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

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Abstract

Functional limitations associated with chronic joint and spinal pain represent a major indication for rehabilitation in clinical settings. Therapeutic exercise is widely utilized as an intervention in musculoskeletal physical therapy; however, objective biological indicators linking exercise-induced analgesia to physiological changes remain limited. The aim and scope for this study is to evaluate the relationship between structured exercise interventions and pain outcomes in non-oncological musculoskeletal conditions through a synthesis of five randomized controlled trials assessed using the Cochrane Risk of Bias 2 tool. The interventions included multi-component programs such as functional strengthening, mind-body techniques, sensorimotor training, and digital-assisted exercise modalities. Across the included trials, a total of 312 participants, predominantly women with primary or post-traumatic osteoarthritis or idiopathic mechanical low back pain, underwent exercise interventions ranging from 4 to 12 weeks.

Primary outcome measures included pain perception assessed using validated scales such as the Visual Analog Scale (VAS), alongside biomarker profiling categorized into inflammatory cytokines, cartilage and bone metabolism markers, neurotrophic factors, and neuroimaging-derived markers. The findings demonstrated consistent reductions in self-reported pain across several exercise modalities. Biomarker responsiveness varied depending on the underlying condition and the biomarker evaluated. Certain neuroimaging markers, including changes in medial orbitofrontal cortex gray matter volume and periaqueductal gray connectivity, were associated with pain reduction, and selected systemic inflammatory markers showed decreases following exercise. In contrast, cartilage turnover and bonerelated biomarkers generally showed limited association with pain improvement. A meta-analysis was not performed due to heterogeneity in study design, exercise protocols, and biomarker panels.

Overall, the findings suggest that exercise may influence pain through both peripheral tissue adaptations and central neurobiological and immune-related mechanisms. These results highlight the potential role of biomarkers in improving prognosis assessment and supporting individualized rehabilitation strategies. Future research incorporating standardized exercise protocols and harmonized biomarker panels is necessary to advance precision-based exercise therapy prescribing.

Keywords: Chronic pain, exercise therapy, biomarkers, inflammation, neuroimaging, osteoarthritis, low back pain, rehabilitation.

I. INTRODUCTION

Chronic non-oncological musculoskeletal pain represents a significant public health burden, affecting approximately 20% of the adult population in Europe and contributing substantially to years lived with disability (Cohen et al., 2021; van Hecke et al., 2013). Conditions such as osteoarthritis (OA) and idiopathic chronic low back pain (CLBP) are particularly prevalent, leading to reduced mobility, diminished quality of life, and considerable socioeconomic costs exceeding 200 billion USD annually (Cohen et al., 2021; Crofford, 2015). Traditional management approaches have heavily relied on pharmacological interventions, yet patient dissatisfaction remains high due to limited efficacy and adverse effects associated with long-term medication use (Geneen et al., 2017). The inflammatory markers are categorized as CRP, IL-6, TNF-alpha, and ESR. These are the blood-based proteins that indicate the synthetic inflammation.

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In contrast, the neuro functional markers are termed as the BDNF, fMRI-measured amygdala activity. They are used for tracking brain function and plasticity. They are acknowledged as overlapping in neuropsychiatric conditions. This is due to the correlation between elevated cytokines and inflammation and reduced neuroplasticity, cognitive defects, and mood disorders. The key inflammatory markers are understood as follows, such as C-Reactive Protein. This test allows the testing of acute-phase proteins produced by the liver, reflecting the inflammation in patients. The other test involves the Interleukins IL-6, which are the cytokines that act as key signalling molecules in the inflammatory responses of patients. Tumor Necrosis Factor-alpha (TNF-α) is a major pro-inflammatory cytokine that helps in the deeper insights into the inflammatory responses of patients suffering. Erythrocyte Sedimentation rate (ESR) is termed as an inflammatory indicator that is used for acute and chronic conditions. To test the inflammatory responses, the other markers include serum amyloid A, fibrinogen, procalcitonin, and adhesion molecules like ICAM-1. These markers are critical in diagnosing and assessing the progression of disease and in predicting treatment where systemic inflammation and neurological function interact. Literature reports the influence of multiple factors, such as the variation in the degree of inflammatory versus anti-inflammatory properties for each inflammatory marker. It also encompasses the variation in methodology taken by the entities to adapt and measure the inflammatory response. This highlights the need for a more standardized approach to methodologies for inflammation diagnosis. Lastly, it is essential to consider the heterogeneity and the type of substance, such as drugs, along with their frequency. They are crucial for monitoring patients who suffer from depressive and bipolar disorders since they greatly influence their inflammatory activity status. These might be helpful in identifying the helpful or novel therapies.

