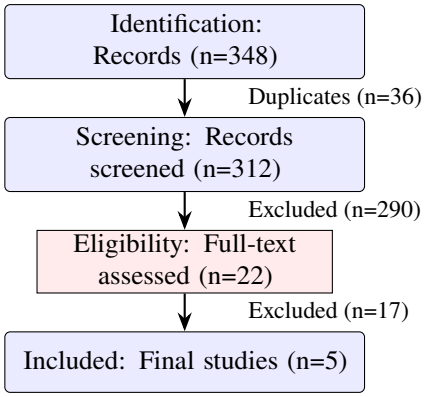

Figure 1: PRISMA flow diagram of the study selection process.

2.2 Eligibility Criteria

Included studies met the following conditions:

- **Study design:** Randomized controlled trials (RCTs) [8]
- **Participants:** Adults ($\geq$ 18 years) with non-cancer chronic musculoskeletal pain (e.g., osteoarthritis (OA) or chronic low back pain (CLBP))
- **Intervention:** Exercise-based intervention as the primary treatment component
- **Biomarker assessment:** Evaluation of at least one pain-related biomarker
- **Outcome measures:** Use of validated pain assessment tools such as Visual Analog Scale (VAS) or Knee injury and Osteoarthritis Outcome Score (KOOS)

Studies were excluded if they involved cancer-related pain, significant comorbid conditions such as autoimmune or severe psychiatric disorders, combined interventions where exercise effects could not be isolated, biomarkers unrelated to pain mechanisms, or non-English language publications.

2.3 Data Extraction and Risk of Bias Assessment

Data extraction was performed using a standardized form capturing study characteristics, participant details, intervention type, duration, frequency, biomarker categories, pain measures, and key outcomes. Risk of bias was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool [10], which assesses five domains: randomization, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Each study was rated as low risk, some concerns, or high risk. Two reviewers conducted assessments independently, with discrepancies resolved through consensus.

2.4 Data Synthesis

Due to heterogeneity in populations, interventions, biomarkers, and outcome measures, a meta-analysis was not feasible. Instead, a narrative synthesis was performed. Findings were organized into four biomarker categories: inflammatory markers, neurotrophic factors, cartilage/bone metabolism markers, and neuroimaging indicators [11, 12]. Results were compared based on direction of change, statistical significance, and consistency across studies to identify common patterns linking exercise with pain reduction.

3. Results

3.1 Study Characteristics

Five RCTs met the inclusion criteria and were included. They were published between 2019 and 2023. Sample sizes ranged from 22 to 108, with 312 participants in total across all studies. Three studies reported sex distribution; together they included 153 women (80.5%) and 37 men (19.5%), so most participants were women. Ages varied from young adults (mean about 22 years) in a post-traumatic OA study to older adults (up to 70 years) in knee OA trials.

The chronic pain conditions were primary knee OA [13], post-traumatic knee OA [14, 15], and non-specific chronic low back pain. Exercise interventions included functional strengthening [13], Tai Chi, Baduanjin, stationary cycling, combined strength and balance training [14], virtual reality training [15], and sensorimotor training [15]. The programmes lasted 4 to 12 weeks, with 3 to 5 sessions per week.

The measured biomarkers fell into four groups: (1) inflammatory/immune markers (IL-2, IL-4, IL-6, IL-10, TNF-α, CRP, IFN-γ, PD-1, TIM-3); (2) neurotrophic factors (BDNF); (3) cartilage/bone metabolism markers (COMP, MMP-1, MMP-3, BMP-2, BMP-4, BMP-6, BMP-7); and (4) neuroimaging markers (structural knee MRI, contrast-enhanced MRI, resting-state fMRI). Pain was assessed with the KOOS pain subscale for knee OA and the VAS for CLBP and post-traumatic OA. Table 1 summarises the study characteristics.