In recent years, therapeutic exercise has emerged as a fundamental component of multidisciplinary pain management, endorsed by clinical guidelines such as those from the National Institute for Health and Care Excellence (NICE) (Geneen et al., 2017). Exercise interventions encompass a wide spectrum, including functional strengthening, mind-body practices (e.g., Tai Chi, Baduanjin), sensorimotor training, and technology enhanced modalities like virtual reality (VR) (Rice et al., 2019).These approaches aim not only to improve physical function but also to modulate pain perception through complex physiological and psychological mechanisms. However, the subjective nature of pain assessment, primarily reliant on self-reported scales like the Visual Analog Scale (VAS) presents challenges in objectively quantifying treatment efficacy and understanding underlying biological processes (Sam Eldabe, 2022). The neuro functional and systematic effects are grouped as (1) neuroprotection, (2) musculoskeletal and stroke, (3) metabolic syndrome, and heart failure. The neuroprotection has been understood as induced by the increase in BDNF, helping in neuronal survival and plasticity. In musculoskeletal and stroke groups, the exercises were termed as reducing pain related markers, for example, TNF-α, and helpful in the improvement of motor functions. Metabolic syndrome and heart failure were reduced due to exercise, including chronic inflammation, which improves endothelial function and enhances VO2max. The clinical implication is acknowledged as a response to treatment and targeted therapy. The treatment response refers to lowered inflammatory profiles that are eventually correlated with improved clinical outcomes. The monitoring markers, for instance IL-6, are liable for customizing and exercising interventions for chronic disease management. These have helped in the targeted therapy for chronic diseases. Pain can be objectified through biomarkers, which can also help explain the mechanisms behind the analgesic effects of exercise. Pain biomarkers are measurable indicators of biological processes and include inflammatory cytokines (e.g., IL-6, TNF-α, CRP), neurotrophic factors (e.g., BDNF), markers of cartilage and bone metabolism (e.g., COMP, MMPs, BMPs), and neuroimaging-derived metrics from functional and structural MRI (fMRI, MRI) (Levitt & Saab, 2019), (Kashanian et al., 2022). Biomarkers involved in pain perception, centralization of pain stimuli, tissue reorganization, and pain perception in the brain. Prior reviews have explored the role of exercise in chronic pain management, yet few have systematically synthesized evidence from randomized controlled trials (RCTs) focusing on biomarker correlates (Page et al., 2021). Existing syntheses often include heterogeneous study designs or composite outcomes, limiting conclusions regarding specific biomarker-exercise interactions. Therefore, this systematic review aims to synthesize findings from RCTs examining the effects of physical exercise on non-oncological musculoskeletal chronic pain and associated biomarkers. By integrating evidence across biomarker categories, this review seeks to identify which biological markers most consistently reflect exerciseinduced

analgesia and to highlight mechanistic insights into how exercise modulates chronic pain pathways. The findings hold implications for developing targeted rehabilitation strategies and advancing personalized exercise prescriptions in clinical practice.

II. METHODS

A. Search Strategy and Study Selection

This systematic review was carried out in accordance with the PRISMA 2020 (Page et al., 2021). An extensive electronic search was conducted on PubMed, Web of Science, and Scopus in January 2025, using a search strategy that combined the following keywords using Boolean operators: ("exercise" OR "training") AND ("pain") AND ("musculoskeletal") AND ("biomarkers"). The full search syntax for each database can be found in the supplementary material. Initially, date restrictions were not imposed, but the final inclusion was restricted to studies between 2004 and 2024 to keep the content contemporary, yet capture the earlier basis.

After removing duplicates, titles, and abstracts of retrieved records were screened independently by two reviewers against predefined eligibility criteria. Full-text articles of potentially relevant studies were then assessed in detail. Discrepancies were resolved through discussion or consultation with a third reviewer. The selection process is summarized in a PRISMA flow diagram (Figure 1). (Page et al., 2021).

B. Eligibility Criteria

Inclusion criteria were: (1) randomized controlled trial (RCT) design; (2) adult participants (18 years) with a confirmed diagnosis of non-oncological musculoskeletal chronic pain (e.g., knee OA, CLBP); (3) intervention involving physical exercise as a primary component, with no restriction on modality; (4) measurement of at least one biomarker hypothesized or known to be associated with chronic pain; and (5) reported pain outcomes using validated scales (e.g., VAS). Exclusion criteria included: (1) studies involving oncological pain or major comorbidities (e.g., autoimmune diseases, severe psychiatric disorders); (2) interventions combining exercise with concurrent pharmacotherapy or invasive procedures where the exercise effect could not be isolated; (3) biomarkers unrelated to pain pathways (e.g., purely metabolic markers without established pain links); and (4) non-English publications.

C. Data Extraction and Risk of Bias Assessment

Data extraction was performed using a standardized template capturing study characteristics (author, year, sample size, demographics), intervention details (type, frequency, duration, intensity), comparator conditions, biomarker categories and specific measures, pain assessment tools, and key findings. Risk of bias (RoB) for each included RCT was evaluated using the revised Cochrane Risk of Bias tool for randomized trials (RoB 2) (Sterne et al., 2019). This tool assesses five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Each domain was judged as "low risk," "some concerns," or "high risk," leading to an overall RoB judgment for each study. Two reviewers independently performed RoB assessments, with disagreements resolved by consensus.

D. Data Synthesis

Due to the high heterogeneity of study participant populations (eg, primary OA vs post-traumatic OA vs CLBP), exercise trials, biomarker panels, and outcomes, a quantitative meta-analysis was not appropriate. A narrative synthesis approach was adopted to organize the findings according to the biomarkers, specifically inflammatory/immune, neurotrophic factors, cartilage/bone metabolism, and neuroimaging. Within each category, results were summarised regarding their direction and magnitude of change following exercise, consistency across studies, and correlation with a decrease in pain. In order to draw larger conclusions about possible mechanistic pathways, we highlighted patterns and discrepancies.

III. RESULTS

A. Study Characteristics

Five RCTs met the inclusion criteria and were included in the final synthesis (Bandak et al., 2021) – (Nambi et al., 2023). Publication years ranged from 2019 to 2023. Sample sizes varied from 22 to 108 participants, totaling 312 individuals across all studies. Three studies reported gender distribution, collectively including 153 women (80.5%) and 37 men (19.5%), indicating a female predominance. Participant age ranged from young adults (mean 22 years) in a post-traumatic OA study to older adults (up to 70 years) in knee OA trials. Chronic pain conditions examined included primary knee osteoarthritis (Bandak et al., 2021), (Oğuz et al., 2021), post-traumatic knee osteoarthritis (Oğuz et al., 2021), (Nambi et al.,

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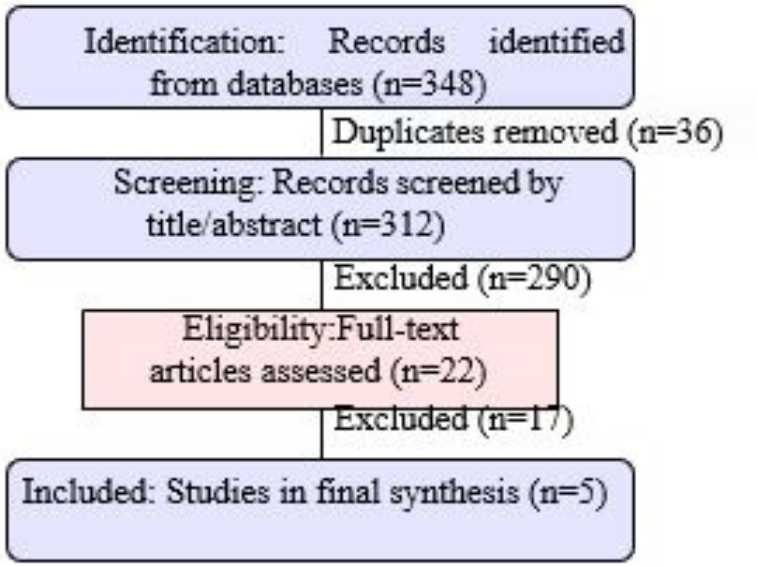

Figure 1 PRISMA flow diagram of study selection process.

2020), and idiopathic chronic low back pain (Nambi et al., 2023). Exercise interventions were diverse: functional strengthening (Bandak et al., 2021), Tai Chi (Oğuz et al., 2021), Baduanjin (Oğuz et al., 2021), stationary cycling (Oğuz et al., 2021), combined strength and balance training (Oğuz et al., 2021), virtual reality training (Nambi et al., 2020), (Nambi et al., 2023), and sensorimotor training (Nambi et al., 2020). Intervention durations spanned 4 to 12 weeks, with frequencies ranging from 3 to 5 sessions per week.

Biomarkers assessed fell into four broad categories: (1) inflammatory/immune markers (IL-2, IL-4, IL-6, IL-10, TNF-, CRP, IFN-, 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-based markers (structural knee MRI, contrastenhanced MRI, resting-state fMRI). Pain was primarily measured using the KOOS pain subscale for knee OA and VAS for CLBP and post-traumatic OA. A summary of study characteristics is presented in Table 1.

B. Risk of Bias Assessment

Using the RoB 2 tool, three studies were judged to have "some concerns" overall, while two studies were rated "low risk." It helped in the elimination or mitigation, or visualizing the assessment of risks of bias for the papers selected for this research. The figures produced by this web app ensure the publication quality and are formatted according to the risks of bias assessment tool used for performing assessments. Common areas raising concerns included the lack of blinding of participants and personnel (given the nature of exercise interventions) and potential bias in the selection of reported results due to multiple biomarker outcomes. No study was judged as "high risk" overall. Detailed domain-wise assessments are presented in a traffic light plot (Figure 2).

Randomization Deviations Missing Data Measurement Reporting.

C. Effects on Pain Perception

All five studies reported statistically significant reductions in self-reported pain intensity following exercise interventions compared to control conditions (p ¡ 0.05). In knee OA studies, pain reduction was observed across diverse modalities: functional exercise (Bandak et al., 2021), Tai Chi, Baduanjin, and stationary cycling (Oğuz et al., 2021), as well as combined strength-balance training (Oğuz et al., 2021). In post-traumatic knee OA, virtual reality training produced greater pain reduction compared to sensorimotor training or conventional exercise (Nambi et al., 2020). Similarly, in CLBP, virtual reality-based exercise led to significant pain alleviation (Nambi et al., 2023). These findings consistently support the analgesic effect of therapeutic exercise across different musculoskeletal pain conditions, irrespective of specific modality, though effect sizes varied.