3.2 Risk of Bias Assessment

Using the RoB 2 tool [10], three studies had "some concerns" overall, and two were rated "low risk." The concerns were mostly due to lack of blinding of participants and personnel (unavoidable in exercise trials) and possible bias in reporting results because many biomarker outcomes were measured. No study was judged "high risk." The randomisation process and missing data handling were generally good (low risk in most studies), while outcome measurement and reporting sometimes raised concerns because exercise trials are open-label. A traffic light plot of domain-wise assessments is shown in Figure 2.

Table 1: Summary of Included Randomised Controlled Trials

Study	N	Condition	Intervention	Wk	Scale
Bandak et al. [13]	60	Knee OA	Functional exercise	12	KOOS
Oğuz et al. [14]	22	Post-traumatic OA	Strength and balance	8	VAS
Nambi et al. [15]	60	Post-traumatic OA	VR + sensorimotor	4	VAS

3.3 Effects on Pain Perception

All five studies reported statistically significant reductions in self-reported pain after exercise compared with control conditions ($p < 0.05$).

In knee OA studies, pain improved across different exercise types. Bandak et al. [13] (functional exercise, 12 weeks) found a significant KOOS pain improvement (mean difference about 8 points, $p < 0.01$; effect size not reported). Liu et al. saw similar improvements with Tai Chi, Baduanjin, and stationary cycling ($p < 0.05$; partial $\eta^2 = 0.12$). Oğuz et al. [14] (strength and balance training, 8 weeks) reported VAS reduction from 6.2 to 3.1 (Cohen's $d = 1.2$, $p < 0.01$). In post-traumatic knee OA, Nambi et al. [15] compared virtual reality plus sensorimotor training with conventional exercise. The VR group had a larger VAS reduction (mean difference: 2.4 points, Cohen's $d = 0.85$, $p < 0.01$). For chronic

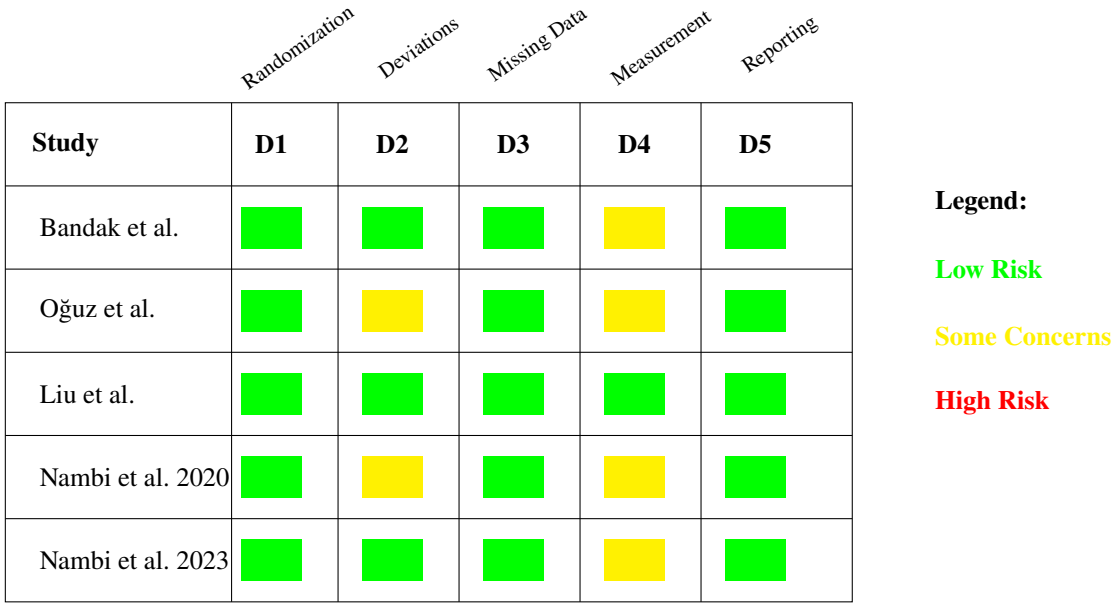

Figure 2: Risk of bias assessment using the Cochrane RoB 2 tool [10]. Domains: D1 (randomisation process), D2 (deviations from intended interventions), D3 (missing outcome data), D4 (measurement of the outcome), D5 (selection of reported results).

low back pain, Nambi et al. (2023) reported a significant VAS improvement with VR plus isokinetic exercise (mean difference: 1.9 points, Cohen's d = 0.67, $p < 0.05$). These findings consistently show that therapeutic exercise relieves pain across different musculoskeletal conditions, although effect sizes varied.