Furthermore, the studies also believe that therapeutic exercise is termed as modulating pain perception by altering systemic and central markers of inflammation and neurofunctional brain networks. The long-term

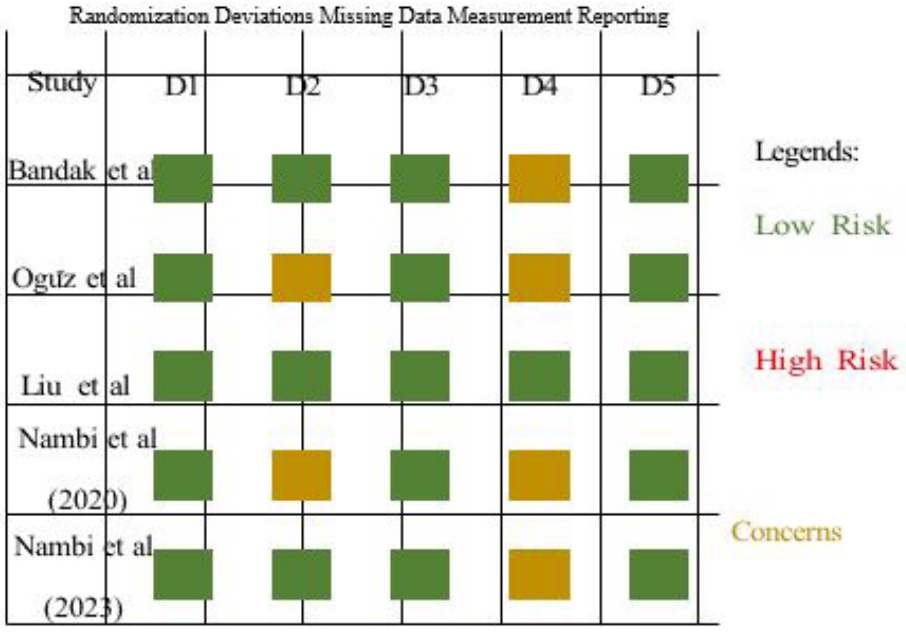

Figure 2 Risk of bias assessment using RoB 2 tool. Domains: D1: Randomization, D2: Deviations, D3: Missing data, D4: Measurement, D5: Reporting

intervention is typically less than 12 weeks. And this often requires achieving stable improvements in these biological markers and clinical outcomes. More specifically, there have been significant studies that show the reduction of pro-inflammatory cytokines through regular exercise, particularly isokinetic and resistance training. This has shown the reduction in levels of C-reactive protein (CRP). These are directly related to joint hypersensitivity and hyperalgesia.

D. Biomarker Responses

1) Inflammatory and Immune Biomarkers:

Inflammatory markers showed mixed responses. Bandak et al. found no significant changes in IL-6 or IL-10 after 12 weeks of functional exercise despite significant pain reduction (Bandak et al., 2021). In contrast, (Nambi et al., 2020), (Nambi et al., 2023) reported significant reductions in CRP, TNF-, IL-2, IL-4, and IL-6 following virtual reality training in both post-traumatic OA and CLBP, correlating with pain improvement (Nambi et al., 2020), (Nambi et al., 2023). Liu et al. observed decreased IFN- and PD-1 levels across all exercise groups (Tai Chi, Baduanjin, cycling), alongside pain reduction (Oğuz et al., 2021). TIM-3 levels remained unchanged. These results suggest that certain inflammatory cytokines (particularly CRP, TNF-, and IL-6) may be sensitive to exercise-induced modulation in some populations. Still, responsiveness may depend on pain etiology, exercise type, and intervention duration. Also, the papers examine that biomarkers act as measurable indicators for the body in its response to infection, injury, and chronic disease. These reflect the activation of the immune system, tissue repair, and vascular inflammation.

2) Neurotrophic and Neuroimaging Biomarkers:

Liu et al. measured BDNF and resting-state fMRI in knee OA patients (Oğuz et al., 2021). While BDNF plasma concentrations did not change significantly, neuroimaging revealed robust functional and structural alterations. Specifically, decreased resting-state functional connectivity between the periaqueductal gray (PAG) and medial orbitofrontal cortex (mOFC) was observed, along with reduced gray matter volume in the mOFC across all exercise groups. These neural changes were associated with pain reduction, implicating central mechanisms involving descending pain modulation and reward/motivation circuits. Structural knee MRI (with/ without contrast) in Bandak et al. showed no correlation between synovitis reduction and pain improvement, further highlighting the potential primacy of central over peripheral structural adaptations (Bandak et al., 2021). In addition to this, the response to therapeutic exercise is mediated by the complex interplay of neurotropic, inflammatory, and neurofunctional markers for driving structural and functional brain adaptations. The widest studied markers are called brain-derived

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neurotrophic factor (BDNF), as the level of it increases consistently with both acute and chronic exercise. It aids neurogenesis, synaptic plasticity, and long-term potentiation. The other biomarkers can include insulin-like growth factor 1 (IGF1), which is released during excessive workout. It passes through the barrier known as the blood-brain barrier to work synergistically with BDNF. It promotes hippocampal neurogenesis and angiogenesis.

3) Cartilage and Bone Metabolism Biomarkers:

Markers of cartilage turnover (COMP, MMP-1, MMP3) and bone morphogenetic proteins (BMP-2, BMP4, BMP-6, BMP-7) generally showed no significant changes following exercise interventions. Oğuz et al. found no alterations in COMP, MMP-1, or MMP-3 after 8 weeks of training (Oğuz et al., 2021). Similarly, Nambi et al. (2020) reported no meaningful variations in BMP concentrations despite significant pain reduction (Nambi et al., 2020). This dissociation suggests that exerciseinduced analgesia in OA may not be mediated through short-term modulation of cartilage or bone metabolism, at least as captured by these biomarkers within the studied timeframes. The modulation of therapeutic exercise is understood as the cartilage and bone metabolism through a complex interplay of mechanical loading and systemic inflammatory and neurofunctional responses. The cartilage turnover includes the degradation of metabolism. This biomarker of testing this response is known as the cartilage oligomeric matrix protein (COMP). It is the most sensitive marker for acute loading and often increases from 16 percent to 36 percent after running. It follows the synthesis procedures that reflect the collagen production. The bone turnover is classified as formation and resorption. For the formation of bone turnover, the Osteocalcin (OC) is working as the key marker that is typically lowered after excessive workout or extreme exercise like a marathon or sprints before rebounding during recovery. The resorption state reflects the bone breakdown, and the markers related to these are highly sensitive to prolonged non-impact exercise like cycling, such as the C-terminal telopeptide of type 1 collagen (CTX-1).

IV. DISCUSSION

The synthesis of five RCTs indicates that therapeutic exercise consistently reduces self-reported pain in patients with non-oncological musculoskeletal chronic pain, aligning with prior meta-analyses and clinical guidelines (Geneen et al., 2017; Rice et al., 2019). However, biomarker responses were heterogeneous, revealing differential sensitivity to exercise across biological domains. Inflammatory markers such as CRP, TNF-, and IL-6 decreased significantly in studies employing virtual reality training (Nambi et al., 2020; Nambi et al., 2023) but not in others using functional exercise (Bandak et al., 2021). This discrepancy may reflect differences in exercise modality, intensity, or patient population (posttraumatic OA vs. primary OA). Virtual reality training often integrates cognitive engagement and motor learning, which may exert stronger anti-inflammatory effects via neuro-immune cross-talk, though this hypothesis requires direct testing.

Neuroimaging biomarkers provided compelling evidence for central nervous system involvement in exercise induced analgesia. Reduced functional connectivity between PAG and mOFC, along with decreased mOFC gray matter volume, suggests modulation of descending pain inhibitory pathways and reward processing (Oğuz et al., 2021). The PAG is a key node in the endogenous opioid system, while the mOFC is implicated in affective pain processing. Exercise may enhance endogenous opioid and dopaminergic neurotransmission, thereby reducing pain perception independently of peripheral tissue changes. This central mechanism is consistent with models of

Table 1 Summary of included randomized controlled trials

Study	N	Cond.	Interv.	Wks	Biomarkers	Scale
Bandak et al. (Bandak et al., 2021)	60	Knee OA	Func. ex.	12	MRI, IL-6/10	KOOS
Oguz et al. [˜13]	22	Post-T OA	Str.+bal.	8	COMP, MMPs	VAS
Liu et al. (Oğuz et al., 2021)	108	Knee OA	Tai Chi/Cyc.	12	fMRI, BDNF, IFN-γ	KOOS
Nambi et al. (Nambi et al., 2020)	60	Post-T OA	VR+sensor.	4	BMPs, CRP, TNF-α	VAS
Nambi et al. (Nambi et al., 2023)	62	CLBP	VR+isokin.	4	CRP, TNF-α	VAS

OA: osteoarthritis; Post-T: post-traumatic; CLBP: chronic low back pain; VR: virtual reality.

chronic pain emphasizing maladaptive neuroplasticity and deficient endogenous pain inhibition (Reckziegel et al., 2019).

Contrarily, markers for remodeling in peripheral tissues (cartilage oligomeric matrix protein, matrix metalloproteinase, bone morphogenetic proteins) showed little variation, indicating that the structural integrity of the joints may not be a short-term to medium-term target of exercise. This has clinical implications: while exercise would improve symptoms and function, it does not seem to affect the structural progression of osteoarthritis at usual timescales for rehabilitation. Nonetheless, studies that go on longer would examine disease-modifying effects.

The female predominance in the included samples mirrors the higher prevalence of musculoskeletal pain conditions among women (Overstreet et al., 2023). Gender differences in pain perception, immune function, and hormonal influences may affect both biomarker expression and exercise responsiveness. Future trials should stratify by gender to explore these interactions and inform gender tailored rehabilitation approaches.