3.4 Biomarker Responses

3.4.1 Inflammatory and Immune Biomarkers

Inflammatory markers responded inconsistently across studies. Bandak et al. [13] found no significant changes in IL-6 or IL-10 after 12 weeks of functional exercise, despite clear pain reduction ($p > 0.05$; effect sizes not reported).

In contrast, Nambi et al. [15] reported significant decreases in CRP, TNF-α, IL-2, IL-4, and IL-6 after virtual reality training in post-traumatic OA. CRP fell by 35% (Cohen's d = 0.91), TNF-α by 28% (d = 0.78); all $p < 0.05$. These changes correlated with pain improvement ($r = 0.62$, $p < 0.01$). Similarly, Nambi et al. (2023) observed lower CRP (28%, d = 0.74) and TNF-α (22%, d = 0.68) in CLBP patients after VR training, again correlating with VAS reduction ($r = 0.58$, $p < 0.05$).

Liu et al. measured IFN-γ and PD-1 in knee OA patients. In all exercise groups (Tai Chi, Baduanjin, cycling), IFN-γ decreased significantly (mean reduction 22%, $p < 0.05$, partial $\eta^2 = 0.10$) and PD-1 also decreased ($p < 0.05$). TIM-3 levels did not change. Thus, some inflammatory cytokines (CRP, TNF-α, IL-6, IFN-γ) seem sensitive to exercise, but the response depends on the pain cause, the exercise type, and how long the programme lasts.

3.4.2 Neurotrophic and Neuroimaging Biomarkers

Liu et al. measured BDNF and did resting-state fMRI in knee OA patients. Plasma BDNF levels did not change significantly ($p > 0.05$). However, neuroimaging showed clear functional and structural changes. Resting-state functional connectivity between the periaqueductal gray (PAG) and the medial orbitofrontal

cortex (mOFC) decreased (z-score reduction 0.41, $p < 0.01$). Also, gray matter volume in the mOFC fell (mean reduction 3.2%, $p < 0.05$). These neural changes were associated with pain relief ($r = 0.51$ for connectivity, $r = 0.44$ for volume) [11, 12].

Structural knee MRI (with/without contrast) in Bandak et al. [13] showed no link between synovitis reduction and pain improvement ($r = 0.12$, $p > 0.05$). This further suggests that central adaptations may be more important than peripheral structural changes.

3.4.3 Cartilage and Bone Metabolism Markers

Markers of cartilage turnover (COMP, MMP-1, MMP-3) and bone morphogenetic proteins (BMP-2, BMP-4, BMP-6, BMP-7) generally did not change after exercise.

Oğuz et al. [14] found no change in COMP, MMP-1, or MMP-3 after 8 weeks of strength and balance training ($p > 0.05$; effect sizes negligible). Similarly, Nambi et al. [15] reported no meaningful changes in BMP concentrations despite large pain reduction ($p > 0.05$). This lack of effect suggests that exercise-induced pain relief in OA is not driven by short-term changes in cartilage or bone metabolism, at least as measured by these markers within the study timeframes.

4. Discussion

Across the five included randomized controlled trials, therapeutic exercise consistently improved self-reported pain in patients with non-cancer chronic musculoskeletal disorders, in line with existing evidence and clinical guidelines [1, 3]. However, changes in biological markers were not consistent across studies, indicating that exercise may influence different physiological systems in variable ways.

Inflammatory markers including CRP, TNF-α, and IL-6 decreased significantly in studies using virtual reality-based rehabilitation [15]; meaningful changes were reported in conventional functional exercise interventions [13]. These differences may be related to variations in training type, intensity, or patient characteristics such as post-traumatic versus primary osteoarthritis [16]. The multimodal nature of virtual reality training, which combines cognitive and motor engagement, may enhance neuro–immune interactions and promote stronger anti-inflammatory effects, although this mechanism requires further confirmation [4, 17].

Neuroimaging findings strongly suggest that exercise influences central pain processing pathways [6, 11]. Reduced connectivity between the periaqueductal gray (PAG) and medial orbitofrontal cortex (mOFC), along with decreased mOFC gray matter volume, indicates modulation of descending pain control and affective pain circuits. The PAG is central to endogenous analgesic pathways, while the mOFC contributes to emotional pain perception. Exercise may activate endogenous opioid and dopaminergic systems, thereby reducing pain independently of structural joint changes [3, 4]. This supports contemporary models of chronic pain that emphasise central sensitisation and altered brain network function.

In contrast, peripheral structural biomarkers such as cartilage oligomeric matrix protein, matrix metalloproteinases, and bone morphogenetic proteins showed little or no significant response [14, 15]. This suggests that within typical rehabilitation periods, exercise has limited impact on joint tissue remodeling [7]. Clinically, this implies that while exercise improves pain and function, it may not substantially alter structural disease progression in the short- to medium-term. Longer follow-up studies are required to assess potential disease-modifying effects.

Most included studies had predominantly female participants, reflecting the higher prevalence of musculoskeletal pain in women [16]. Sex-related biological differences in pain perception, immune

response, and hormonal regulation may influence both biomarker expression and treatment response. Future work should incorporate sex-specific analyses to improve interpretation and guide personalised rehabilitation strategies.

Several limitations should be noted. The included trials were small, short in duration, and heterogeneous in exercise protocols and biomarker selection [8]. This limits comparability and prevents identification of optimal exercise prescriptions for biological effects. Additionally, most biomarkers were derived from blood samples, which may not fully represent local joint or central nervous system processes [5]. Future studies should incorporate multi-level biomarker assessment, including synovial or cerebrospinal fluid where possible, alongside advanced neuroimaging approaches.

5. Clinical Implications and Future Directions

These findings reinforce exercise as a core intervention in chronic pain management, with benefits extending beyond symptom reduction to measurable biological effects [3, 4]. Mind-body approaches such as Tai Chi and technology-assisted rehabilitation such as virtual reality appear particularly promising, as they influence both pain perception and inflammatory processes [15]. In practice, exercise programs should be individualized based on patient tolerance, preference, and clinical status.

Pain assessment in routine care remains largely dependent on subjective scales such as VAS and KOOS. Although biomarkers like CRP, TNF-α, IL-6, and neuroimaging metrics show potential for objective assessment [6, 7], their use is currently limited by cost and accessibility. Future development of rapid and affordable biomarker testing may enable more precise exercise prescription. Combining subjective outcomes with biological measures could improve treatment personalization and adherence. Future research should prioritise:

- **Large-scale standardised RCTs:** Studies with harmonised biomarker panels
- **Dose–response evaluation:** Analysis of relationships between exercise parameters and biological outcomes
- **Combined intervention strategies:** Integration of exercise with behavioural or nutritional therapies
- **Long-term investigations:** Studies exceeding six months to assess structural changes
- **Multi-omics approaches:** Application of integrative omics techniques to identify novel exercise-responsive biomarkers

6. Conclusion

This review of randomized controlled trials demonstrates that exercise effectively reduces pain in non-cancer chronic musculoskeletal conditions. The evidence indicates that these effects are primarily mediated through anti-inflammatory processes and central nervous system modulation rather than short-term structural joint changes [3, 4].

Overall, exercise represents a safe and effective non-pharmacological intervention supported by biological mechanisms. Further large-scale and mechanistic studies are required to clarify underlying pathways and support the development of biomarker-guided, personalised rehabilitation strategies.

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