The studies examined had methodological limitations, such as small sample sizes, short duration of intervention, differences in exercise protocols, and differences in biomarker panels. These factors prevent us from concluding the best parameters for exercise to modulate our biomarker. Moreover, the majority of biomarkers could be evaluated in peripheral blood, which potentially does not reflect local joint or CNS processes. In future studies, incorporating multi-compartment analyses of biomarkers (e.g., synovial fluid, cerebrospinal fluid when practical) in conjunction with sophisticated advanced neuroimaging will uncover adaptations occurring throughout the system. Effect sizes were inconsistently reported across included trials, limiting quantitative comparison of treatment magnitude. The author conducted a systematic review with meta-analysis to evaluate the effects of exercise on inflammatory markers in individuals with musculoskeletal pain. In the last decade or the past ten years, the literature has discussed similar reviews on the effect of exercise on the response of inflammatory markers in healthy individuals, patients with metabolic syndrome, and postmenopausal women. The results of this research suggest that differences in gender have an impact on responses towards biomarkers. It also suggests that exercise plays a significant role in affecting and promoting inflammatory biomarkers. These are higher in intense exercise compared to moderate exercise.

V. CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The findings imply that due to its positive impacts on functioning and efficacy to affect biological mechanisms, exercise should be considered as a pillar of multidisciplinary pain management. According to the review, mind-body exercises like Tai Chi and technology assisted modalities like VR positively impacted pain and inflammation markers. Clinicians may take into account these options. Advice about changing exercise should be tailored to condition and preferences to cope with pain.

Standardized scales are used to assess subjective clinical markers. They include MADRS, GAF, HAM-A, GAD7, PRIME-MD, etc. Those objective indicators usually apply to a certain group, such as patients with medical comorbidities.

An objective assessment of treatment response is usually made with inflammatory markers (CRP, TNF-, IL-6) and neuroimaging markers in selected patients. In practice, however, the rarity of use is due to cost and availability. The assay that works on a biomarker for diagnosis must be simple for point-of-care use. Incorporating patient-reported data and biomarkers may enhance exercise prescription and predict long-term adherence.

Moreover, clinical implications also include physiological responses. These include (1) immune system modulation, (2) myokine-mediated effect, and (3) neurofunctional reorganization. This means the regular and moderate intensity exercise can act as an anti-inflammatory tool by regulating the release of anti-inflammatory cytokines such as IL-10 and producing the reduction of pro-inflammatory cytokines such as TNF. The contraction-induced myokine, like IL-6 in its early phases, promotes the anti-inflammatory environment, leading to implications that exercises can help in the reduction of chronic systemic and low-grade inflammation. The factors of increased exercise, such as neurotrophic factors- support neurogenesis and increase brain activity. In a clinical context, the intensity of exercise, such as moderate, leads to a maximum heart rate of about 60 to 70 percent, which has been understood as effective at reducing inflammation. At the same time, high-intensity exercise can, in particular, boost the marker for neuroplasticity. The modality refers to a mixture of aerobic exercise, which is generally running and cycling, and resistance training, which is recommended for maximum immunological and cognitive benefits. The duration for training is 8-12 weeks for achieving the lasting reduction in pro-inflammatory markers and sustained improvements

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in neuroplasticity. It acts as a potential immunomodulatory and neuroprotective intervention since it reduces systemic inflammation and enhances neuroplasticity. In clinical reference, it improves the results or outcomes in muscle pain, stroke, and neurodegeneration by reversing or reordering neuro inflammation to improve the synaptic plasticity and bolstering the integrity of the brain barrier.

1. Future research may include: (1) well-designed large RCTs with standardized exercise protocols and harmonized biomarker panels; (2) dose response studies that determine how biomarker responses vary with different exercise intensity and frequencies and durations; (3) studies that combine exercise and nutrition or cognitive behavioral therapy to see whether they affect biomarker changes; (4) long (6 months) structural biomarker and disease progression studies; and (5) multiomics (proteomics, metabolomics) studies to discover new pain biomarkers that can be modified by exercise. 2. The focus of future studies needs to be on providing a comprehensive review of gender specific differences in inflammatory changes due to substance use and mood disorders. However, other future studies can include following, such as the comprehensive reviews that will be focused on neuroimaging studies in understanding inflammatory mechanism and associated cognitive and structural changes. This also includes the brain metabolite changes in autoimmune disease, for example, autoimmune encephalopathy (AE) and autoimmune psychosis (AP). 3. Future studies can also include the following, such as the consistent sex difference in inflammatory changes in mood disorders. The area to discover here is the lack of sex hormone measurement, including the effects of drugs to determine whether it is acute or chronic. Other future research can include the impact of drug-induced overdose on neuro inflammation. The difference in gender is the major factor that impacts the response to inflammatory and neuro biomarkers. Women tend to inhibit the heightened stress-related responsivity while showing a more significant pro-inflammatory response marked by higher levels of TNF. Women tend to contain more depressive symptoms.

VI. CONCLUSION

The systematic review of randomized controlled trials indicates that physical exercise is effective in reducing pain in musculoskeletal chronic pain conditions. A study of biomarkers suggests that the antipain effects of exercise appear to be a result of its actions on inflammation and the brain, rather than on cartilage or bone. The benefits of exercise are multiple in nature. Therefore, it is best defined as a non-pharmacological option with biological plausibility. In the future, exercising studies in larger cohorts and mechanistic collaborations that sensitively investigate exercise perturbations and recovery will be needed for biomarker success. Further, it can be concluded that the therapeutic exercise serves as a better means to have a positive response towards inflammatory biomarkers. It acts as a non-pharmacological and multisystem approach for controlling the chronic disease. This acts for both inflammatory and neuro functional markers for effectively reducing systemic inflammation and promoting neuroprotection. It becomes a crucial component in rehabilitative and chronic disease management. Future research must focus on or carry out research work on the optimization of exercise intensity and duration to maximize these effects. This should be done for the older population, especially since they cannot perform gym training activities or excessive workouts. This also includes the population with neurodegenerative or chronic pain diseases.

VII. LIST OF ABBREVIATIONS

The abbreviation list below refers to the medical terminologies used in this research. These also include the general biomarkers that are not used in this research. The list below provides the general terms used for this topic of research, as mentioned in other systematic literature reviews.

Inflammatory Markers (Systemic/Local)

CRP: C-Reactive Protein
IL-6: Interleukin-6
TNF-α: Tumor Necrosis Factor-alpha
IL-1β: Interleukin-1 beta
IL-10: Interleukin-10
IL-1RA: IL-1 receptor antagonist
IFN-γ: Interferon-gamma
MCP-1: Monocyte chemoattractant protein-1
ESR: Erythrocyte Sedimentation Rate
WBC: White Blood Cell count
NLR: Neutrophil-to-Lymphocyte Ratio
PLR: Platelet-to-Lymphocyte Ratio
SII: Systemic Immune-inflammation Index
ROS/RNS: Reactive Oxygen/Nitrogen Species Neurofunctional & Neurotrophic Markers BDNF: Brain-Derived Neurotrophic Factor
IGF-1: Insulin-like Growth Factor 1

VEGF: Vascular Endothelial Growth Factor
FGF-2: Fibroblast Growth Factor 2
GFAP: Glial Fibrillary Acidic Protein
NfL: Neurofilament Light Chain
Aβ42/40: Amyloid-beta 42/40
S100β: S100 calcium-binding protein B

Physiological Response Markers
HRV: Heart Rate Variability
CK: Creatine Kinase
VO2max: Maximal Oxygen Uptake
ANS: Autonomic Nervous System
CNS: Central Nervous System
SCWT: Stroop Color and Word Test
SF-MPQ: Short-Form McGill Pain Questionnaire

Molecular/Metabolic Markers
NF-κB: Nuclear Factor kappa-light-chain- enhancer of activated B cells
MAPK: Mitogen-Activated Protein Kinase
AMPK: AMP-activated Protein Kinase
TLR: Toll-Like Receptor
HPA Axis: Hypothalamic–Pituitary–Adrenal Axis

VIII. DECLARATION

Ethical approval: The ethical approval was obtained from researchers who fully understand the research purpose, methods, risks, and benefits. They were also informed that they had the right to withdraw from the research without penalty before agreeing to participate. They were also informed that there were potential or significant harms, such as physical, psychological, or social harms. Their data were to be handled with confidentiality and privacy.

Consent for publication: The authors and researchers who were involved in the process were provided with the final manuscript before publishing to understand that the publication would be online and would have open access. The explicit documentation was required in written or electronic form.

Data availability and materials: The data were available online on different research websites, platforms, or tools. These provide free access to scholarly articles and academic journals. Materials that were required were a writing desk, a computer, internet, and a notepad. Other than this, no other materials were required.

Conflict of Interests: There had been no such conflict of interest among authors or researchers. The research took place in the absence of commercial or financial relationships as declared by the authors.

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Author's contribution: The author understood or conceived the topic, drafted its abstract, and planned the systematic review. They outlined the methodology and collected research papers. Each author has participated in this work and has given their approval to submit.

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REFERENCES

Cohen, S. P., Vase, L., & Hooten, W. M. (2021). Chronic pain: an update on burden, best practices, and new advances. The Lancet, 397(10289), 2082-2097. https://doi.org/ https://doi.org/10.1016/S0140-6736(21)00393-7

van Hecke, O., Torrance, N., & Smith, B. H. (2013). Chronic pain epidemiology and its clinical relevance. British Journal of Anaesthesia, 111(1), 13-18. https://doi.org/10.1093/bja/aet123

Crofford, L. J. (2015). Chronic Pain: Where the Body Meets the Brain. Trans Am Clin Climatol Assoc, 126, 167-183.

Geneen, L. J., Moore, R. A., Clarke, C., Martin, D., Colvin, L. A., & Smith, B. H. (2017). Physical activity and exercise for chronic pain in adults: an overview of Cochrane Reviews. Cochrane Database of Systematic Reviews(4). https://doi.org/10.1002/14651858.CD011279.pub3

Rice, D., Nijs, J., Kosek, E., Wideman, T., Hasenbring, M. I., Koltyn, K., Graven-Nielsen, T., & Polli, A. (2019). Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. The Journal of Pain, 20(11), 1249-1266. https://doi.org/ https://doi.org/10.1016/j.jpain.2019.03.005

Sam Eldabe, I. O., Catherine Panwar, David Caraway. (2022). Biomarkers for Chronic Pain: Significance and Summary of Recent Advances. Pain Research and Management 2022. https://doi.org/ https://doi.org/10.1155/2022/1940906

Levitt, J., & Saab, C. Y. (2019). What does a pain 'biomarker' mean and can a machine be taught to measure pain? Neuroscience Letters, 702, 40-43. https://doi.org/ https://doi.org/10.1016/j.neulet.2018.11.038

Kashanian, A., Tsolaki, E., Caruso, J., Bari, A., & Pouratian, N. (2022). Imaging as a Pain Biomarker. Neurosurgery Clinics of North America, 33(3), 345-350. https://doi.org/ https://doi.org/10.1016/j.nec.2022.02.011

Kawi, J., Lukkahatai, N., Inouye, J., Thomason, D., & Connelly, K. (2016). Effects of Exercise on Select Biomarkers and Associated Outcomes in Chronic Pain Conditions: Systematic Review. Biol Res Nurs, 18(2), 147-159. https://doi.org/10.1177/1099800415599252

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 372, n71. https://doi.org/10.1136/bmj.n71

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H.-Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., . . . Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ, 366, l4898. https://doi.org/10.1136/bmj.l4898

Bandak, E., Boesen, M., Bliddal, H., Daugaard, C., Hangaard, S., Bartholdy, C., Damm Nybing, J., Kubassova, O., & Henriksen, M. (2021). The effect of exercise therapy on inflammatory activity assessed by MRI in knee osteoarthritis: Secondary outcomes from a randomized controlled trial. The Knee, 28, 256-265. https://doi.org/ https://doi.org/10.1016/j.knee.2020.12.022

Oğuz, R., Belviranlı, M., & Okudan, N. (2021). Effects of Exercise Training Alone and in Combination With Kinesio Taping on Pain, Functionality, and Biomarkers Related to the Cartilage Metabolism in Knee Osteoarthritis. CARTILAGE, 13(1_suppl), 1791S-1800S. https://doi.org/10.1177/19476035211007895

Liu, J., Chen, L., Chen, X., Hu, K., Tu, Y., Lin, M., Huang, J., Liu, W., Wu, J., Qiu, Z., Zhu, J., Li, M., Park, J., Wilson, G., Lang, C., Xie, G., Tao, J., & Kong, J. (2019). Modulatory effects of different exercise modalities on the functional connectivity of the periaqueductal grey and ventral tegmental area in patients with knee osteoarthritis: a randomised multimodal magnetic resonance imaging study. British Journal of Anaesthesia, 123(4), 506-518. https://doi.org/ https://doi.org/10.1016/j.bja.2019.06.017

Nambi, G., Abdelbasset, W. K., Elsayed, S. H., Khalil, M. A., Alrawaili, S. M., & Alsubaie, S. F.

(2020). Comparative effects of virtual reality training and sensory motor training on bone morphogenic proteins and inflammatory biomarkers in post-traumatic osteoarthritis. Scientific Reports, 10(1), 15864. https://doi.org/10.1038/s41598-020-72587-2

Nambi, G., Alghadier, M., Kashoo, F. Z., Aldhafian, O. R., Nwihadh, N. A., Saleh, A. K., Omar, M. A., Hassan, T. G. T., Ibrahim, M. N. A., El Behairy, H. F., Attallah, A. A., & Ismail, M. A. (2023). Effects of Virtual Reality Exercises versus Isokinetic Exercises in comparison with Conventional Exercises on the Imaging Findings and Inflammatory Biomarker Changes in Soccer Players with Non-Specific Low Back Pain: A Randomized Controlled Trial. International Journal of Environmental Research and Public Health, 20(1), 524. https://www.mdpi.com/1660-4601/20/1/524

Reckziegel, D., Vachon-Presseau, E., Petre, B., Schnitzer, T. J., Baliki, M. N., & Apkarian, A. V. (2019). Deconstructing biomarkers for chronic pain: context- and hypothesis-dependent biomarker types in relation to chronic pain. PAIN, 160. https://journals.lww.com/pain/fulltext/2019/05001/deconstructing_biomarkers_for_chronic_pain_.6.aspx

Overstreet, D. S., Strath, L. J., Jordan, M., Jordan, I. A., Hobson, J. M., Owens, M. A., Williams, A. C., Edwards, R. R., & Meints, S. M. (2023). A Brief Overview: Sex Differences in Prevalent Chronic Musculoskeletal Conditions. International Journal of Environmental Research and Public Health, 20(5), 4521. https://www.mdpi.com/1660-4601/20/5/4521